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DRUG EVALUATION

Efficacy and safety of plecanatide in treating constipation predominant irritable bowel syndrome

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ABSTRACT

Introduction: Uroguanylin interacting with intestinal Guanylate Cyclase C (GC-C) receptors plays an important role in gastrointestinal fluid and electrolyte homeostasis. Plecanatide is the first uroguanylin analog that stimulates GC-C receptors on gastrointestinal mucosa with pH-sensitive receptor binding. Binding to the GC-C receptor activates intracellular conversion of GTP to cGMP resulting in the stimulation of intestinal fluid secretion.

Areas covered: Herein, all published research regarding the development of and clinical experience with plecanatide is reviewed. Clinical study results in patients with Chronic Idiopathic Constipation (CIC) and Irritable Bowel Syndrome with Constipation (IBS-C) are also reviewed. Success in the treatment of CIC and IBS-C is supported by beneficial effects on stool viscosity, Complete Spontaneous Bowel Movements and visceral sensation. Finally, the discussion within focuses on the importance of plecanatide in understanding the physiology of uroguanylin, the pathophysiology of IBS-C and the potential for development of uroguanylin and guanylin analogs.

Expert opinion: Given this broad spectrum of potential activity for GC-C agonists, it would not be surprising to see that the use of agents such as plecanatide in new areas grow to a level even greater than the use for the present CIC and IBS-C indications.

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constipation; functional gastrointestinal disorders; guanylate cyclase C agonists; irritable bowel syndrome with constipation; linaclotide; plecanatide

1. Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder with subclassifications associated with bowel function: IBS-C, which is constipation predominant; IBS-D, which is diarrhea predominant; and IBS-M, which has both diarrhea and constipation. In preparation for the 1988 International Congress of Gastroenterology in Rome, the first compilation of guidelines for the diagnosis of functional GI disorders, including IBS, was created. The guidelines provided a widely accepted platform to design high quality investigative protocols for functional diseases. Each update of the 'Rome Criteria' reflects improved understanding of the pathophysiology of functional diseases while dealing with the practical issues of conducting multicenter investigative studies [1]. The recently released Rome 4 is yet to be applied to published clinical trials. Table 1 lists the Rome 3 criteria for subtyping IBS by predominant stool pattern [2].

Although appropriate for designing clinical trials, Rome Criteria leaves many of the clinical observations recognized in patients with IBS unaddressed. The development of a 'Mixture Model Analysis' of IBS patients, by Polster et al. [3] stratified each IBS category into groups with and without comorbid extra-intestinal and psychological symptoms. This study punctuates the complex pathophysiology of IBS while illustrating the limitations of Rome Criteria in clinical care outside of research protocols. Primary care health professionals and gastroenterologists will attest to the high prevalence of functional GI diseases in their practices. A community study estimated the total United States IBS prevalence based on screening interviews was 14.1% with the majority of the subjects in this group (76.6%) meeting IBS Criteria and the remainder (23.4%) also carrying a medical diagnosis of IBS [4]. The Global prevalence by meta-analysis was also high with a pooled prevalence of 11.2%, however there was wide variation in prevalence amongst countries [5]. Estimates of the increased economic burden for IBS-C patients in a commercially insured population support an incremental cost of $3,856 for IBS-C patients ($8,621 for IBS-C patients compared with $4,765 for control subjects) [6].

The pathophysiology of IBS is multifactorial, partly because multiple abnormalities of GI function produce a limited number of overlapping symptoms. Treatment often addresses a single symptom, bowel movement frequency, rather than dealing with the elusive pathophysiology of IBS-C in an individual patient. Regarding the single symptom treatment approach to treat IBS-C, therapeutic failure exceeds therapeutic success. Recent US FDA guidance for development of drugs for IBS-C reinforces the recognition of multiple symptoms in patients with IBS-C as the expectation for registration now requires that two symptoms improve – constipation defined by the number of complete spontaneous bowel movements (CSBMs) and abdominal pain. Occasionally in a subset of IBS patients, a specific pathophysiologic mechanism becomes clear and the diagnosis of IBS is replaced with the newly

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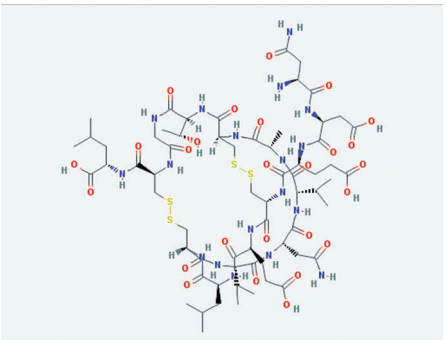
Box 1. Drug summary.

Drug name (generic)
Plecanatide
Phase (for indication under discussion)
Phase 3 is complete with the Supplemental New Drug Application submitted
Indication (specific to discussion)
Adults with IBS-C

Pharmacology description/mechanism of action
Identical to uroguanylin, with the exception of a single amino acid substitution; activates GC-C receptors in a pH-sensitive manner
Route of administration
Orally once a day with or without food. May also be crushed and dissolved in apple sauce or water or given through an NG or G feeding tube
Chemical structure



Pivotal trial(s)
NCT02387359; NCT02493452

found 'disease'. For example, once the importance of disaccharidase deficiency was understood, the IBS symptoms associated with *lactose intolerance* allowed the diagnosis of IBS in these patients to be abandoned in favor of a pathophysiologically based explanation for symptoms associated with *lactase deficiency*. Until the pathophysiology of IBS is completely understood, treatment will continue to be symptom based. In the complex IBS arena, plecanatide has been shown to offer important symptomatic relief in many patients with IBS-C.

2. Overview of the market

The greatest unmet need in IBS is the inability to distinguish the origin of the symptoms in an individual patient. Without understanding the pathophysiology, treatment algorithms become symptom focused. Central to the success of randomized, double-blind, placebo-controlled clinical trial method is a primary aim that can be assessed with a patient-related outcome. The FDA now requires two co-primary endpoints (increase in the number of CSBM and decrease in worst abdominal pain scores) in IBS-C studies reflecting the difficulty of assessing IBS-C. With the number of possible disordered physiologic pathways contributing to IBS-C symptoms, it is not surprising that most IBS-C studies have highly variable placebo responses and the therapeutic gain (difference from the

Table 1. Rome 3 criteria for subtyping irritable bowel syndrome (IBS) by predominant stool pattern [2].

(1) IBS with constipation (IBS-C) – hard or lumpy stools at least 25% and loose (mushy) or watery stools <25% of bowel movements (in the absence of laxatives).
(2) IBS with Diarrhea (IBS-D) – loose (mushy) or watery stools at least 25% and hard lumpy stools <25% of bowel movements.
(3) Mixed IBS (IBS-M) – hard or lumpy stools at least 25% and loose (mushy) or watery stools at least 25% of bowel movements.
(4) Unsubtyped IBS – insufficient abnormality of stool consistency to meet criteria for IBS -C, -D, or -M

treatment response and placebo response) is lower than that seen in studies addressing other GI conditions. Low therapeutic gain should be *expected* when the symptom(s) being addressed in a clinical trial may be caused by multiple physiologic aberrations while the therapeutic agent being tested has a precise pharmacophysiology. Additionally, these trials utilize multicomponent endpoints as required by regulatory agencies. These regulatory endpoints are typically not in keeping with the clinical expectations of healthcare providers or patients and when these clinical endpoints are examined therapeutic gain is often larger.

Predicting the *clinical significance* of a study with low therapeutic gain requires consideration of the medical complexity of the illness and the potential pathophysiologic pathways for disease expression. A statistically significant improvement in a clinical trial indicates successful treatment of *a* pathophysiologic pathway related to the induction of symptoms and not necessarily *the* pathophysiologic pathway. In IBS, it seems unlikely that a single treatment will be able to manage all of the recognized pathways to the clinical symptoms of IBS. Reiterating the unmet need, advancing the treatment of IBS will require a better understanding of the pathophysiology of IBS and a strategy to stratify treatment by pathophysiology.

Many medications have been used with varying success in IBS-C. Most of these medications have dealt with changing the symptom of constipation.

FDA approved medications for IBS-C include lubiprostone (activates ClC-2 Chloride channels), linaclotide (guanyl cyclase C agonist) and tegaserod (5-hydroxytrypamine type-4 agonist). Plecanatide is approved for chronic idiopathic constipation with the Supplemental New Drug Application for IBS-C submitted.

Two well-studied pharmacophysiologic development programs illustrate the concept of similar patient symptoms responding to apparently unrelated pharmacophysiologic pathways. Serotonin (5-HT) is a monoamine neurotransmitter with a high concentration in the GI tract. Administration of 5-HT4 agonists (tegaserod, prucalopride) in adult patients with CIC or IBS-C improved constipation by enhancing GI motility [7–9] while also attenuating the visceral hypersensitivity [7,10] associated with IBS-C. Tegaserod was withdrawn from the market for non-GI reasons. Prucalopride is available in Europe. Uroguanylin [11] secretion in the GI tract occurs in response to a meal. Through the activation of the guanylate cyclase C receptor, uroguanylin promotes the secretion of fluid in the small intestine with a pH-dependent mechanism. At the slightly acidic pH concentration in the proximal small bowel, uroguanylin has high receptor affinity [12,13] promoting

intestinal secretion. As small bowel contents progress, the intestinal pH gradually increases and the binding affinity of uroguanylin for guanylate cyclase C receptor decreases. As receptor occupancy decreases, intestinal fluid secretion drops. This physiologic mechanism regulates fluid secretion with high secretory activation in the proximal small intestine to improve the digestive process while decreasing distal small intestinal fluid secretion to limit the amount of fluid entering the colon. Successful pharmacologic activation of these two distinct receptors (5-HT4 and GC-C) improves symptoms of CIC and IBS-C. Since there is no obvious overlap of pharmacophysiology between serotonin agonists and GC-C agonists, the successful development of both classes of drugs in IBS-C confirms the complex pathophysiology IBS-C.

There are two GC-C receptor agonists, plecanatide and linaclotide that are currently available in the United States. Linaclotide is currently approved for the treatment of CIC and IBS-C in adults. Plecanatide is approved for CIC and currently before the FDA for the IBS-C indication. Although there are significant differences in these two GC-C agonists, no comparative studies have been done to compare efficacy and safety.

3. Introduction to the compound

Investigation of the pathophysiologic cause of cholera led to the discovery of enterotoxigenic *Escherichia coli* and subsequent isolation of the *E. coli* heat-stable enterotoxin (STa) as the cause of Traveler's diarrhea [14]. STa binds to the guanylate cyclase C receptor in the mucosa of the small bowel [15] activating small bowel fluid secretion through guanylate cyclase-C conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) [16,17]. The search for the natural ligand to the receptor led to the discovery of uroguanylin [18] and identified the guanylate cyclase C receptor. Recognizing the potential for drug development, two development pathways emerged, one (linaclotide) captured the potential of the ST-peptide and the other developed a natural analog to native uroguanylin (plecanatide). Although both are agonists for the GC-C receptor, they are pharmacophysiologically distinctly different with plecanatide retaining the pH-dependent receptor binding characteristics of uroguanylin.

3.1. Chemistry

With the exception of a single amino acid substitution (glutamic acid for aspartic acid in the three positions), plecanatide is structurally identical to human uroguanylin. Uroguanylin has two disulfide bonds and two charged aspartate amino acids within the pH-sensitive region. These structural characteristics ensure the stable peptide conformation necessary for binding to the GC-C receptor. Plecanatide also contains two disulfide bonds in the same positions as uroguanylin (Figure 1 [19]). *In vitro* receptor binding studies demonstrate an eightfold increase in receptor binding compared with uroguanylin while retaining the pH-sensitive receptor binding affinity. See Box 1, Drug Summary.

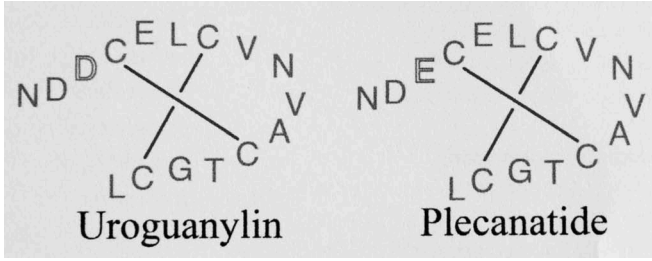


Figure 1. Amino acid structures of the endogenous guanylate cyclase agonist, uroguanylin and the uroguanylin analog plecanatide. The stenciled letter 'D' (aspartic acid) in uroguanylin has been replaced with the stenciled letter 'E' (glutamic acid) in plecanatide. The two disulfide bonds are represented by the straight lines [19].

3.2. Pharmacodynamics [20]

3.2.1. Food Effect

Healthy volunteers who received either a low-fat, low calorie (LF-LC) meal or a high fat, high calorie (HF-HC) meal reported looser stools than fasted subjects up to 24 h after a single dose of plecanatide 9 mg (three times the recommended dose). In clinical studies, plecanatide was administered with or without food.

3.3. Pharmacokinetics and metabolism [20]

3.3.1. Absorption

Plecanatide and the active metabolites are minimally absorbed with negligible systemic availability following oral administration. Concentrations of plecanatide and its active metabolite in plasma are below the limit of quantitation after an oral plecanatide dose of 3 mg. Therefore, standard pharmacokinetic parameters such as AUC, maximum concentration (C_{max}), and half-life ($t_{1/2}$) cannot be calculated.

3.3.2. Distribution

Given that plecanatide concentrations following clinically relevant oral doses are not measurable, plecanatide is expected to be minimally distributed in tissues. Oral plecanatide is localized to the GI tract where it exerts its effects as a GC-C agonist with negligible systemic exposure. Plecanatide exhibits little to no binding to human serum albumin or human alpha-1-acid glycoprotein.

3.3.3. Elimination

3.3.3.1. Metabolism. Plecanatide is metabolized in the GI tract to an active metabolite by loss of the terminal leucine moiety. Both plecanatide and the metabolite are proteolytically degraded within the intestinal lumen to smaller peptides and naturally occurring amino acids.

3.3.3.2. Excretion. No excretion studies have been conducted in humans. Plecanatide and its active metabolite are not measurable in plasma following administration of the recommended clinical doses.

3.3.4. Drug interaction studies

Neither plecanatide nor its active metabolite inhibited the cytochrome P450 (CYP) enzymes 2C9 and 3A4, and they did not induce CYP3A4 *in vitro*.

Plecanatide and its active metabolite are neither substrates nor inhibitors of the transporters P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) *in vitro*.

3.4. Clinical efficacy

3.4.1. Phase 1 studies

A Phase 1 study with plecanatide has been published [21]. This was a single site, randomized, double-blind, placebo-controlled, single-dose, ascending-dose study of orally administered plecanatide or placebo in healthy volunteers. Nine dose levels of plecanatide were evaluated (0.1, 0.3, 0.9, 2.7, 5.4, 8.1, 16.2, 24.3, and 48.6 mg).

Plasma concentration with a sensitivity of 10 ng/ml was determined pre-dose, then at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 h post-dosing. Since no plecanatide was detected in any sample, the 48.6 mg samples were reanalyzed with an assay sensitive to 1 ng/ml with no plecanatide detected. Uroguanylin is sensitive to proteolytic degradation. Since plecanatide is an analog of uroguanylin, proteolytic degradation in the intestinal tract is expected.

Pharmacodynamic assessments included time to first bowel movement, stool consistency (Bristol Stool Form Scale), and stool frequency comparing the 0–24 h and 24–48 h intervals to pre-dose values. Space limitation restricted the detail provided in the manuscript, however, it was noted that the time to first bowel movement trended toward lower mean times with increasing doses of plecanatide with the lowest mean time of 6.3 h noted in the 16.2 mg dose cohort. Using mean Bristol Stool Form Scale (BSFS) values in a study of normal subjects with few subjects in each cohort makes interpretation difficult. The BSFS values in the 0–24 h interval were generally higher than the pre-dose and 24–48 h period although the majority of BSFS values were in the 3 to 5 range (considered normal). The mean BSFS data in the 0.1 mg dose cohort were nearly identical to the BSFS values in the 48.6 mg dose cohort, with the mean BSFS well within the normal range. These results may be expected in a study designed to evaluate a homologue of a naturally occurring peptide as the pharmacophysiology of the synthetic peptide should replicate normal physiology, and, in a normal volunteer, the pre-study physiology should be normal. The remarkable finding is the stability of the stool consistency through the entire range of plecanatide doses. This finding strongly supports the ability of plecanatide to replicate the effect of uroguanylin in the control of small intestinal fluid dynamics. Dose escalation of plecanatide tended to increase BSFS, however the majority of BSFS values of the first stool were in the normal range. There were no dose related trends of stool frequency with dose escalation.

Treatment Emergent Adverse Events (TEAE) in healthy volunteers were nearly identical in the placebo and treatment cohorts. Diarrhea was the most common adverse events (AE) occurring in 15.1% of plecanatide-treated patients and 16.7% of the placebo cohort. There was no apparent relationship to dose with only one (of the eight plecanatide related diarrhea AEs) above the 5.4 mg dose. The single case was at the 24.3 dose. In the plecanatide cohorts, the AEs of nausea (n = 3), abdominal discomfort (n = 3) and vomiting (n = 2) all occurred in the 24.3 and 48.6 mg cohorts except for one instance of vomiting in the 8.1 mg plecanatide cohort.

3.4.2. Phase 2 studies

No Phase 2 studies have been published as abstracts or manuscripts.

3.4.3. Phase 3 studies

Both Phase 3 clinical trials with plecanatide in adult patients with CIC are published. The first study was a randomized Phase 3 clinical trial of plecanatide in patients with Chronic Idiopathic Constipation [22]. In the intention-to-treat population, plecanatide doses of 3 mg (n = 453) and 6 mg (n = 441) were compared to placebo-treated subjects (n = 452) in a 12-week treatment trial. The primary efficacy measure was achieved with both doses (placebo 10.2%, plecanatide 3 mg 21.0% and plecanatide 6 mg 19.5%; $p < 0.001$ for each dose vs. placebo). No statistical difference between the two plecanatide doses was observed. The BSFS was statistically improved with both plecanatide doses over placebo ($p < 0.001$) with the resulting mean BSFS 4.1 in the plecanatide-treated subjects. The most common TEAE was diarrhea occurring in 1.3% of the placebo subjects, 5.9% of the 3 mg plecanatide treatment group and 5.7% of the 6 mg plecanatide treatment group.

The Phase 3 Clinical Trial of Plecanatide in IBS with Constipation was presented at Digestive Disease Week in May 2017 [23]. The presentation discussed the results of the two registration trials that demonstrated clinically significant improvement in the treated subjects compared with placebo-treated patients. The primary endpoint was an Overall Responder, defined as a ≥ 30% reduction in worst abdominal pain and an increase of ≥1 CSBM in the same week for ≥50% of the 12 treatment weeks. Table 2 presents the results from the abstract. Safety was reported as TEAEs. Diarrhea was the most common TEAE with few withdrawals from the study (Table 3). Serious AEs (SAE) were similar in all treatment groups and were not associated with GI symptoms and there were no SAE reports of dehydration. There were 17 SAE events with 11 of these occurring in Study 1 (1.0%) and 6 in Study 2 (0.5%).

3.5. Safety and tolerability

In all clinical trials with plecanatide, few TEAEs are reported. This may be expected with a drug that cannot be detected in the blood after dosing. There were only 17 SAEs with 11 of these in Study 1 and 6 in Study 2 with no SAEs related to GI symptoms or dehydration. The diarrhea AEs are summarized in the table in the Phase 3 discussion (Table 3)

3.6. Regulatory affairs

The two Phase 3 studies have been submitted as a Supplemental New Drug Application for the clinical indication of IBS with Constipation in adults.

Table 2. Percent of Overall Responders [23]*.

	Placebo	CI (%)**	Plecanatide 3 mg	CI (%)**	*p*-value	Plecanatide 6 mg	CI (%)**	*p*-value
Study 1 (n = 1055)	17.8%	14.0, 22.2	30.2%	25.4, 35.3	$p < 0.001$	29.5%	24.8, 34.6	$p < 0.001$
Study 2 (n = 1135)	14.2%	10.9, 18.2	21.5%	17.4, 26.0	$p = 0.009$	24.0%	19.8, 28.6	$p < 0.001$

*Overall Responder is defined as patient with ≥30% reduction in worst abdominal pain and an increase of ≥1 complete spontaneous bowel movement from the baseline in the same week for ≥50% of the 12 treatment weeks. **CI–Confidence Interval.

Table 3. Percent of subjects with the adverse event of Diarrhea [23].

	Placebo	Discontinuation	Plecanatide 3 mg	Discontinuation	Plecanatide 6 mg	Discontinuation
Study 1	0.6%	0%	5.4%	1.7%	4.3%	1.2%
Study 2	1.3%	0%	3.2%	0.8%	3.7%	1.6%

3.7. Post-marketing surveillance

Standard, routine post-marketing surveillance is in progress. There are no cautionary signals in the clinical data to warrant special consideration.

4. Conclusion

The use of plecanatide in IBS-C is supported by the Phase 3 clinical trial data, which should lead to approval by the FDA for drug registration for the indication of IBS-C. As discussed in the earlier sections, the complex pathophysiology of IBS-C suggests no single treatment will be able to manage all subclasses of IBS. In this context, the 'Overall Responder' rate seen in these two trials is gratifying. A clear advantage is the absence of plecanatide in the systemic circulation explaining the low systemic AE profile.

5. Expert opinion

5.1. What, if any, improvement does the drug hold over other therapies?

Pharmacologic activation of the GC-C receptor may best be managed by a peptide analogue of uroguanylin, the physiologically active peptide for the GC-C receptor.

In my opinion, the single amino acid modification of uroguanylin that allows plecanatide to engage with the GC-C receptor with an eightfold increase in receptor affinity while retaining the pH-sensitive binding characteristics provides the ideal pharmacophysiology for dealing with the problem of constipation in CIC and IBS-C. On a clinical note, patients may take their daily dose of plecanatide at any time of day, with or without food. There is no requirement to wait 30 min after ingestion to have a meal.

5.2. What, if any, impact is this drug likely to have on current treatment strategies?

Current management of IBS-C is symptom based. Selection of pharmaceutical management is usually focused on the dominant symptom, and management strategy may change following an assessment of response. Plecanatide will be used successfully for many patients with IBS-C as the two FDA-required patient outcomes for registration for the indication of IBS-C have been met. It is unclear how well other symptomatic aspects of IBS-C will be improved. Additional clinical investigations may guide stratification of the population into highly responsive subsets of patients. This would clarify the pathophysiology of IBS-C as well as focusing therapy on responsive patients.

5.3. How likely are physicians to prescribe the drug?

The safety profile is very favorable due to the low systemic availability of plecanatide and the low incidence of diarrhea makes this an ideal drug to try as the risk-to-reward ratio suggests very low risk with potentially high therapeutic gain. Physicians are very likely to prescribe this drug.

5.4. What data is still needed?

There are obvious needs that include an understanding of pathways controlling secretion and absorption profile throughout the GI tract and the abnormal sensation associated with IBS. The simplest explanation for the success of GC-C agonists in IBS-C is that the change in defecation physiology induced by the fluid changes in the intestinal tract is responsible for the improvement in symptoms. Although this is reasonable, the accumulating information supports a primary role for GC-C agonists in downregulating painful GI sensation. Numerous mechanisms have been proposed including direct changes in sensory response and immune mediated pain pathways. Patient stratification into subsets by specific pathophysiologic etiology is important for both IBS-C and CIC to enhance symptom response with targeted medications. The success of 5-HT4 agonists and GC-C agonists in IBS-C illustrates the need for better understanding of the factors involved in these medical problems.

Far more important is that the door to the uroguanylin physiology mystery has been cracked open. The elegance of the control of small bowel fluid secretion by uroguanylin is awe inspiring. The immediate and profuse secretion of uroguanylin in the proximal small intestine stimulates fluid secretion through binding and activation of the GC-C receptor. The increased small bowel fluid facilitates the dilution of chyme promoting absorption and transit during the early digestive process. The activation of the GC-C receptor is facilitated by pH-associated structural changes in uroguanylin to enhance GC-C receptor binding and activation. In the distal small bowel where the dilute intestinal contents need to become

concentrated to limit the fluid entering the colon and increase the intestinal concentrations of Vitamin B12 and bile acids to facilitate active mucosal transport, the intestinal pH rises and the binding affinity of uroguanylin to the GC-C receptor decreases along with an accompanying decrease in the volume of fluid secretion. Plecanatide was developed to function like uroguanylin in the activation of the GC-C receptor with increased binding affinity while retaining the pH-associated changes in binding affinity. The clinical studies in CIC and IBS-C patients provide compelling evidence that plecanatide is pharmacologically successful in improving CSBM and abdominal symptoms. The low incidence of diarrhea and the near normalization of the BSFS strongly suggest the pH-associated change in GC-C binding affinity is retained by plecanatide. The Phase 1 data provides remarkable supportive data that plecanatide successfully mimics the activity of uroguanylin. While the authors of this Phase 1 study seemed to be struggling to justify a slight change in BSFS reflects an increase in fluid secretion in normal subjects that would encourage drug development for constipation, I was ecstatic that a wide range of plecanatide doses did NOT show a marked change in the BSFS nor did it cause diarrhea. This supports the hypothesis of decreased plecanatide binding to the GC-C receptors associated with the gradual increase in small intestinal pH. If plecanatide acts through the proposed MOA, then its physiologic effect will be parallel to that of uroguanylin and stools of normal subjects *should* continue to be normal. Furthermore, the nausea and abdominal pain in normal subjects at high doses may be explained by increased luminal distention of the proximal small bowel due to a greater increase in fluid secretion following plecanatide administration above that elicited by endogenous uroguanylin because of the higher receptor binding affinity of plecanatide.

The potential for exploitation of the physiology of uroguanylin is enormous. Efficient and symptom free digestion is extraordinarily complex involving appetite, appropriate taste and smell sensations, control of motility, regulating a changing luminal osmolarity to allow proximal dilution of chyme and to regulate stool viscosity, luminal pH, an adaptive immune response permitting tolerance of benign immune stimulation and activating immunologic protection against harmful immune stimulates, downregulation of the sensation of the normal digestive process while retaining the protective pain activation pathways, limiting environmental damage to the mucosa that may lead to neoplasia, and many, many more. The law of biologic conservation of function suggests that an effective biologic pathway will be used for many different functions. Uroguanylin and guanylin influence several of these examples with evidence of effects on appetite, olfactory function, sophisticated fluid control in the small intestine, decrease intestinal inflammation, regulation of intestinal permeability, regulation of visceral sensation, modulation of immunologic function, and protecting against mitotic change [11,24]. In addition to the effect of uroguanylin on the GC-C receptor, there is evidence that uroguanylin modulates mRNA on a transcriptional level [25]. Plecanatide represents the successful development of the first uroguanylin analog that activates intestinal secretion in a precise fashion with the sophisticated control of function tied into intestinal pH level. It is clear to me we stand on the threshold of greater understanding of the physiology of the guanylin peptides and new horizons in pharmacophysiology.

5.5. Where is drug likely to be in 5 years' time?

I expect that there will be exceptional advances in the development of all the other physiologic pathways regulated by activation of the GC-C receptor (e.g., mucosal barrier maintenance, inflammation, and cell proliferation) and compensation for altered physiology associated with several disease processes such as inflammatory bowel diseases and colorectal cancer. Given this broad spectrum of potential activity for GC-C agonists, I would not be surprised to see that the use of agents such as plecanatide in new areas grows to a level even greater than the use for the present CIC and IBS-C indications.

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This manuscript has not been funded.

Declaration of Interest

Philip B Miner Jr was the Principal Investigator for CIC and IBS-C trials conducted on site at the Oklahoma Foundation for Digestive Research. Furthermore, he has declared that he has served on Medical Advisory Boards for Synergy focusing on the development and marketing of plecanatide and has participated as a speaker for Synergy's 'Speaker's Bureau for CIC and Plecanatide'. He declares that he has no investments in the pharmaceutical industry other than those contained within mutual funds. He has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. One referee declares that they have served as a consultant for Synergy, Ironwood and Allergan.

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