

**FDA APPROVES SYMPROIC® (NALDEMEDINE) ONCE-DAILY TABLETS C-II FOR THE TREATMENT OF OPIOID-INDUCED CONSTIPATION IN ADULTS WITH CHRONIC NON-CANCER PAIN**

OSAKA, Japan & FLORHAM PARK, N.J. & STAMFORD, CN – Shionogi Inc. and Purdue Pharma L.P. announced today that the U.S. Food and Drug Administration (FDA) approved Symproic® (naldemedine) 0.2 mg tablets C-II as a once-daily oral peripherally-acting mu-opioid receptor antagonist (PAMORA) medication for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

Symproic is currently a Schedule II controlled substance because it is structurally related to naltrexone. Shionogi Inc. submitted a petition for the descheduling of Symproic, or removal of the controlled substance classification, to the U.S. Drug Enforcement Administration (DEA), which is currently under evaluation. Symproic will be jointly launched and commercialized in the U.S. with Purdue Pharma and is expected to be commercially available mid-summer.

“The FDA approval of Symproic provides a safe and effective therapy for adult patients suffering from chronic non-cancer pain and struggling with opioid-induced constipation,” said John Keller, President and Chief Executive Officer, Shionogi Inc. “We believe Symproic will offer a new therapeutic option to help reduce the needless suffering for those who experience OIC. The launch of Symproic with Purdue Pharma this summer will mark yet another milestone in our commitment to protect the health and well-being of patients we serve.”

The FDA approval of Symproic was based on data from the COMPOSE program, a global comprehensive development program comprised of clinical studies conducted in adult patients with OIC and chronic non-cancer pain. It was comprised of three studies: COMPOSE I, COMPOSE II and COMPOSE III. COMPOSE I and II were 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies, while COMPOSE III was a 52-week, randomized, double-blind, placebo-controlled, long-term safety study.

“By entering this exciting new therapeutic area with Shionogi Inc., we have the opportunity to further help patients with chronic non-cancer pain by offering more comprehensive care to both patients and doctors,” said Mark Timney, President and Chief Executive Officer, Purdue Pharma L.P. “The approval of Symproic marks a significant advancement in our partnership with Shionogi as well as the diversification of our product portfolio.”

Please see Important Safety Information, including Warnings & Precautions and Adverse Reactions below.

**About Opioid-Induced Constipation**

Constipation is one of the most commonly reported side effects associated with opioid treatment, including

## Opioid-Induced Constipation (OIC)

In adult patients with chronic non-cancer pain

# FACTS

### About Opioid-Induced Constipation

Constipation is one of the most commonly reported side effects associated with opioid treatment, including among adult patients with chronic non-cancer pain.<sup>1</sup>

OIC is characterized by any of the following after initiating opioid therapy:<sup>2</sup>

✓

Reduced bowel movement frequency

✓

Development or worsening of straining to pass bowel movements

✓

A sense of incomplete rectal evacuation

✓

Harder stool consistency

33%

of patients in a survey of 322 patients taking daily opioids for chronic pain missed, decreased or stopped opioid use to ease a bowel movement.<sup>3</sup>

40-50%

In patients with chronic non-cancer pain, the prevalence of OIC ranges from approximately 40% to 50%.<sup>4,5</sup>

Non-pharmacological treatment options include an INCREASE IN DIETARY FIBER, FLUID INTAKE, AND PHYSICAL ACTIVITY.<sup>6</sup>

AGENTS COMMONLY USED TO MANAGE OIC, SUCH AS LAXATIVES

do not address the full spectrum of underlying opioid receptor-mediated causes of constipation.<sup>9</sup>

LAXATIVES DO NOT TARGET THE UNDERLYING CAUSE OF OIC

(opioid binding to the mu-receptors in the enteric system of the gastrointestinal tract).<sup>8</sup>

If first-line non-pharmacologic treatments and OTC laxatives do not work, then treatment with an **OIC-specific prescription medication should be considered.**<sup>11-12</sup>

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MR-03393

**REFERENCES**

<sup>1</sup> Gilpin N, Colucci A, Smith W. Chronic pain treatment with opioid analgesics: benefits versus harms of long-term therapy. *Expert Rev Neurother*. 2013;13(12):1203.

<sup>2</sup> Coudreau R, Chalmers D, Bester C, Hester J, Cline A, Mose D. Emerging treatments in opioid-induced constipation: a multicenter working group consensus statement on opioid-induced constipation. *Neurogastroenterol Motil*. 2014;26(1):136-139.

<sup>3</sup> Hall T, Chouinard C, Macdonald C, Ridge SC, Johnson T, Williams B. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (POCBE). *J Pain Med*. 2010;15(1):26-32.

<sup>4</sup> Hays R, Chouinard C, Moore BA, McChesney M. Opioid-induced constipation: a systematic review of efficacy and safety. *Pharm*. 2004;11(2):24-30.

<sup>5</sup> Cook DJ, Lavoie L, Zhou X, et al. Gastrointestinal side effects in chronic opioid users: results from a population-based survey. *Aliment Pharmacol Ther*. 2007;21(2):1209-1212.

<sup>6</sup> Spivey R, Constable R, Fleming M. Nausea effects and cognitive function among chronic pain patients taking opioids for chronic noncancer pain. *J Opioid Manage*. 2006;2(3):137-146.

<sup>7</sup> Takay M, Bittman J, Doolittle GJ, Lerner AG. Opioid-induced bowel dysfunction and narcotic bowel syndrome in patients with chronic non-cancer pain. *Neurogastroenterol Motil*. 2015;27(4):424-430.

<sup>8</sup> Kessler D, Berman C, Conroy R. Opioid-induced constipation: pathophysiology, clinical consequences, and management. *Constipation Res Rev*. 2015;2(2):141-157.

<sup>9</sup> Capura R, LoCascio R, Datta G, Serran C, Neumann K, Tack J. Opioid-induced constipation in patients with chronic noncancer pain in the USA, Canada, Germany, and the UK: descriptive analysis of baseline patient-reported outcomes and associations with pain. *Constipation Res Rev*. 2015;2(2):87-97.

<sup>10</sup> Van L, Lamba A, Cameron E. Opioid-induced bowel dysfunction: epidemiology, pathophysiology, diagnosis, and initial therapeutic approach. *Am J Gastroenterol*. 2014;109:21-37.

<sup>11</sup> Nelson MZ, Cavallier D. Chronic opioid-induced constipation in patients with noncancer pain: challenges and opportunities. *Ther Adv Gastroenterol*. 2015;8:209-220.

<sup>12</sup> Wang C, Barnes M, Cantile M, et al. Consensus recommendations on opioid management strategies for opioid-induced constipation. *Pharm Med*. 2015;16:228-237.

among patients with chronic non-cancer pain.<sup>1</sup> When opioids bind to specific proteins called mu-opioid receptors in the gastrointestinal (GI) tract, constipation may occur. Opioid-induced constipation (OIC) is a result of increased fluid absorption and reduced GI motility due to opioid receptor binding in the GI tract. OIC is

PRACTICAL GASTROENTEROLOGY • APRIL 2017

defined as a change in bowel habits that is characterized by any of the following after initiating opioid therapy: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency.<sup>2</sup> In patients with chronic non-cancer pain, the prevalence of OIC ranges from approximately 40-50 percent.<sup>3,4,5,6</sup> In a survey of 322 patients taking daily opioids for chronic pain, 33 percent of patients missed, decreased or stopped opioid use to ease bowel movements.<sup>7</sup>

**Indication**

Symproic® (naldemedine) CII is an opioid antagonist indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

**Important Safety Information about Symproic**

Symproic is contraindicated in:

Patients with known or suspected gastrointestinal (GI) obstruction and patients at increased risk of recurrent obstruction, due to the potential for GI perforation.

Patients with a history of a hypersensitivity reaction to Symproic. Reactions have included bronchospasm and rash.

**Warnings and Precautions**

Cases of GI perforation have been reported with use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract. Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue if this symptom develops.

Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, increased lacrimation, hot flush/flushing, pyrexia, sneezing, feeling cold, abdominal pain, diarrhea, nausea, and vomiting have occurred in patients treated with Symproic.

Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia. Take into account the overall risk-benefit profile when using Symproic in such patients. Monitor for symptoms of opioid withdrawal in such patients.

**Drug Interactions**

Avoid use with strong CYP3A inducers (e.g. rifampin, carbamazepine, phenytoin, St. John’s Wort) because it may reduce the efficacy of Symproic.

Avoid use of Symproic with another opioid antagonist due to potential for additive effect and increased risk of opioid withdrawal.

**Use in Specific Populations**

Symproic crosses the placenta and may precipitate opioid withdrawal in a fetus due to the immature fetal blood-brain barrier. Symproic should be used during pregnancy only if the potential benefit justifies the potential risk.

Because of the potential for serious adverse reactions, including opioid withdrawal, in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**Controlled Substance**

Symproic contains naldemedine, a Schedule II controlled substance.

**Adverse Reactions**

The most common adverse reactions with Symproic as compared to placebo in clinical trials were: abdominal pain (8% vs 2%), diarrhea (7% vs 2%), nausea (4% vs 2%), and gastroenteritis (2% vs 1%).

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch). Please see complete U.S. Prescribing Information and Medication Guide at:

**shionogi.com**

**About Shionogi**

Shionogi & Co., Ltd., is a Japanese pharmaceutical company with a 139-year history discovering and developing innovative therapies. Shionogi Inc., the U.S. based subsidiary of Shionogi & Co., Ltd., continues this focus on the development and commercialization of high quality medicines that protect the health and well-being of the patients we serve. The company currently markets products in several therapeutic areas including anti-infectives, pain and cardiovascular diseases. Our pipeline is focused on infectious disease, pain, CNS and oncology.

For more details on Shionogi Inc., visit:

**shionogi.com**

**About Purdue Pharma L.P.**

Purdue Pharma is a privately-held pharmaceutical company and is part of a global network of independent associated companies that is known for pioneering research in chronic pain and opioids with abuse-deterrent properties. The company’s leadership and employees are committed to providing healthcare professionals, patients and caregivers quality products and educational resources to support their proper use. Purdue Pharma is engaged in the development, production and distribution of both prescription and over-the-counter medicines and hospital products. With Purdue Pharma’s expertise in drug development, commercialization and life-cycle management, the company is diversifying in high-need areas to expand through strategic acquisitions and creative partnerships.

For more information, please visit:

**purduepharma.com**

**References**

1. Sehgal N, Colson J, Smith HS. Chronic pain treatment with opioid analgesics: benefits versus harms of long-term therapy. *Expert Rev Neurother*. 2013;13:1201-1220.
2. Camilleri M, Drossman DA, Becker G, Webster LR, Davies AN, Mawe GM.

Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. *Neurogastroenterol Motil.* 2014; 26: 1386-1395.

3. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic noncancer pain: systematic review of efficacy and safety. *Pain.* 2004;112:372-80.
4. Cook SF, Lanza L, Zhou X, et al. Gastrointestinal side effects in chronic opioid users: results from a population based survey. *Aliment Pharmacol Ther.* 2008;27(12):1224-1232.
5. Brown RT, Zuelsdorff M, Fleming M. Adverse effects and cognitive function among primary care patients taking opioids for chronic nonmalignant pain. *J Opioid Manag.* 2006;2(3):137-146.
6. Tuteja AK, Biskupiak J, Stoddard GJ, Lipman AG. Opioid induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. *Neurogastroenterol Motil.* 2010;22(4):424-430.
7. Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid induced bowel dysfunction: Results of a US and European Patient Survey (PROBE 1). *Pain Med.* 2009; 10:35-42.

## OLYMPUS ENDOCUFF NOW FDA 510(K)-CLEARED TO CLAIM IMPROVEMENT IN ADENOMA DETECTION RATE DURING COLONOSCOPY

CENTER VALLEY, PA – Olympus, a global technology leader in designing and delivering innovative solutions for medical and surgical procedures, among other core businesses, announced that it has received FDA 510(k) clearance of claims that the ENDOCUFF® endoscopic device, the previous iteration of its recently launched ENDOCUFF VISION, improves Adenoma Detection Rates (ADR) during colonoscopy over standard colonoscopy. Due to its relative newness, peer-reviewed studies are still required to show clinical equivalency of the ENDOCUFF VISION, though the material, proprietary hinge design and therefore moment of force are identical among the two products.

Colorectal cancer (CRC) is the second most common cause of cancer-related mortality. Colonoscopy has long been considered the gold standard for detecting colon cancer, and Olympus is the leading provider of colonoscopy technology to caregivers. However, interval cancers do arise because of adenomas (pre-cancerous polyps) that are missed by the physician and can become malignant (colorectal cancer). For each 1% increase in adenoma detection rate (ADR) there is a 3% reduction in the risk of interval cancer.<sup>i</sup>

A meta-analysis has determined that the ENDOCUFF results in a statistically significant and clinically relevant improvement in ADR, as compared with unassisted colonoscopy, due to its design which enables manipulation of bowel folds for maximized visualization of mucosa. The analysis was based on several multi-center studies, one of which indicated that ENDOCUFF increases the ADR by 14.7% (95%CI 6.9-22.5%).<sup>ii</sup>

In addition to being designed to increase ADR, the ENDOCUFF and ENDOCUFF VISION allow for controlled withdrawal of the colonoscope; are designed to minimize difficulties associated with “looping” of the scope; can minimize intubation force and insertion



resistance; as well as minimize risk of mucosal trauma, among other claims.

The ENDOCUFF and ENDOCUFF VISION are devices that attach to the distal end of a colonoscope, with multiple flexible “arms” that fold within the product during intubation and forward movement and open out when drawn backward, thereby controlling the field of view. How the ENDOCUFF VISION works:

- During intubation, the flexible arms of ENDOCUFF VISION slip into the body of the device so that forward movement is not hindered.
- The arms open and smooth the folded bowel for inspection, everting large mucosal folds and providing clear views of mucosa previously difficult to visualize.
- During withdrawal, the flexible arms reduce the risk of sudden slippage and manipulate colonic folds, enabling a more thorough examination to be performed.

“The ENDOCUFF is the first colonoscope technology to be cleared by the FDA to claim improved adenoma detection rates,” said Kurt Heine, Group Vice President of the Endoscopy Division at Olympus America Inc. “Since the time that the industry has been using ADR as a standard, Olympus has been dedicated to helping its customers achieve ADR improvements – which can result in better quality of care, reduced cost, and enhanced patient satisfaction.”

To learn more about the ENDOCUFF VISION, please call 1-800-848-9024 or visit us at:

[medical.olympusamerica.com](http://medical.olympusamerica.com)

### About Olympus Medical Systems Group

Olympus Medical Systems Group, a division of global technology leader Olympus, develops solutions for healthcare professionals that help improve clinical outcomes, reduce overall costs and enhance quality of life for their patients. By enabling less invasive procedures, innovative diagnostic and therapeutic endoscopy, and early stage lung cancer evaluation and treatments,

Olympus is transforming the future of healthcare.  
For more information visit Olympus at:  
**68medical.olympusamerica.com**

i Douglas A. Corley, Christopher D. Jensen, Amy R. Marks, Wei K. Zhao, Jeffrey K. Lee, Chyke A. Doubeni, Ann G. Zauber, Jolanda de Boer, Bruce H. Fireman, Joanne E. Schottinger, Virginia P. Quinn, Nirupa R. Ghai, Theodore R. Levin, and Charles P. Quesenberry, *N Engl J Med* 2014;370:1298-306.

ii Floer M, Biecker E, Fitzlaff R, Römning H, Ameis D, Heinecke A, Kunsch S, Ellenrieder V, Ströbel P, Schepke M, Meister T. *PLoS One*. 2014; 9(12):e114267

**SYNERGY PHARMACEUTICALS SUBMITS SUPPLEMENTAL NEW DRUG APPLICATION (sNDA) FOR TRULANCE™ (PLECANATIDE) FOR THE TREATMENT OF ADULTS WITH IRRITABLE BOWEL SYNDROME WITH CONSTIPATION (IBS-C)**

NEW YORK – Synergy Pharmaceuticals Inc. (NASDAQ:SGYP) announced that the company has submitted a supplemental New Drug Application (sNDA) for TRULANCE™ (plecanatide) for the treatment of adults with irritable bowel syndrome with constipation (IBS-C).

On January 19, 2017, TRULANCE was approved in the United States for the treatment of adults with chronic idiopathic constipation (CIC) and is now available in U.S. pharmacies. The recommended dosage of TRULANCE is 3 mg taken orally, once daily, with or without food at any time of the day.

“Following the successful launch of TRULANCE in CIC, the submission of this supplemental application marks another important milestone for Synergy in our ongoing quest to bring new treatments that address significant unmet medical needs to patients living with GI disorders,” said Gary S. Jacob, Ph.D., Chairman and CEO, Synergy Pharmaceuticals Inc. “We are sincerely grateful to the patients and researchers in these studies as well as our clinical and regulatory teams for their tireless efforts in bringing us one step closer to providing a new treatment for this condition. If approved, we believe TRULANCE will provide an additional, much-needed, new treatment option for people with IBS-C.”

The application is based on data from two randomized, 12-week, double-blind, placebo-controlled Phase 3 studies evaluating the efficacy and safety of TRULANCE for the treatment of adults with IBS-C. Across the two trials, more than 2,100 patients received a once-daily tablet of TRULANCE (3 mg or 6 mg doses) or placebo.

Synergy announced positive results from the two Phase 3 trials of TRULANCE in adults with IBS-C in December 2016. In both trials, TRULANCE 3 mg and 6 mg doses met the primary endpoint showing statistical significance in the percentage of patients who were Overall Responders compared to placebo during the 12-week treatment period. (Study 1: 21.5% in 3 mg and 24.0% in 6 mg dose groups compared to 14.2%

in placebo;  $p=0.009$  for 3 mg and  $p<0.001$  for 6 mg; Study 2: 30.2% in 3 mg and 29.5% in 6 mg dose groups compared to 17.8% in placebo;  $p<0.001$  for 3 mg and  $p<0.001$  for 6 mg). An Overall Responder, as currently defined by the U.S. Food and Drug Administration (FDA), is a patient who fulfills both  $\geq 30\%$  reduction in worst abdominal pain and an increase of  $\geq 1$  complete spontaneous bowel movement (CSBM) from baseline, in the same week, for at least 50% of the 12 treatment weeks. This is the current primary endpoint required for FDA approval in IBS-C.

In both studies, the most common adverse event was diarrhea (Study 1 = 3.2% at 3 mg and 3.7% at 6 mg compared to 1.3% at placebo; Study 2 = 5.4% at 3 mg and 4.3% at 6 mg compared to 0.6% at placebo).

The company plans to present additional Phase 3 data from the two IBS-C trials at upcoming scientific meetings later this year.

**Indications and Usage**

TRULANCE is a guanylate cyclase-C (GC-C) agonist indicated in adults for the treatment of chronic idiopathic constipation (CIC).

**IMPORTANT SAFETY INFORMATION**

**Warning: Risk of Serious Dehydration in Pediatric Patients**

Trulance™ is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile mice administration of a single oral dose of plecanatide caused deaths due to dehydration. Use of Trulance should be avoided in patients 6 years to less than 18 years of age. The safety and efficacy of Trulance have not been established in pediatric patients less than 18 years of age.

**Contraindications**

Trulance is contraindicated in patients less than 6 years of age due to the risk of serious dehydration.

Trulance is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

**Warnings and Precautions**

**Risk of Serious Dehydration in Pediatric Patients**

Trulance is contraindicated in patients less than 6 years of age. The safety and effectiveness of Trulance in patients less than 18 years of age have not been established. In young juvenile mice (human age equivalent of approximately 1 month to less than 2 years), plecanatide increased fluid secretion as a consequence of stimulation of guanylate cyclase-C (GC-C), resulting in mortality in some mice within the first 24 hours, apparently due to dehydration. Due to increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than older patients to develop severe diarrhea and its potentially serious consequences.

Use of Trulance should be avoided in patients 6 years to less than 18 years of age. Although there were no

deaths in older juvenile mice, given the deaths in young mice and the lack of clinical safety and efficacy data in pediatric patients, use of Trulance should be avoided in patients 6 years to less than 18 years of age.

**Diarrhea**

Diarrhea was the most common adverse reaction in the two placebo-controlled clinical trials. Severe diarrhea was reported in 0.6% of patients.

If severe diarrhea occurs, the health care provider should suspend dosing and rehydrate the patient.

**Adverse Reactions**

In the two combined CIC clinical trials, the most common adverse reaction in Trulance-treated patients (incidence  $\geq 2\%$  than in the placebo group) was diarrhea (5% vs 1% placebo).

**About TRULANCE™**

TRULANCE™ (plecanatide) is a once-daily tablet approved for adults with CIC and is being evaluated for IBS-C. With the exception of a single amino acid substitution for greater binding affinity, TRULANCE is structurally identical to uroguanylin, a naturally occurring and endogenous human GI peptide. Uroguanylin activates GC-C receptors in a pH-sensitive manner primarily in the small intestine, stimulating fluid secretion and maintaining stool consistency necessary for regular bowel function.

**About Irritable Bowel Syndrome with Constipation (IBS-C)**

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder characterized by recurrent abdominal pain and associated with two or more of the following: related to defecation, associated with a change in the frequency of stool, or associated with a change in the form (appearance) of the stool. IBS can be subtyped by the predominant stool form: constipation (IBS-C), diarrhea (IBS-D) or mixed (IBS-M). Those within the IBS-C subtype experience hard or lumpy stools more than 25 percent of the time they defecate, and loose or watery stools less than 25 percent of the time. It is estimated that the prevalence of IBS-C in the U.S. adult population is approximately 4 to 5 percent, although this number can vary as patients may fluctuate between the three subtypes of IBS.

**About Synergy Pharmaceuticals**

Synergy is a biopharmaceutical company focused on the development and commercialization of novel GI therapies. The company has pioneered discovery, research and development efforts on analogs of uroguanylin, a naturally occurring and endogenous human GI peptide, for the treatment of GI diseases and disorders. Synergy's proprietary uroguanylin analog platform includes one commercial product TRULANCE and a second lead product candidate, dolcanatide.

For more information, please visit:  
**synergypharma.com**

**Forward-Looking Statement**

This press release and any statements made for and during any presentation or meeting contain forward-looking statements related to Synergy Pharmaceuticals Inc. under the safe harbor provisions of Section 21E of the Private Securities Litigation Reform Act of 1995 and are subject to risks and uncertainties that could cause actual results to differ materially from those projected. These statements may be identified by the use of forward-looking words such as “anticipate,” “planned,” “believe,” “forecast,” “estimated,” “expected,” and “intend,” among others. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, the development, launch, introduction and commercial potential of TRULANCE; growth and opportunity, including peak sales and the potential demand for TRULANCE, as well as its potential impact on applicable markets; market size; substantial competition; our ability to continue as a going concern; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payer reimbursement; dependence upon third parties; our financial performance and results, including the risk that we are unable to manage our operating expenses or cash use for operations, or are unable to commercialize our products, within the guided ranges or otherwise as expected; and risks related to failure to obtain FDA clearances or approvals and noncompliance with FDA regulations. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. There are no guarantees that future clinical trials discussed in this press release will be completed or successful or that any product will receive regulatory approval for any indication or prove to be commercially successful. Investors should read the risk factors set forth in Synergy's most recent periodic reports filed with the Securities and Exchange Commission, including Synergy's Form 10-K for the year ended December 31, 2016. While the list of factors presented here is considered representative, no such list should be considered to be a complete statement of all potential risks and uncertainties. Unlisted factors may present significant additional obstacles to the realization of forward-looking statements. Forward-looking statements included herein are made as of the date hereof, and Synergy does not undertake any obligation to update publicly such statements to reflect subsequent events or circumstances except as required by law.