Targeting Specific Microbiota to Influence Therapeutic Outcomes for Irritable Bowel Syndrome with Constipation (IBS-C)

Microbiome Drug Development Summit

28 June 2017
Forward-Looking Statements

Synthetic Biologics, Inc. (NYSE MKT: SYN)

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 ribaxamase and SYN-004 clinical trials and reporting of data, the size of the market, benefits to be derived from use of ribaxamase and SYN-004, 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, 2016, 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.
Synthetic Biologics, Inc. (NYSE MKT: SYN)

Highly experienced management and development team

- **Jeffrey Riley, CEO**
  Pfizer, Nichols Institute (Quest), SmithKline Beecham, QIC

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

- **Joseph Sliman, MD, MPH, CMO**
  Vanda Pharmaceuticals, Inc., MedImmune, Inc., DynPort Vaccine

- **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

- **Christopher da Costa, MD, PhD, FACP, VP Clinical Development**
  Pfizer, GlaxoSmithKline, Janssen

- **Jaimee Martinez, Director of Marketing**
  Hewlett Packard
# Synthetic Biologics Product Pipeline

Protecting the gut microbiome while targeting pathogen-specific diseases

<table>
<thead>
<tr>
<th>Therapeutic Area / Product Candidate</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
</table>
| IBS-C  SYN-010<sup>C</sup>  
*Oral modified-release lovastatin lactone* |   |   | | | * |
| Prevention of CDI and AMR  SYN-004 (ribaxamase)  
*Oral enzyme to degrade IV β-lactam antibiotics* | | | | Breakthrough Therapy Designation (FDA) | |
| Prevention of CDI and AMR (oral antibiotics)  SYN-007  
*Novel oral ribaxamase formulation to degrade orally-administered β-lactam antibiotics* | | | | | |
| Prevention of CDI and AMR (expanded antibiotic spectrum)  SYN-006  
*Oral enzyme to degrade IV carbapenem antibiotics* | | | | | |
| Prevention/Treatment of Pertussis (Whooping Cough)  SYN-005<sup>LT</sup>  
*Monoclonal antibodies* | | | | | |
| Phenylketonuria (PKU)  SYN-200<sup>L</sup>  
*Biotherapeutics* | | | | | |
| Restore gut barrier function/treat inflammation  SYN-020  
*Oral intestinal alkaline phosphatase* | | | | | |

*Two Phase 2 studies completed; agreement with FDA on Phase 2b/3 pivotal clinical trial
C - Cedars-Sinai Medical Center collaboration.
I - Intrexon Corporation collaboration
T - The University of Texas at Austin collaboration
Irritable Bowel Syndrome (IBS)

Chronic functional gastrointestinal disorder

• Recurrent abdominal pain associated with abnormal bowel movements, gas and bloating
  – Multiple subtypes characterized by stool consistency and frequency

• 15% of the world’s population suffers from IBS
  – 30-40 million people in the USA
  – 50% of gastroenterologist visits
  – USD 30 billion in healthcare costs

• Tremendous impact on QoL
  – Patients seek healthy BM habits

¹Longstreth GF et al. (2006) *Gastroenterology* **130**: 1480-91
SYN-010 is a Unique IBS-C Therapy

SYN-010 treats a microbial cause of IBS-C symptoms

**Stimulate intestinal water influx**
- Linaclotide
- Lubiprostone
- Plecanatide
- Tenapanor
- Miralax
- Senna

**Stimulate intestinal contractions**
- Bisacodyl
- Erythromycin
- Prucalopride
- Senna

**Reduce intestinal methane**
- SYN-010

**Move the Mass**

**Hydrate the Stool**

¹Directly inhibit a cause of key IBS-C symptoms pain, constipation and bloating; by treating a cause of IBS-C symptoms, continued use of SYN-010 is also expected to prevent symptom recurrence
Methane production (methanogenesis) is a ubiquitous process in the human intestine, disposing of hydrogen and other by-products formed during bacterial fermentation\(^1\)

Methane production in humans is almost entirely due to the archeon *Methanobrevibacter smithii* (*M. smithii*)

1. *M. smithii* resides predominantly in the colon but is found at lower levels in the small intestine of some patients
2. Archea ≠ bacteria and have limited susceptibility to antibiotics\(^2\)

\(^1\)Gottlieb K et al. (2015) *Aliment Pharmacol Ther* **43**: 197-212
\(^2\)Archeal cell membrane synthesis requires HMG-CoA reductase (*HMGR*), an enzyme integral to cholesterol biosynthesis in humans
SYN-010 Technology Background

Elevated intestinal methane is a cause of IBS-C symptoms

• A growing body of clinical evidence has established that elevated intestinal methane production reduces intestinal motility and is a cause of constipation, pain and bloating in IBS-C¹
  • 50-90% of IBS-C patients are breath methane positive (≥3 ppm)

• Causality demonstrated by fecal microbial transplantation (FMT)²

¹Triantafyllou K et al. (2014) J Neurogastroenterol Motil 20: 31-40; Ghoshal U et al. (2016) Gut Liver 10: 932-8
²Chang B et al. (2016) Am J Gastroenterol 112: 186-7

CDI = Clostridium difficile infection unresolved by vancomycin and metronidazole
SYN-010 Technology Background

Lovastatin lactone is a unique inhibitor of methanogenesis

Lovastatin lactone, but not the β-hydroxyacid, inhibited methane production by *M. smithii* in stool samples from IBS-C patients

Lovastatin lactone
No effect on HMGR
Inhibits methane production¹

Stomach acid; Esterases

Lovastatin action in IBS-C is distinct from its cholesterol lowering effects³

Lovastatin β-hydroxyacid
Inhibits HMGR
Blocks cholesterol synthesis²

²Mevacor® lovastatin tablets were first approved in 1987 for use in lowering cholesterol
β-Hydroxyacid statins were ineffective inhibitors of CH₄ production.

**Lovastatin Lactone is the Best Statin CH₄ Inhibitor**

To account for inter-sample baseline variability, data are presented as change from time 0 to 270 min (ΔCH₄) expressed as a percentage of the control.

Statins (5 mg/g stool wet weight) were incubated for 270 min in homogenates made from stool samples provided by high breath CH₄ IBS-C patients.


---

1. To account for inter-sample baseline variability, data are presented as change from time 0 to 270 min (ΔCH₄) expressed as a percentage of the control.
Computational studies indicate direct inhibition of methane production

Lovastatin lactone binds more effectively to $F_{420}$-dependent methylenetetrahydromethanopterin dehydrogenase (mtd) than does the native co-factor $F_{420}$

¹Gottlieb K et al. (2015) *Aliment Pharmacol Ther* 43: 197-212
SYN-010 Modified Release Lovastatin Lactone

HPMC capsule containing combinations of different enteric coated tablets

SYN-010 42 mg¹

<table>
<thead>
<tr>
<th>Stomach</th>
<th>Duodenum</th>
<th>Jejunum</th>
<th>Ileum</th>
<th>Cecum</th>
<th>Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 1.4-2.0</td>
<td>pH 5.9-6.6</td>
<td>pH 6.6-7.4</td>
<td>pH 7.3-7.8</td>
<td>pH 5.6-5.9</td>
<td>pH 5.6-6.8</td>
</tr>
</tbody>
</table>

Capsule dissolves and enteric coatings prevent hydrolysis of lovastatin lactone²

Duodenal release (DR) tablet disintegrates to release active lovastatin lactone into duodenum

Ileocecal release (ICR) tablets disintegrate to release active lovastatin lactone into the ileocecal junction and colon

Reduce methane without killing microbes³

④ Systemic absorption is not required for lovastatin efficacy in IBS-C

¹Each tablet contains 7 mg of lovastatin lactone; SYN-010 21 mg capsule contains 1 x DR and 2 x ICR tablets

²Gastric absorption accounts for up to 30% of an IR lovastatin dose; SYN-010 release profile preserves lovastatin in the antimethanogenic lactone form in the intestine and lowers systemic levels of the cholesterol-lowering β-hydroxyacid

SYN-010 Pharmacokinetics in Healthy Volunteers

Lovastatin plasma pharmacokinetic profile after a single dose

1 Separate parallel groups of fasted healthy volunteers (n=8 per group); plasma samples analyzed using an LC MS/MS method
2 A head-to-head comparison was not conducted in this study; however, AUC and C_{max} of lovastatin \( \beta \)-hydroxyacid after SYN-010 42 mg were \~50\% lower than values reported for equivalent (40 mg) doses of Mevacor\® or Altocor/Altoprev\® in fasted volunteers (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21316_Altocor_BioPharmr.pdf)

Drug is not released into the stomach

Continued drug release well into the colon

Reduced \( \beta \)-hydroxyacid levels compared to marketed formulations

SYN-010 21 mg - lactone
SYN-010 21 mg - \( \beta \)-hydroxyacid
SYN-010 42 mg - lactone
SYN-010 42 mg - \( \beta \)-hydroxyacid
SYN-010 Stool Concentrations in Healthy Volunteers

SYN-010 delivered methane-inhibiting levels of lovastatin lactone to the colon

Lovastatin lactone levels for 21 mg and 42 mg doses are equivalent to levels that reduced CH$_4$ production in vitro by 60% and 90% respectively$^2$

¹Data are mean±SD concentrations in stool samples collected on the 4$^{th}$ dosing day from fasted healthy volunteers administered single, oral doses of SYN-010 21 mg (n=6) or SYN-010 42 mg (n=7) each morning for 4 days; *P<0.05 v 21 mg (unpaired t-test)

²Lovastatin lactone, β-hydroxyacid and other statins were incubated for up to 270 min with stool samples from high breath methane IBS-C patients; Marsh E et al. (2015) Am J Gastroenterol 110 (Suppl 1): S753
SYN-010 Phase 2a Clinical Study Design

Consecutive trials of daily, oral SYN-010 doses in IBS-C patients

- Multicenter, randomized, controlled, double-blinded, 4-week trial (RCT) followed by an 8-week open-label extension (EXT)

**SYN-010 Phase 2a Clinical Study Design**

**Randomized (RCT)**

1. Placebo (22)
2. SYN-010 21 mg (22)
3. SYN-010 42 mg (20)

**Open-Label Extension (EXT)**

1. SYN-010 42 mg (20)
2. SYN-010 42 mg (20)
3. SYN-010 42 mg (17)

Screen 1, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84

- CH₄ > 10 ppm determined by lactulose breath test

1 Subjects randomized at 12 sites in the USA
2 RCT completers were eligible to continue into the EXT, no new subjects were enrolled in the EXT
## SYN-010 Phase 2a Clinical Study Population

Baseline demographic parameters for all subjects entering the RCT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong>¹</td>
<td>RCT</td>
<td>EXT</td>
<td>RCT</td>
</tr>
<tr>
<td>SYN-010 dose</td>
<td>Placebo</td>
<td>42 mg</td>
<td>21 mg</td>
</tr>
<tr>
<td>Dosing period, weeks</td>
<td>1-4</td>
<td>5-12</td>
<td>1-4</td>
</tr>
<tr>
<td><strong>Baseline Demographics (day 1)²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. Subjects (Female %)</td>
<td>22 (77.3%)</td>
<td>22 (86.4%)</td>
<td>19 (73.7%)</td>
</tr>
<tr>
<td>White / Black, African American / Other, %</td>
<td>72.7% / 18.2% / 9.1%</td>
<td>95.5% / 4.5% / --</td>
<td>87.8% / 12.2% / --</td>
</tr>
<tr>
<td>Age, years</td>
<td>46.4±10.3</td>
<td>42.6±6.0</td>
<td>44.7±9.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.4±3.3</td>
<td>26.2±3.1</td>
<td>26.4±3.2</td>
</tr>
<tr>
<td>Study Drug Compliance, %</td>
<td>99.2±3.8%</td>
<td>97.9±6.2%</td>
<td>98.4±3.5%</td>
</tr>
<tr>
<td><strong>Baseline Symptoms (day 1)²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breath methane, ppm</td>
<td>25.3±18.7</td>
<td>24.9±26.2</td>
<td>24.0±15.5</td>
</tr>
<tr>
<td>Breath methane AUC, ppm*h</td>
<td>86.8±75.9</td>
<td>83.3±75.1</td>
<td>87.4±61.0</td>
</tr>
<tr>
<td>No. Complete Spontaneous Bowel Movements (CSBM)s per week</td>
<td>0.41±0.73</td>
<td>0.27±0.63</td>
<td>0.53±0.70</td>
</tr>
<tr>
<td>Bristol Stool Form Scale (BSFS; 1-7)³</td>
<td>1.67±0.90</td>
<td>1.63±0.99</td>
<td>1.71±0.70</td>
</tr>
<tr>
<td>Worst Abdominal Pain Score (0-10)³</td>
<td>5.19±1.77</td>
<td>5.65±1.77</td>
<td>5.43±1.30</td>
</tr>
<tr>
<td>Bloating Score (0-4)³</td>
<td>2.44±0.65</td>
<td>2.52±0.76</td>
<td>2.46±0.56</td>
</tr>
</tbody>
</table>

¹RCT completers were eligible to continue into the EXT, no new subjects were enrolled in the EXT; >90% identified as Hispanic
²Data are mean±SD; BMs (if any), BSFS, worst abdominal pain score and bloating score were reported by subjects each day in an electronic diary. ³BSFS, worst abdominal pain and bloating scores are weekly average scores
% Subjects with increase of ≥1 CSBM per week vs baseline in ≥50% of weeks

Complete Spontaneous Bowel Movements (CSBMs; if any) were reported by subjects each day in an electronic diary.

Nominal P values (Chi²): †P<0.05 for within-group comparison to Month 1; aP=0.055 vs Placebo

Increase from baseline in weekly No. CSBMs for SYN-010 21 mg in Month 1 was statistically different to Placebo (P<0.05)

CSBM Response for combined EXT subjects (n): Month 2 = 51.9% (52), Month 3 = 59.2% (49); Months 2&3 = 55.8% (52)

Largest response in Cohort 2 which had lowest baseline CSBMs

Increased response with longer dosing
SYN-010 Improved Monthly Abdominal Pain Response

% Subjects with ≥30% decrease in abdominal pain vs baseline in ≥50% of weeks

1Abdominal pain score is the weekly average of the worst abdominal pain score reported by subjects each day in electronic diaries
2Nominal P values (Chi²): †P<0.05, ‡P<0.005, bP=0.088 for within-group comparison to Month 1; aP=0.088 vs Placebo
3Abdominal Pain Response for combined EXT subjects (n): Month 2 = 58.8% (51), Month 3 = 61.7% (47); Months 2&3 = 62.7% (51)
**SYN-010 Improved Monthly Bloating Response**

% Subjects with ≥30% decrease in bloating score vs baseline in ≥50% of weeks

1. Bloating score is the weekly average of the bloating score reported by subjects each day in electronic diaries.
2. Nominal P values (Chi²): †P<0.05, §P<0.0005, aP=0.0503, bP=0.0729 all for within-group comparison to Month 1.
3. Bloating Response for combined EXT subjects (n): Month 2 = 60.8% (51), Month 3 = 76.6% (47); Months 2&3 = 72.6% (51).

---

**Table:**

<table>
<thead>
<tr>
<th>Month</th>
<th>Placebo (RCT)</th>
<th>Placebo (EXT)</th>
<th>42 mg (RCT)</th>
<th>42 mg (EXT)</th>
<th>21 mg (RCT)</th>
<th>21 mg (EXT)</th>
<th>42 mg (RCT)</th>
<th>42 mg (EXT)</th>
<th>42 mg (RCT)</th>
<th>42 mg (EXT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31.8%</td>
<td>53.3%</td>
<td>76.9%</td>
<td>78.9%</td>
<td>52.6%</td>
<td>78.9%</td>
<td>76.5%</td>
<td>73.3%</td>
<td>42.1%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>22.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

1. Bloating score is the weekly average of the bloating score reported by subjects each day in electronic diaries.
2. Nominal P values (Chi²): †P<0.05, §P<0.0005, aP=0.0503, bP=0.0729 all for within-group comparison to Month 1.
3. Bloating Response for combined EXT subjects (n): Month 2 = 60.8% (51), Month 3 = 76.6% (47); Months 2&3 = 72.6% (51).
SYN-010 Groups Used Less Rescue Medication

Subjects reporting bisacodyl use each day during the RCT (mITT population)

- Placebo [12/22 subjects used bisacodyl during study; 54.5%]
- SYN-010 21 mg [4/22 subjects used bisacodyl; 8.2%; \( p = 0.013 \) vs Placebo]
- SYN-010 42 mg [4/19 subjects used bisacodyl; 21.1%; \( p = 0.03 \) vs Placebo]

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
Breath Methane and Bowel Movements

Lower breath methane associated with more frequent bowel movements

Correlation line represents least-squares linear regression modeling

$\Delta$AUC CH$_4$ from Baseline day 1 (n=48) $-19\pm8$ ppm*h (mean±SEM; P<0.005 vs baseline)
## SYN-010 Very Well-Tolerated in Phase 2a Studies

Few treatment emergent adverse events (TEAEs), no serious adverse events (SAEs)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td>RCT</td>
<td>EXT</td>
<td>RCT</td>
</tr>
<tr>
<td>SYN-010 Dose</td>
<td>Placebo</td>
<td>42 mg</td>
<td>21 mg</td>
</tr>
<tr>
<td>Enrolled, n</td>
<td>22</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>Withdrew, n</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Reported SAE, n</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reported TEAE, n</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

**Description of TEAE (Relationship to Treatment)**¹

<table>
<thead>
<tr>
<th>RCT, weeks 1-4s</th>
<th>01 Gastroenteritis (unlikely)</th>
<th>04 Headache (probable)</th>
<th>07 Elevated GGT (probable)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>05 Intermittent rectal bleeding (unrelated)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>08 Elevated AST creatine kinase (possible)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXT, weeks 5-12</th>
<th>02 Diarrhea (unrelated)²</th>
<th>05 Proctitis (unrelated)</th>
<th>09 Elevated creatine kinase (unrelated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>03 Elevated ALT AST ALP LDH GGT (unlikely)³</td>
<td>06 First degree AV block (unrelated)</td>
<td>10 Elevated creatine kinase (unrelated)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leg cramp (possible)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headache (possible)</td>
<td></td>
</tr>
</tbody>
</table>

¹Numbers are masked Subject ID; TEAEs were all of mild or moderate intensity
²Commenced after last dose of study drug
³Resulted in withdrawal from the study
SYN-010 Clinical Study Conclusions

Results validate advancement of SYN-010 to pivotal clinical trials

- Daily doses of SYN-010 were well-tolerated by IBS-C patients over the 12 week treatment period (at least 8 weeks of SYN-010 42 mg)
  - No SAEs, few TEAEs and no incidences of drug-related diarrhea

- Compelling improvements were observed in CSBM frequency, abdominal pain and bloating in SYN-010 treatment groups¹,²
  - SYN-010 effects increased with longer dosing and in subjects transferred to SYN-010 42 mg for the 8 week EXT

- SYN-010 has a significantly different release profile to lovastatin products used in cholesterol-lowering therapy
  - Dual-pulse, intestine-acting, antimethanogenic therapy delivers lovastatin lactone to intestinal sites where *M. smithii* resides

¹IBS-SSS (symptom severity score) was also improved vs day 1 baseline after 12 weeks (P<0.005)
²Studies were not prospectively powered for formal statistical evaluation of clinical endpoints
SYN-010 Clinical Development Status

Agreement with FDA on SYN-010 pivotal clinical trials

• Successful End-of-Phase 2 (EOP2) meeting with the FDA in Q3 2016
  • FDA enunciated clear interest in IBS-C therapies with novel modes-of-action

• FDA recommended a first Phase 2b/3 adaptive design clinical trial
  • Multicenter, randomized, double-blind, placebo-controlled study
  • 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

• Anticipate utilization of 21 CFR 505(b)(2) pathway to leverage innovator (Mevacor®; Merck) safety data
  • FDA acknowledged in EOP2 meeting minutes that Mevacor® safety data would be supportive
  • Requires a pharmacokinetic study vs reference listed drug for 505(b)(2) pathway
Why Include Patients with Low Breath Methane?

Not all IBS-C Pts with constipating stool *M. smithii* levels have high breath methane.

---

**Breath CH$_4$ Positive (≥3 ppm)**

**M. smithii**

cfu/mL stool)

~$10^6$

~$10^4$

---

**Elevated Gut CH$_4$**

---

IBS-C patients with low breath CH$_4$ but high gut CH$_4$ should also benefit from SYN-010

---

¹Kim G et al. (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 Pivotal Clinical Trials in IBS-C

Phase 2b/3 adaptive study then a Phase 3 study with randomized withdrawal

Phase 2b/3
- Both low (<5 ppm) and high breath CH₄ patients included in each dosing arm
- SYN-010 42 mg q.d. (n=280)
- SYN-010 21 mg q.d. (n=280)
- Placebo q.d. (n=280)

12 Weeks¹

Phase 3
- SYN-010 dose(s) and breath CH₄ status determined from Phase 2b/3 study
- SYN-010

Randomized Withdrawal (per guidance)

12 Weeks

4 Weeks

• Primary Endpoint: Percentage of patients who are Overall (12-Week) Responders²
• Secondary Endpoints: Include changes in bowel movements, abdominal pain, bloating, safety, QoL

¹Interim futility analysis based on dose may be conducted after 50% of subjects have completed 12 weeks
²An Overall (12-Week) Responder has a Weekly Response in at least 50% of weeks in the 12-week treatment period. A Weekly Response is defined as a stool frequency increase of ≥1 CSBMs per week compared with baseline and a decrease in weekly average score for worst abdominal pain of at least 30% compared with baseline in the same week
SYN-010 Opportunity

Restoring healthy bowel habits; addressing multiple methane-related conditions

• Novel mode-of-action, distinct from current IBS-C therapies
  • Treats a cause of IBS-C symptoms without causing diarrhea

• Multiple prescribing opportunities
  • Stand alone chronic therapy
  • Follow-up therapy after use of antibiotics¹, prescription IBS-C medicines or OTC laxatives to prevent recurrence of constipation and IBS-C symptoms

• Potential expanded use in methane-related conditions
  • Pediatrics², chronic idiopathic constipation (CIC), obesity, metabolic disease

¹To treat conditions where both hydrogen and methane are problematic (e.g. SIBO)
²IBS-C is the predominant IBS subtype diagnosed in children with few treatment options; potential expansion into pediatric CIC
Reference Slides
Lovastatin Lactone Inhibits Methane Production

Incubation of lovastatin lactone with stool samples from IBS-C patients

**Figure 1:** Lovastatin lactone (0.04-10.0 mg/g stool wet weight) was incubated for 270 min in homogenates made from stool samples provided by high breath CH\(_4\) IBS-C patients\(^1\). CH\(_4\) was measured in the reactor headspace using gas chromatography\(^2\). To account for baseline variability, data are presented as change from time 0 \(\Delta\text{CH}_4 = \text{CH}_4\) at time (n) – \(\text{CH}_4\) at time 0.

**Figure 2:** Lovastatin lactone concentrations in the stool of healthy volunteers administered SYN-010 for 4 days were equivalent to concentrations that inhibited methane production by \(~60\%\) (21 mg dose) and \(~90\%\) (42 mg dose) in stool in vitro. \(\Delta\text{CH}_4\ AUC\text{0-270} = \text{area under the } \Delta\text{CH}_4\ \text{concentration vs time curve from 0-270 min.}\)

---

\(^1\)Five females subjects with an average breath methane (CH\(_4\)) of 69.6 ppm provided a total of 8 fresh stool samples each

Lovastatin Lactone is not Microbicidal

Lovastatin species did not eradicate methanogens or bacteria in rat intestine

Male Sprague-Dawley rats (n=30) were fed a high-fat diet for 7 weeks to increase *M. smithii* levels throughout the intestinal tract. Rats were then divided into 3 groups and administered single daily oral gavage doses of eitherLovastatin lactone (1.5 mg/rat), β-hydroxyacid (1.5 mg/rat) or vehicle for 10 days. Rats were then euthanized, DNA was extracted from the contents of ligated bowel segments, and total lumenal bacteria and *M. smithii* determined by qPCR¹,²

---

¹†Methanobrevibacter smithii (*M. smithii*) is the predominant methanogen in the mammalian intestinal tract
²Morales W et al. (2015) *Gastroenterology* **148 (Suppl 1)**: S-779-80. *P<0.05 vs Placebo (Mann-Whitney test)
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 variable¹
  - ≥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


**Figure 1:** 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
Lactulose Breath Test (LBT)

Single-point breath methane equivalent to full LBT for stratification

Breath hydrogen increases as the lactulose is metabolized by intestinal bacteria

Pre-lactulose methane ≥5 ppm provides the same stratification of high- and low-methane producers as full LBT¹

Breath methane is largely unchanged over the course of the LBT

¹Gottlieb K et al. (2017) Gastroenterol Rep (Oxf) e-Pub Jan 27