



**Synergy Pharmaceuticals**

NASDAQ:SGYP

*Inventing the future for GI disease*

## DRUG FACT SHEET:

# ***SP-333 FOR THE TREATMENT OF ULCERATIVE COLITIS (UC)***

### **WHAT IS SP-333?**

SP-333 is an investigational drug discovered and being developed by Synergy Pharmaceuticals Inc. for the treatment of ulcerative colitis (UC). SP-333 is a synthetic analog of uroguanylin, and is Synergy's second candidate in a new class of essentially non-systemic oral drugs known as guanylate cyclase-C (GC-C) agonists.<sup>1</sup>

SP-333 is highly resistant against proteolysis by digestive enzymes present in the simulated intestinal fluid, which is an important attribute to enhance drug activity of peptides and proteins. Ulcerative colitis predominantly causes inflammation in the colon. Thus, peptide drugs that are resistant to proteolysis are expected to be more suitable for treatment of ulcerative colitis and other diseases in the distal intestine.

### **WHAT IS ULCERATIVE COLITIS?**

UC is a painful and debilitating type of inflammatory bowel disease (IBD) that affects more than a half million Americans.<sup>2</sup> UC causes chronic inflammation of the colon, and patients with UC are at increased risk for colon cancer. There is currently no cure for UC (other than surgical removal of the colon) and long-term remission with current treatments is limited. New treatments for UC patients are urgently needed.

### **FACT:**

*SP-333 is Synergy's next-generation guanylate cyclase-C (GC-C) agonist in clinical development for the treatment of ulcerative colitis (UC).*

*More than a half million Americans suffer with UC, a painful and debilitating type of inflammatory bowel disease.*

## HOW DOES SYNERGY'S UROGUANYLIN ANALOG, SP-333, RELIEVE ULCERATIVE COLITIS?

Uroguanylin is a natural human peptide hormone normally produced in the lumen of the gastrointestinal (GI) tract. Recent studies suggest that expression of uroguanylin is down-regulated in inflamed GI tissue in patients with UC.<sup>3</sup> It is thought that uroguanylin deficiency may be associated with disruption of intestinal barrier function, which is known to be one of the primary causes of the pathogenesis of IBD, including UC and Crohn's disease.<sup>4</sup>

Preclinical studies indicated that oral treatment SP-333 ameliorates GI inflammation in several experimental models of acute and chronic colitis in mice, suggesting that SP-333 has the potential to be developed as a safe oral drug candidate for treatment of ulcerative colitis.<sup>5</sup>

## WHAT IS THE NOVEL MECHANISM OF ACTION OF SP-333?

Orally-administered SP-333 binds to and activates GC-C receptors expressed on GI mucosal epithelial cells, thereby stimulating cyclic guanosine monophosphate (cGMP) in target tissues. Results from several experimental models of colitis in mice have demonstrated that SP-333 ameliorates GI inflammation through a novel cGMP-mediated mechanism involving inhibition of NF-kappa B signaling to suppress production of pro-inflammatory cytokines.<sup>5,6</sup>

## HOW DOES SP-333 DIFFER FROM PLECANATIDE?

SP-333 is similar to Synergy's first GC-C agonist peptide, plecanatide, except that the N- and C-terminal amino acids have been altered to reduce the potential for proteolytic degradation in the gut.<sup>5</sup>

## IN WHAT STAGE OF DEVELOPMENT IS SP-333?

Synergy completed a single-dose, dose-escalating, placebo-controlled Phase I trial of SP-333 in healthy adult volunteers in December 2012. Eight cohorts

## FACT:

*The SP-333 peptide was designed to resist degradation by digestive enzymes and remain biologically active in the gut.*

*SP-333 has shown potent anti-inflammatory activity in animal studies of colitis.*



were dosed, ranging from 0.1 to 60 mg of SP-333. There were no serious or unexpected adverse events in this study. Importantly, SP-333 exhibited gastrointestinal pharmacodynamic characteristics that were anticipated based on its GC-C receptor agonist activity.<sup>7</sup>

In January 2013, Synergy initiated oral dosing of healthy volunteers in a Phase Ib multiple-dose clinical trial of SP-333. The trial, designed as a placebo-controlled, dose-escalating, multiple-dose study in 64 healthy adult volunteers, is focused on exploring the safety profile of SP-333.<sup>8</sup> The study is being conducted at a single site in the U.S. and is expected to be completed in 2Q2013.

### WHAT MAKES SP-333 SO PROMISING?

The novel mechanism of action, superior stability against degradation by digestive enzymes and orally safe attributes of SP-333 may offer a new way to treat patients with mild-to-moderate UC. SP-333 has exhibited potent anti-inflammatory activity in animal models of colitis. Data from a Phase I clinical study support the safety and predicted pharmacodynamics of SP-333 in humans.

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