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Core Aspects of Clinical Development and Trials in Chronic Idiopathic Constipation

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1. Introduction

Chronic constipation is one of the most common conditions, with prevalence by various estimates ranging from 1.9% to 27.2% in the American population (Bharucha et al., 2000; Higgins & Johanson, 2004; Shah et al., 2008). Treatment options range from older over-the-counter laxatives to recently approved prescription drug therapies (Longstreth et al., 2006; Motola et al., 2002; Ramkumar & Rao, 2005; Tack & Müller-Lissner, 2009; Tack et al., 2011; Tramonte et al., 1997). It has been estimated that 6 million to 8.5 million patients seek medical care for constipation each year. Over 70% of these individuals express dissatisfaction with prior medications, pointing to the need for new therapies (Johanson & Kralstein, 2007).

Drugs that have been recently approved or which are in late-stage trials for treatment of constipation are listed in Table 1. These include prokinetic agents (5-HT_4 receptor agonists),

Drug class	Agent	Mechanism of action	Status
5-HT_4 receptor agonist	Prucalopride	Prokinetic: Stimulation of colonic peristalsis	Approved in Europe and Switzerland
	Velusetrag		Completed Phase 2
	Naronapride		Completed Phase 2
Secretagogue	Lubiprostone	ClC2 channel and CFTR channel activator	Approved in US and Switzerland for CIC and IBS-c
	Linaclotide	GCCR agonist	Phase 3 completed in US and Europe
	Plecanatide	GCCR agonist	Phase 2 in US
	A3309	IBAT inhibitor	Phase 2 completed
Absorption inhibitor	Na-H exchange inhibitor	RDX-5791	Phase 2 in US

Table 1. Drugs recently approved or in late-stage clinical trials for chronic idiopathic constipation

secretagogues (guanylate cyclase C receptor agonists, bile acid transport inhibitors, Cl channel activators), and Na-H exchange inhibitors. Prokinetic agents promote colonic motor activity and propulsion, while secretagogues and Na-H exchange inhibitors either induce secretion of water and electrolytes or inhibit their absorption, resulting in more water in luminal contents. All of these agents appear to accelerate colonic transit time and accentuate stool output. There is little known at this point regarding comparative efficacy and safety between individual drugs or drug classes. Although speculative, it is likely that different drugs and drug classes will be used concomitantly in patients who fail to achieve the desired therapeutic response.

Serotonin (5-hydroxytryptamine, 5-HT) is a critical regulator of gastrointestinal motility, sensitivity, and secretion (Gershon, 2004). 5-HT triggers and coordinates intestinal peristalsis through 5-HT_4 receptors expressed mainly on enteric neurons (Gershon & Tack, 2007). The safety of the 5-HT_4 subclass has been brought into scrutiny because of the withdrawal of two previously marketed drugs, as will be discussed below. The highly selective 5-HT_4 agonists currently under development are expected to exhibit more favorable safety profiles with low potential for cardiovascular side effects (DeMaeyer et al., 2008).

This review will provide an oversight of drugs that have been recently approved or are currently in late-stage clinical development for chronic idiopathic constipation (CIC). We will focus on methodologies (endpoints, study populations, biomarkers) that have been employed in proof-of-concept (Phase 2) and late-stage confirmatory clinical trials (Phase 3). We will discuss specific drug properties (dosing, drug-drug interactions, and specificity) that are the expected outcome of these trials. The goal of the clinical development program in CIC is to thoroughly document a drug profile with an acceptable balance between efficacy and safety.

The use of opioids and the side effects of opioid use have reached near epidemic proportions in the United States. The prevalence of constipation in this population is estimated to range between 20% and 70% (Bell et al., 2009; Brown et al., 2006; Kalso et al., 2004). While there have been considerable efforts directed towards the development of drugs for treating opioid-induced constipation, our review will focus on constipation from other causes.

2. Drug properties impacting clinical development

2.1 Pharmacokinetic and pharmacodynamic profiles

Compounds currently in clinical development are intended to be used as chronic oral therapies rather than periodically as rescue treatment. Therefore, pharmacokinetics of each compound after repeated dosing will play an important role in differentiating ease of use (i.e., once daily), potential accumulation, drug-drug interaction, etc. Drugs that promote more frequent and complete defecation may act locally on the GI mucosa or exert their effects systemically. The degree in which systemic exposure drives clinical efficacy varies by drug class, expected site of action in GI tract, and pharmacokinetics of each compound. High molecular weight (e.g., peptides) ordinarily renders a drug non-absorbable. Some constipation drugs have been postulated to exert their effects by local and systemic mechanisms simultaneously (Hoffman et al., 2010). 5-HT_4 agonists currently under development are small molecules that are absorbed and systemically available, while the

newer secretagogues, such as linaclotide and plecanatide, are peptides that are unabsorbed and systemically inert (Harris & Cromwell, 2007; Shailubhai et al., 2010). The maximal tolerated dose (MTD) of a systemically available drug depends on many factors, including end-organ toxicities and drug interactions, while the therapeutic limit of non- or minimally absorbed drugs mainly reflects GI tolerance. Irrespective of these considerations, all compounds for the treatment of constipation possess the inherent potential to produce diarrhea when administered at sufficient doses, due presumably to their exaggerated pharmacology rather than some off-target activity. Diarrhea led to study discontinuation in almost 5% of subjects in recent Phase 3 trials of linaclotide (Lembo et al., 2010a).

Absence of systemic exposure minimizes but does not eliminate the possibility drug-drug interactions or drug toxicity. Drug interactions, for example, could still occur with efflux proteins (e.g., p-glycoprotein) at the enterocyte brush border (Huang & Woodcock, 2009). A3309, a non-absorbed inhibitor of bile acid transport (IBAT) that blocks bile acid re-absorption by the terminal ileum (Chey et al., 2011a) could theoretically impair long-term fat-soluble vitamin absorption (Vitamin A, E, D) or lead to other nutritional deficiencies. The choleretic compound class has also been associated with higher rates of abdominal cramping and diarrhea in clinical trials (Odynsi-Shiyanbade et al., 2010).

There have been few examples of non-GI adverse events using the newer 5-HT_4 agonists. As will be discussed below, the infrequency of these events probably relates to higher specificity for the 5-HT_4 receptor than earlier agents. Certain 5-HT_4 agonists (prucalopride and velusetrag) have been associated with a low but increased incidence of headaches and nausea compared with placebo. Although these side effects were reported in smaller percentages of patients in clinical trials of naronapride, the relationship between these adverse events and degree of CNS penetration is unclear (Palme et al., 2010). These side effects have been shown to resolve after the first day of treatment (Camilleri et al., 2008; Goldberg et al., 2010).

Linaclotide is a GCCR agonist and synthetic analog of E. coli ST_a toxin that stimulates intracellular c-GMP activity and active Cl secretion. Linaclotide is released and degraded rapidly in the duodenum (Kessler et al., 2008). This being the case, the stool hydrating effect of linaclotide must rely on a rapid burst of secretion in the upper intestine. Colonic motor dysfunction could potentially blunt or eliminate the subsequent therapeutic responses to linaclotide, reflecting the prodigious organ specific capacity for water reabsorption by the colon, coupled with prolonged transit (Debongnie & Phillips, 1978). Titration of distal stool volume might be difficult to control by a proximally active mechanism, resulting in wider swings in fecal output and higher rates of diarrhea-associated adverse events. Consistent targeting of specific sites along the length of the GI tract could be difficult with a luminally active agent. A 10-fold to 100-fold inter-individual variability in GCC mRNA expression has been observed in the human intestine (Bharucha et al., 2010), adding to the challenge of proper dosing in individual patients.

Plecanatide is a synthetic analogue of naturally occurring uroguanylin that mediates basal secretion and cell volume in humans (Shailubhai et al., 2010). In contrast to linaclotide, which is stabilized by three disulfide bonds that maintain the peptide in a tight configuration (Harris & Cromwell, 2007), the molecular structure of plecanatide contains only two disulfide bonds (Shailubhai et al., 2010), potentially rendering it less stable at its

intestinal site of action. Furthermore, its binding to GCC receptors is pH-dependent. Perhaps as a result of these properties, plecanatide manifests three-fold to five-fold lower potency compared with linaclotide in human studies on a concentration basis (Lembo et al., 2010a; Shailubhai et al., 2010). Plecanatide was associated with a lower incidence of diarrhea in a preliminary trial of constipated patients, but this could potentially be representative of lower rates of intestinal secretion induced by the compound (Shailubhai et al., 2010).

2.2 Receptor specificity and off-target effects

5-HT in the GI tract is primarily stored in gut enterochromaffin cells, with a much smaller portion in enteric neurons. High selectivity is an important feature of newer 5-HT_4 agonists like prucalopride, velusetrag, and naronapride. Early 5-HT_4 agonists were associated with non-specific receptor binding and off-target cardiac findings. Metoclopramide, a mixed 5-HT_4 agonist and D_2 antagonist, has been associated with tardive dyskinesia as a result of antagonism of striatal dopamine receptors, leading the FDA to issue a black box warning restricting recommended use (Metozolv Prescribing Information, 2009). Up to 30% of patients using metoclopramide discontinue treatment due to various other CNS side effects (Lee and Kuo, 2010).

Cisapride, a benzamide, was a 5-HT_4 agonist that facilitated release of acetylcholine throughout the gut. It was used widely for treatment of gastro-esophageal reflux disease, gastroparesis and functional dyspepsia (Wiseman & Faulds, 1994). While the efficacy of cisapride in upper gastrointestinal tract motility was widely recognized, its effects on constipation and lower GI motility have been questioned (Abourmarzouk 2011). The loss of effect in the lower GI tract was attributed to concomitant antagonism of the 5-HT_3 and potentially 5-HT_2 receptor, leading to opposing effects on colonic transit and secretion (Masaoka & Tack, 2009).

In 2000, cisapride was withdrawn from the market due to fatal arrhythmias and dose-dependent QT interval prolongation (Masaoka & Tack, 2009). These events occurred notably in patients taking other medications that are known to inhibit the CYP450 3A4 isozyme, e.g., erythromycin, fluconazole and amiodarone. Although the basis of cisapride's arrhythmogenic effect was not fully understood, it has been attributed to blockade of hERG (human ether-a-go-go) potassium channels, and a resulting delay in cardiac action potential repolarization in ventricular muscle and Purkinje fibers, and unrelated to its 5-HT_4 agonist properties (Tonini et al., 1999).

Tegaserod, a 5-HT_4 receptor partial agonist of aminoguanidine indole class, was approved in the United States for the treatment of chronic constipation and irritable bowel syndrome with constipation (Al-Judaibi et al., 2010). Although several studies (Prather et al., 2000; Foxx-Orenstein et al., 2005) demonstrated prokinetic action of tegaserod in both upper and lower GI tract, data regarding improvement of gastric emptying in humans are inconsistent (Talley et al., 2006; Degen et al., 2001, 2005). Tegaserod was withdrawn from the market in 2007 because of a reported numerical imbalance in the number of patients with cardiovascular ischemic adverse events in trials for patients who received tegaserod compared with those on placebo (Pasricha, 2007). Subsequent epidemiologic studies (Anderson et al., 2009; Loughlin et al., 2010) failed to confirm a reported large event differential for tegaserod that was noted incidentally in this clinical trial database.

Tegaserod is now recognized to have significant affinity for non-5-HT_4 receptors, including the 5-HT_{1B}, 5-HT_{1D} and 5-HT_{2B} subtypes (Borman et al., 2002; DeMaeyer et al., 2008). The effects of tegaserod on 5-HT_1 receptors present on blood vessels and platelet aggregation have been implicated as a mechanism accountable for ischemic changes (Chan et al., 2009; DeMaeyer et al., 2008; Serebruany et al., 2010). Moreover, the potent 5-HT_{2B} antagonism of tegaserod has been postulated to counteract its 5-HT_4 prokinetic effect (Borman et al., 2002). Low oral bioavailability (10%) may also have reduced the efficacy of the compound (Johanson et al., 2004; Kamm et al., 2005).

3. First-in-human trials

3.1 Exposure-response relationship and dose-selection

Single and repeat dose studies are routinely conducted first in healthy volunteers with normal bowel function. The benefit of this approach is the ability to establish preliminary pharmacokinetics and safety profiles in subjects without significant pre-existing conditions. These compounds induce defecatory changes in healthy volunteers, such as increasing bowel movement frequency. However, the doses responsible for these changes in healthy volunteers appear to be higher than the therapeutic dose in chronic constipation patients. GI pharmacodynamic effects in healthy volunteers are dose-dependent and the GI adverse events (i.e., diarrhea) tend to subside after the first dose. In general, there is very limited information on the pharmacokinetic-pharmacodynamic relationship for drugs for this indication. These first-in-man studies are typically followed by pilot dose-ranging safety and efficacy trials in the affected population. Study phases were compressed in the plecanatide program (Shailubhai et al., 2010), which chose to progress to initial repeat-dose studies directly in constipated patients rather than after single-dose studies in normal volunteers. This accelerated approach would seem justified due to the absence of systemic bioavailability and dose accumulation.

In addition to the typical Phase 1 safety studies, gut transit time measurements have been employed to test the prokinetic effects of these compounds in the upper and lower GI tract. These studies have utilized scintigraphic techniques in patients and healthy volunteers (Degen et al., 2001, 2005; Camilleri et al., 2007; Manini et al., 2010; Talley et al., 2006). Endpoints have included colonic transit time (GC24), ascending colon emptying (ACE) $T_{1/2}$, gastric emptying (GE) time and colonic filling at 6 hours (CF6). These endpoints have served as biomarkers for drug effect in the upper and lower GI tract and have guided subsequent indications. Pharmacodynamic endpoints such as scintigraphic transit time are easier to achieve and require fewer subjects than those than those employed in registration trials. This approach minimizes study timeline and cost. It is worth noting that subsequent therapeutic doses for chronic constipation also tend to be lower than the doses needed to demonstrate pharmacodynamic effect in transit studies (Goldberg et al., 2010; Manini et al., 2010).

Dose proportional effects on stool frequency, stool consistency, and other symptoms associated with constipation are ordinarily observed with compounds in both the 5-HT_4 and secretagogue drug classes. With the possible exception of plecanatide, the incidence of diarrhea rises with use of these agents at higher doses. Drugs such as prucalopride, velusetrag, linaclotide, plecanotide, A3309, and RDX-5791 exhibit prolonged pharmacokinetic exposures and/or pharmacodynamic effects and offer the advantage of once daily dosing.

4. Late-stage clinical trials

4.1 Study population

Despite treatment dissatisfaction with OTC medications (Johanson & Kralstein, 2007), there have been no prospective definitions of treatment failure with prior treatment in clinical trials. To date, treatment failure has not been an entry requirement into any late-stage constipation trial. In one of the three pivotal trials that formed the basis of the approval of prucalopride for CIC in Europe in 2009, 87% of subjects with constipation reported dissatisfaction with prior laxative regimens (Tack et al., 2009). Other than this one trial, the concept of treatment refractoriness has not been adequately addressed in registrational trials, which regulatory authorities use to develop label claims. It will be important to make this distinction prospectively if the role of newer medications in the constipation treatment paradigm is to be fully understood. Other study population considerations are outlined in Table 2.

Rome III Criteria (Modified) - ≤ 3 SBM per week - One or more of the following symptoms occurring on ≥ 25% of BM for at least 12 weeks during the preceding 12 months • Straining during bowel movements • Lumpy or hard stools • Sensation of incomplete evacuation
Treatment dissatisfaction or failure
Gender
Elderly population (over 65 years of age)
Pelvic floor dyssynergia
Renal or hepatic impairment
Exploratory: Transit time measurements

Table 2. Key Inclusion/Exclusion Criteria and Considerations in Constipation Trials

It is important to demonstrate safety and efficacy in most patients who are most often affected. In general, CIC is more common in women (Chuong et al., 2007), and not surprisingly, the majority of subjects who have participated in clinical trials have been women. The label claim of prucalopride was restricted to women because the enrollment of low number of male subjects in clinical trials precluded proof of efficacy in men. Although the data are very limited, the effective dose in males may also be higher than females (European Medicines Agency, 2009).

Constipation affects up to 50% of elderly individuals and is especially prevalent in nursing home residents (Camilleri et al., 2009; Chuong et al., 2007; Müller-Lissner et al., 2010). However, pharmacokinetics, the safety and tolerability profile and clinical efficacy in elderly patients may be different than in the younger population. The elderly population is routinely restricted in earlier pharmaceutical development due to safety considerations. The efficacy of prucalopride in the elderly population was demonstrated in a late-stage, multicenter trial of 300 elderly patients (Müller-Lissner et al., 2010). A subsequent safety

trial was conducted in frail elderly patients residing in a nursing facility (Camilleri et al., 2009). Dosing should take diminishing renal function into the consideration if the drug is eliminated through the kidney. The effect of age on the pharmacokinetics of prucalopride was studied in an open, parallel-group trial in 12 healthy elderly (age range 65 to 81 years) and 12 young subjects (European Medicines Agency, 2009). Peak plasma concentrations and AUC of prucalopride were 26% to 28% higher in elderly subjects compared with young adults, due to diminishing renal function with age.

Patients participating in late-stage constipation trials should meet established definitions for chronic idiopathic constipation. The Rome II criteria for CIC were published in 1999 (Thompson et al., 1999), and followed by the Rome III criteria in 2006 (Longstreth et al., 2006). Modifications of these criteria have become working standards for inclusion and exclusion in constipation trials. The Rome criteria provide for a history of ≤ 3 SBMs per week and having one or more of the following symptoms for at least 12 weeks during the 12 months preceding the study: (1) straining during ≥ 25% of BMs; (2) lumpy or hard stools during ≥ 25% of BMs; or (3) sensation of incomplete evacuation during ≥ 25% of BMs.

The unmodified Rome III criteria for CIC include the sensation of anorectal obstruction or need for manual maneuvers to facilitate defecation (e.g., digital evacuation, support of the pelvic floor). Approximately 10% of subjects with CIC have functional outlet obstruction associated with pelvic floor dysfunction (Lembo & Camilleri, 2003). Formal radiographic or manometric testing is required to establish the diagnosis. These patients may be less responsive to pharmaceutical approaches than other patients, and are more appropriately treated with biofeedback or surgical methods (Lembo & Camilleri, 2003; Locke et al., 2000). Study protocols have typically tried to exclude patients with a history of dyssynergic defecation or in whom the history and physical examination was felt to indicate the presence of this type of constipation (Johanson et al., 2004; Lembo et al., 2010b).

To confirm the diagnosis of CIC, patients typically undergo a two-week baseline screening period during which time they must report an average of ≤ 3 CSBMs and ≤ 6 SBMs per week for inclusion. The patient responses are generally captured via an electronic diary or interactive voice response system. Use of a laxative, enema, and/or suppository usage for two or more days, or the report of any watery stools (Type 7) or > 1 loose (mushy) stools (Type 6) on the Bristol Stool Form Scale [BSFS] (Lewis & Heaton, 1997) would exclude a patient from participation.

Although constipation is associated with slower colonic transit, only a small portion of patients with CIC have abnormally slow transit times on formal testing (Lembo & Camilleri, 2003). Although transit time measurements may be a useful gauge for the effectiveness of an investigational agent, particularly in the early stages of clinical development, there would appear to be insufficient rationale to qualify patients for late-stage trials based on these transit time measurements.

4.2 Endpoints

Efficacy in constipation trials should signify improvement in constipation-associated symptoms. Endpoints in constipation trials are therefore patient-reported. Regulatory standards for tools to measure symptom-based endpoints in the United States is built on the FDA Guidance for Patient Reported Outcomes, issued in draft form in February 2006 and

finalized in December 2009 (US Food and Drug Administration, 2009). Primary efficacy endpoints in late-stage constipation trials typically embody increases in the number of bowel movements (BM) per day, either improvement in spontaneous bowel movements (SBM) or complete spontaneous bowel movements (CSBM) (Table 3). A BM is deemed an SBM if no laxative, enema, or suppository was taken in the preceding 24 hours, and a CSBM if the patient indicated that the SBM is associated with a sensation of complete bowel emptying. Until there is a well-validated patient reported outcome tool the FDA accepts, PRO development will need to be considered in parallel with the clinical development program. In addition, translation and validation of these tools in different languages will also be essential for clinical development plans that expand beyond English speaking populations.

Phase of Development	Instrument	Measurement
First-in-man		
Scintigraphy	Whole gut or colon TT	Geometric center
Stool consistency	BSFS	7-point ordinal scale
Early phase (pilot studies)		
SBM	Daily diary	Average change from baseline
CSBM	Daily diary	Average change from baseline
Late-phase		
Primary endpoint:		
Responder definition CSBM	Daily diary	Categorical variables based on MID
– Achieving of ≥ 3 CSBM/week		
– Increase of ≥ 1 CSBM/week (either co-primary or key secondary endpoint)		
Secondary or exploratory endpoints		
– Stool consistency	BSFS	7-point ordinal scale
– Abdominal pain or discomfort	Severity score	11-point ordinal severity scale
– Straining	Severity score	5-point ordinal severity scale
– Bloating	Severity score	5-point ordinal severity scale
– Use of rescue medications		Change in mean
– PAC-SYM	Composite instrument	Total /domain scores
– PAC-QoL	Composite instrument	Total /domain scores
– Global endpoints		
Constipation severity	Severity score	5-point ordinal severity scale
Global relief of constipation	Numerical rating scale	7-point balanced scale
Treatment satisfaction	Numerical rating scale	5-point ordinal scale
Adequate relief	Binary question	Binary (yes/no)

Table 3. Endpoints in Clinical Trials in Constipation. Abbreviations: *BSFS*, Bristol Stool Form Scale; *TT*, transit time; *MID*, minimally important difference; *CSBM*, complete spontaneous bowel movement; *SBM*, spontaneous bowel movement

The conceptual framework of constipation treatment response embodies symptoms considered important to the patient. These typically include stool consistency, straining,

abdominal pain, bloating, and feeling of bowel emptying. Stool consistency is typically measured on the Bristol Stool Form Scale (BSFS). The constipation symptom roster is usually elicited in focus groups of individuals suffering from constipation. Patient responses are then structured into questionnaires using psychometric methods described in the guidance. These symptoms comprise primary and secondary endpoints that form the basis of label claims in the United States.

Earlier stage trials in constipation typically utilize continuous variables, such as mean change in SBM and/or CSBM from baseline across patients groups, for primary efficacy endpoints. These endpoints are easier to power and therefore engender lower sample sizes. Lubiprostone was approved in the US on the basis of trials that employed changes in SBM (Barisch et al., 2010; Johanson et al., 2008). However, the recent guidance makes clear the need for responder definitions in late-stage clinical trials (US Food and Drug Administration, 2009).

Responder definitions should be predicated on subjects achieving minimally important differences (MID) (US Food and Drug Administration, 2009). These differences are derived from factor analyses of clinical data in Phase 2 trials. MIDs are typically determined by comparing symptomatic improvement to global improvement questions. The primary efficacy endpoint in the prucalopride Phase 3 programs utilized the responder definition of ≥ 3 CSBM per week (Camilleri et al., 2008; Quigley et al., 2009; Tack et al., 2009), with the key secondary efficacy endpoint being the proportion of subjects achieving an increase of ≥ 1 CSBM per week. Three CSBM per week, i.e., approximately one BM every other day, represents normalization of bowel function in many individuals (Drossman et al., 1982), and therefore has clinical meaningfulness. The linaclotide Phase 3 program provided for co-primary endpoints that included achieving both ≥ 3 CSBM and improvement of ≥ 1 CSBM/week (Lembo et al., 2010a). The achievement of ≥ 3 CSBM per week is a more stringent and clinically more relevant endpoint than improvement of ≥ 1 CSBM, and efficacy responses on this co-primary endpoint predominantly reflect the subject's response on the first co-primary. It should also be pointed out that CSBM is a more stringent outcome than SBM, and that while endpoints predicated on CSBM may have lower response rates than SBM, the drudging of placebo performance typically results in improved study power, lower sample sizes, and higher chances of trial success.

Drugs have typically achieved responses in the 18% to 29% range on these CSBM-based responder definitions compared with 5% to 15% placebo response in Phase 3 CIC trials. This compares to treatment responses of 30% to 40% using SBM-based definitions, but with higher placebo responses and overall lower levels of statistical significance (Camilleri et al, 2008; Lembo et al, 2010a; Quigley et al, 2009; Tack et al, 2009). The observation that only a quarter of patients normalize bowel function with monotherapy-based trials suggests that the majority of patients will require combination therapy with these agents in the clinic.

Additional efficacy parameters in constipation trials have included the PAC-SYM (Frank et al., 1999), a composite index of constipation-associated symptoms, and PAC-QOL (Marquis et al., 2005), a health-related quality of life instrument, neither of which are recognized by the FDA as acceptable endpoints for clinical trials in the United States. Use of rescue medications and time to first bowel movement have also served as secondary or exploratory endpoints in selected trials. Sponsors have typically included global endpoints such as

constipation severity and adequate relief as secondary or exploratory endpoints (Lembo et al., 2010a), and the FDA supports use of these outcomes other than for primary efficacy endpoints (US Food and Drug Administration, 2009).

4.3 Drug safety

Safety concerns are tantamount in drug development for constipation, which is viewed by both clinicians and regulators a non-lifethreatening condition rather than a disease. The tolerance for safety concerns in the treatment of constipation is understandably low. Safety exposure databases should be expected at a minimum to follow ICH Guidelines for chronic disease and include 300-600 six-month exposures and 100 twelve-month exposures (US Food and Drug Administration, 1995). Higher standards may be set by regulatory agencies in the future, and the requirement for risk management programs could be imposed on drugs seeking approval in the US (US Food and Drug Administration, 2005). Pharmacovigilence post-approval has become standard industry practice. When safety is a concern, it is important that drug development identify a minimal effective dose and provide guidance to clinicians on how dosing should be escalated from that point forward. The burden of safety is likely to be reduced for drugs that are locally active compared with those that are systemically available, meaning lower requirements for pre-approval exposures and lower post-approval safety commitments. The GI tract is ideally suited for local or topical exposure by oral or rectal routes of administration.

Potential for QT interval prolongation and drug-drug interactions that potentiate this effect must be identified early in the development program. QT interval prolongation led to the market withdrawal of cisapride in 2000 (Masaoka & Tack, 2009). Tegaserod was associated with a higher incidence of cardiac ischemic events and withdrawn from the market in 2007 (Pasricha, 2007). This concern has shadowed development with all subsequent 5-HT_4 agonists, although current data suggest that QT prolongation and cardiac ischemia may have been due to off-target effects on other receptors or 5-HT receptor subclasses (Chan et al., 2009; DeMaeyer et al., 2008; Serebruany et al., 2010; Tonini et al., 1999). To date, no such events have been observed with prucalopride or any of the current 5-HT_4 development programs.

4.4 Biomarkers

A biomarker is a measureable physical, functional, or biochemical surrogate for a physiological or disease process that has diagnostic and/or prognostic utility (US Food and Drug Administration, 2010a). For many diseases, there is no good way to document the course of a disease or the response to treatment. A biomarker may represent the features of a biologic processes or a response to a therapeutic intervention and reduce the expense and duration of clinical trials. Changes in biomarkers following treatment may reduce uncertainty in drug development by predicting drug performance, identifying safety problems, or revealing pharmacological activity or other benefit from treatment. The European Medicines Agency has also issued guidance for biomarker development in the European Union (European Medicines Agency, 2008).

Radio-opaque markers have been used to assess colonic transit, but recent studies have demonstrated scintigraphic imaging to be a more precise tool for drug development in

constipation (Camilleri, 2010; Rao S.S. et al., 2011). Scintigraphic transit time fulfills all regulatory criteria for a disease biomarker: known performance characteristics, reproducible and accurate data over a range of conditions, and evidence of linkage to biological processes and clinical endpoints. Changes in colonic transit by scintigraphic technique have generally predicted the responses to treatment across a variety of compounds (Camilleri, 2010). This may prove to be a biomarker in new drug applications in colonic motility disorders. As noted previously, these transit time measurements define transit time abnormalities in only a minority of patients and are therefore of no specific utility towards defining subjects who enter late-stage clinical trials (Lembo & Camilleri, 2003). Stool frequency correlates poorly with colonic transit, but there appears to be good correlation between gut transit and stool consistency (O'Donnell, Virgie & Heaton, 1990). These markers are generally well accepted and are useful for predicting dose range in subsequent efficacy studies.

5. Clinical trials of approved drugs or drugs in development

5.1 5-HT_4 receptor agonists

5.1.1 Prucalopride

Prucalopride (Resolor®) is a benzofuran carboxamide that is structurally distinct from cisapride and tegaserod. Prucalopride exhibits a more than 2-log scale greater selectivity for 5-HT_4 compared with other receptors (DeMaeyer et al., 2008). This selectivity offers promise for greater efficacy and safety. The 2 mg once daily dose was approved in Europe in 2009 for the treatment of chronic constipation in women who fail to respond to laxatives. Due to the pharmacokinetic considerations described above, it is recommended that the drug be initiated at 1 mg in elderly patients and increased to 2 mg as needed (European Medicines Agency, 2009).

In pharmacodynamic studies, prucalopride dose-dependently enhanced colonic transit both in healthy controls and in patients with chronic constipation. In patients with chronic constipation, prucalopride 2 mg and 4 mg were significantly more effective than placebo in decreasing GI and colonic transit time. This was also reflected in increased stool frequency and looser stool consistency (Bouras et al., 1999, 2001; Sloots et al., 2002). Response in patients with constipation was dose-dependent and effective dosage was generally achieved with 2 mg once daily, although some studies reported significant beneficial effects on 1 mg (Emmanuel et al., 2002; Sloots et al., 2002).

A total of 2717 patients with chronic constipation were treated in placebo-controlled, double-blind, Phase 2 and Phase 3 trials (Miner et al., 1999; Emmanuel et al., 2002; Coremans et al., 2003; Camilleri et al., 2008; Quigley et al., 2009; Tack et al., 2009; Müeller-Lissner et al., 2009). Doses of prucalopride ranged from 0.5 to 4 mg per day. Two of these trials recruited patients who were either resistant to, or dissatisfied with laxatives (Coremans et al., 2003, Tack et al., 2009), one of these being pivotal (Tack et al., 2009), and one trial involved patients aged over 65 years (Müeller-Lissner et al., 2009).

In the Phase 3 program that served as the basis of approval of prucalopride in Europe, three identically designed, multicenter, pivotal trials were conducted (Camilleri et al., 2008; Quigley et al., 2009; Tack et al., 2009). More than 85% of the subjects in these trials were women. Patients were included based on the criteria of two or fewer SBMs per week in the

previous 6 months and very hard or hard stools and/or a sensation of incomplete evacuation and/or straining during defecation for at least a quarter of the stools. The primary parameter was the proportion (%) of patients with an average of 3 or more spontaneous, complete bowel movements per week (responders, ≥ 3 CSBM/week). The main secondary endpoint was the proportion of patients with an average increase of ≥ 1 CSBM per week from run-in. The key time-point was assessed at Week 12. Treatment with prucalopride 2 mg and 4 mg once daily resulted in an average of three spontaneous, complete bowel movements (CSBM) per week in 19.5% to 28.5% of subjects treated with prucalopride vs. 9.6% to 13.6% receiving placebo. Significant changes were also seen in the main secondary endpoint.

Clinically relevant improvement in constipation-associated symptoms and quality of life were observed using the PAC-SYM and PAC-QOL questionnaires in these pivotal trials. Nearly 2600 patients were treated with prucalopride in open, long-term studies. 1490 of these subjects received treatment for at least 6 months and 869 received at least 1 year of treatment. The effects of the 2 mg and 4 mg doses of prucalopride were similar, and both were determined to be safe and well tolerated.

Only one cardiovascular event was reported, an episode of supraventricular tachycardia, and extensive cardiovascular safety assessments demonstrated no signals of arrhythmogenic potential (Camilleri et al., 2009). The incidence of serious adverse events was similar to placebo. Headache, nausea, and diarrhea were reported more often in subjects receiving prucalopride, but these adverse events were mainly driven by the occurrence on Day 1 of treatment. It was postulated that this represented a transient effect of 5-HT_4 agonists that penetrate the CNS. However, the relationship between these adverse events and the degree of CNS penetration is inconsistent across this class of compounds.

Data from a series of thorough QT studies appear to show that the influence, if any, of prucalopride on QT interval and other ECG variables is negligible. The number of cardiovascular ischemic-related events was low and comparable between prucalopride groups and placebo (0.1%). Clinical trials with prucalopride were temporarily suspended in 1999 following positive carcinogenicity studies in rodents; however, these findings were deemed to be rodent-specific and were not thought on regulatory review to apply to humans (European Medicines Agency, 2009).

5.1.2 Velusetrag

Velusetrag (TD-5108) is a high-affinity and selective 5-HT_4 receptor agonist with high intrinsic activity at the human 5-HT_4 receptor. Unlike tegaserod, velusetrag has no appreciable affinity for 5-HT_{1D}, 5-HT_{2A}, or 5-HT_{2B} receptors (Beattie et al., 2004; Smith et al., 2007). In contrast to cisapride, velusetrag has no significant affinity for the human ether-a-go-go-related gene potassium channel (Smith et al., 2008). In animal models, velusetrag demonstrated gastrointestinal activity in the digestive tract. To date, no significant effects of velusetrag on blood pressure, heart rate or electrocardiogram have been noted in animals or humans at clinically relevant doses, nor does velusetrag have any contractile activity in porcine- or canine-isolated coronary arteries (Beattie et al. 2007).

A dose-response transit study showed that velusetrag administration was associated with acceleration of colonic and orocecal transit after single dose administration to healthy subjects with substantive and significant effects on gastric and colonic transit were observed

with multiple dosing (Manini et al., 2010). In an evaluation of patients with chronic constipation and matched healthy control subjects, velusetrag pharmacokinetics and effects on laxation and bowel function were similar in chronic constipation and health. Bioavailability of velusetrag from a single, orally administrated dose was good, and the elimination half-life in both populations was consistent with once daily administration (Goldberg, Wong, & Ganju 2007; Wong S.L. et al., 2007).

A Phase 2, double-blind, placebo-controlled, randomized, parallel-group, multicenter trial included 401 subjects with chronic idiopathic constipation (< 3 SBM per week) randomized to velusetrag 15 mg, 30 mg, 50 mg or placebo po QD for 4 weeks (Goldberg et al, 2010). The study population was 92% female. Patients receiving velusetrag achieved statistically significant and clinically meaningful increases in SBM and CSBM relative to placebo at all doses. There were no differences in changes in SBM and CSBM rates between doses. Median times with first SBM were 21, 25 and 18 hours, respectively, compared to 47 hours for placebo ($p < 0.0001$ for all treatments). Use of velusetrag was significantly associated with a relief of straining and bloating, a reduced need for a rescue laxative, and normalization of stool consistency.

The most common adverse events in patients were those frequently associated with 5-HT_4 agents such as prucalopride and included diarrhea, headache, and nausea. These adverse events were dose-related, occurred during the initial days of dosing, and were of mild to moderate intensity. A total of 19 patients discontinued because of adverse events, with the majority occurring in the 50 mg velusetrag group. No clinically relevant changes in hematology, biochemistry, urinalysis, vital signs and ECG parameters were observed in any group.

5.1.3 Naronapride

Naronapride (ATI-7505) is a 5-HT_4 receptor agonist belonging to the benzamide series of similar compounds (Camilleri et al, 2007). The design of naronapride was based on the prototypical benzamide agent, cisapride. Unlike cisapride, naronapride was designed to be devoid of other 5-HT receptor activities and to have negligible inhibitory activity at the hERG channel, with an affinity ratio between I_{Kr} and 5-HT_4 receptors of at least 1000- fold. In addition, the compound was to have low potential for drug–drug interactions. Unlike prucalopride and velusetrag, naronapride does not exhibit CNS penetration, which may lead to a lower incidence of side effects (Aryx Corporation, 2008). However, other 5-HT_4 agonist with limited CNS penetration (i.e., tegaserod) did show comparable rate of adverse events to prucalopride and velusetrag.

A randomized, parallel-group, double-blind, placebo-controlled study evaluated effects of 9-day treatment with naronapride (3, 10 or 20 mg TID) on scintigraphic GI and colonic transit in healthy volunteers (12 per group) (Camilleri et al., 2007). Primary endpoints were gastric-emptying (GE) $T_{1/2}$, colonic geometric centre (GC) at 24 h and ascending colon (AC) emptying $T_{1/2}$. Naronapride increased colonic transit with greatest effect vs. placebo observed at 10 mg TID. The effect on transit was associated with looser stool consistency.

A randomized, multinational, multicenter, double-blind, placebo-controlled, dose-ranging trial was performed in patients with CIC (Palme et al., 2010). Patients were randomized to naronapride 20 mg, 40 mg, 80 mg or 120 mg or placebo BID orally for four weeks. Although

400 subjects were planned in the original study design, the study was terminated early due to business reasons, and only 214 patients were randomized. The primary outcome was total number of SBMs during Week 1 compared with placebo. Treatment response, a secondary endpoint, was defined as the proportion of subjects achieving ≥ 3 CSBM/wk or ≥ 3 SBMs/wk on each of the four weeks in the absence of rescue medications. Despite the reduction from the intended original sample size, all doses of naronapride still met the primary endpoint, and median time to first SBM was reduced in all active treatment groups. SBM response was achieved by 51.2% of subjects treated with naronapride 80 mg vs. 24.4% receiving placebo, while CSBM response was achieved by 26.8% of these subjects vs. 4.9% receiving placebo. Adverse event frequency, including headache, diarrhea, nausea and vomiting, was similar to placebo in all ATI-7505 dose groups except the 120 mg BID group, where abdominal pain and headache were more frequently reported.

5.2 Colonic secretagogues

5.2.1 Lubiprostone

Lubiprostone is a poorly absorbed lipophylic prostanoid component that is thought to stimulate colonic water and electrolyte secretion through the activation of type-2 chloride channels on enterocytes from the luminal side (Lacy & Levy, 2007). There is also evidence that the Cl secretion induced by lubiprostone may be mediated by CFTR channels (Bijvelds et al., 2009). Lubiprostone dose-dependently enhances colonic transit, and this was hypothesized to be an indirect consequence of increased colonic water content (Camilleri et al., 2006).

In two Phase 3 studies of 4 weeks duration, lubiprostone 24 mg BID significantly enhanced SBM frequency (5.69 and 5.89 spontaneous bowel movements per week with lubiprostone vs. 3.46 and 3.99 with placebo, $p < 0.0001$) and relieved other constipation-related symptoms compared with placebo (Barish et al., 2010; Johanson et al., 2008). The incidence of nausea in patients receiving the approved dose of lubiprostone for chronic idiopathic constipation was approximately 29% in clinical trials, and resulted in 9% of patients discontinuing in these studies (Lacy & Chey, 2009; Sucampo Pharmaceuticals, 2009). The prevalence of nausea is increased with higher dose and could be mediated by an adverse prostaglandin-like effect on gastric motility (Lacy & Levy, 2007). Although the systemic availability of lubiprostone is reportedly low (Lacy & Levy, 2007), this side effect could potentially reflect systemic absorption post oral administration.

Lubiprostone was approved by the US FDA in 2006 for the treatment of chronic idiopathic constipation (24 mg BID) and for the treatment of female IBS patients with constipation (8 mg BID) (Drossman et al, 2009) in 2008 but, apart from Switzerland, has not been approved in Europe at this time.

5.2.2 Linaclotide

Linaclotide is a 14-amino acid peptide analog of E. coli ST_a enterotoxin that acts as an agonist at guanylate cyclase-C (GCC) receptor to induce cyclic GMP production and intestinal chloride and fluid secretion (Bharucha, Scott & Waldman, 2010). The drug is non-absorbed and exerts local effects on the enterocyte at the level of the gut lumen. In a mechanistic study, linaclotide enhanced colonic transit in IBS with constipation (Andresen

et al., 2007). It dose-dependently increased SBM and CSBM frequency, loosened stool consistency, and improved other symptoms of constipation over four weeks (Lembo et al., 2010b).

Favorable outcomes were recently achieved in two large Phase 3 studies, each involving more than 600 subjects, and 12 weeks of treatment. Trial design considered the Food and Drug Administration's recent recommendations to transition from global (e.g., overall relief) to symptom-based primary endpoints (US Food and Drug Administration, 2010b). Subjects were randomized to placebo and 133 or 266 mg of linaclotide (Lembo et al, 2010a). The primary endpoint was based on a responder analysis of subjects achieving both ≥ 3 CSBM and an increase of ≥1 CSBM per week. In both trials, significantly higher percentages of patients met the primary endpoint with linaclotide 133 mg (respectively 16% and 21.2%) and 266 mg (respectively 21.4% and 19.3%) compared with placebo (respectively 6% and 3.3%, all p-values < 0.001). The onset of efficacy occurred in the first week and was maintained for 12 weeks. Symptoms of abdominal discomfort, bloating and straining were also significantly improved. There was also improvement in health-related quality of life, and constipation severity. Linaclotide is also under evaluation for IBS with constipation (Johnston et al, 2010), and an application for marketing approval of linaclotide in the US and Europe for both indications is expected in the near future.

5.2.3 Plecanatide

Plecanatide (SP-304) is an oral peptide analogue of uroguanylin, a natriuretic hormone that regulates ion and fluid transport in the GI tract. T84 cell assays have demonstrated that plecanatide has an 8-fold higher binding affinity to GC-C receptors than uroguanylin. In a double-blind, placebo-controlled, randomized, single ascending dose study conducted in healthy volunteers, plecanatide appeared to demonstrate an increase in post-dose stool consistency score versus placebo (Shailubhai et al., 2008). The drug was well-tolerated at all doses with no systemic exposure. A subsequent Phase 2a trial in constipated subjects studied doses between 0.3 and 9 mg once daily for 14 days (Shailubhai et al., 2010). Dose proportionate reduction in time to first BM, SBM, CSBM, and stool consistency, and improvement of straining were observed up to 1.0 mg, subsequent to which no additional effects were noted. There was no detectable absorption of plecanatide at any dose, and minimal adverse events were observed. There were no reports of diarrhea in any dose groups, although the effects of plecanatide on SBM frequency and stool consistency were less pronounced than in earlier linaclotide trials.

5.2.4 A3309

A3309 is a potent and selective inhibitor of the ileal bile acid transporter (IBAT) with minimal systemic exposure. It dose-dependently inhibits the reabsorption of bile acids (BA). This results in an increased concentration of bile acids in the colon, which, in turn, increase fluid secretion and colonic motility.

In a randomized, double-blind, dose-escalating study, 30 patients were administered A3309 (0.1, 0.3, 1, 3 or 10 mg once daily) or placebo for 14 days (Simrén et al., 2011). Colonic transit was measured using radio-opaque markers and fluoroscopy at baseline and at Day 14. Bowel movements (BMs), stool consistency (Bristol Stool Form Scale) and GI symptoms

were recorded daily. Hepatic BA synthesis was estimated by measurement of 7α-hydroxy-4-cholesten-3-one (C4) in peripheral blood. Dose-dependent inhibition of bile acid desorption and acceleration of colonic transit time and SBMs were noted.

In a follow-up trial, 36 female patients were randomized to placebo, 15 mg A3309, or 20 mg A3309 administered orally once daily for 14 consecutive days (Wong B.S. et al., 2011). Whole gastrointestinal and colonic transit, stool consistency, constipation symptoms, serum 7αC4, and fasting serum total and LDL cholesterol (surrogates of inhibition of BA absorption) were measured. Colonic transit at 48h was significantly accelerated with both A3309 dosages. Significantly looser stool consistency, lower constipation severity and straining, and improved ease of stool passage were noted with both A3309 dosages. A3309 treatment significantly and reversibly increased fasting 7αC4. The most common side effect was lower abdominal pain or cramping.

Positive results from a larger, proof-of-concept trial have recently been published (Chey et al., 2011a). 190 patients with severe constipation were treated with 5 mg, 10 mg, or 15 mg A3309 or placebo for 8 weeks. Subjects were mainly female (90%) and averaged 0.4 CSBMs per week at baseline. The primary efficacy endpoint, change from baseline in spontaneous bowel movements (SBMs), showed a dose-dependent increase and highly significant results were obtained for the two highest dose levels. In addition, the secondary endpoints of effects on SBM and CSBM frequencies were also dose dependent and statistically significant. Bloating and straining, important constipation symptoms, also decreased significantly during A3309 treatment. The effect of A3309 was rapid and a significantly higher proportion of the A3309-treated patients had a CSBM within 24 hours of the first administration. The beneficial effects were maintained over the eight-week trial period.

Abdominal pain and diarrhea once again appeared to be the most common side effects with A3309 treatment. These events were observed in 10%, 11%, and 25% and 8%, 11%, and 17%, respectively, in the A3309 5 mg, 10 mg, and 15 mg dose groups, compared with only 0% and 4% in placebo-treated subjects. A similar adverse event profile was recently noted with use of chenodeoxycholic acid in healthy volunteers and female subjects with constipation-predominant IBS (Odynsi-Shiyanbade et al., 2010; Rao A.S. et al., 2010). These observations leave the tolerability of choleretic agent an open-ended question at this time. Increased C4 and reduced LDL cholesterol suggested increased BA synthesis due to inhibition of ileal BA transport. As previously discussed, the long-term effects of this therapeutic approach on fat-soluble vitamin absorption remains to be established.

5.3 Na-H exchange inhibitors

5.3.1 RDX-5791

RDX5791 is a unique, minimally systemic, small molecule NHE3 inhibitor in clinical development for the treatment of CIC. Unlike secretagogues that induce active Cl secretion, RDX5791 inhibits the intestinal Na-H antiport protein (NHE3) that plays a key role in the uptake of sodium and thus water from the intestinal lumen. The most attractive feature of the drug's mechanism is the fact the NHE3 transporter accounts for the principal mechanism of Na and water absorption in humans from duodenum to left colon. Unlike linaclotide, the actions of which may be restricted to the duodenum, RDX5791 may exert its effects along the GI tract. This would theoretically allow for more gradual hydration of

stool, and less of a tendency for diarrhea as the dose is increased. The effects of RDX5791 on stool consistency and transit time have been demonstrated in animal models (Spencer et al., 2011). RDX5791 has been demonstrated to be anti-nocioceptive in an animal model of visceral hypersensitivity (Eutamene et al., 2011). Pharmacokinetic trials have been completed, and proof-of-concept studies are currently underway in patients with IBS-c.

6. Related indications

6.1 Constipation-predominant irritable bowel syndrome

Drugs that are effective in CIC also appear to be effective in patients with irritable bowel syndrome with constipation (IBS-c). The dual effect on CIC and IBS-c appears to apply to most prokinetic agents and secretagogues. The distinction between CIC and IBS-c patients may be difficult in practice, and it is likely many patients are cross-included in their respective clinical trials. Patients typically qualify for IBS-c trials by fulfilling Rome Criteria for IBS-c and demonstrating of minimal level of abdominal pain on pre-randomization screening diaries, at least 3 out of a possible 10 on a numerical rating scale (Chey et al., 2011b). This practice was recently codified in the FDA IBS draft guidance (U.S. Food and Drug Administration, 2010b). However, while there have been minimum pain requirements to enter IBS-c trials, there have been no maximums that would exclude patients from CIC trials. In fact, it is recognized that a number of patients enter CIC trials reporting baseline pain that exceeds the IBS-c minimum (Lembo et al., 2010b). A retrospective analysis of Phase 3 CIC data demonstrated that CIC patients with a pain score ≥ 3 (on a scale of 10) were as likely to respond to linaclotide as the overall study population (Lembo et al, 2011). Interestingly, patients entering a recent multicenter IBS-c trial with linaclotide demonstrated more severe constipation than those entering CIC trials with the same compound (Johnston et al., 2010).

The mechanism of pain relief in IBS-c most likely relates to decompression of colonic distention, although reduction of visceral hypersensitivity has been suggested using animal models (Eutamene et al., 2009). The mechanism of this anti-nocioceptive effect is uncertain, since the phenomenon also appears to apply broadly across a variety of promotility agents that could have utility in CIC and IBS-c (Eutamene et al., 2011, Greenwood-van Meerveld et al., 2006). It has been suggested that stimulation of intracellular c-GMP is responsible for the pain reductions with linaclotide use (Eutamene et al., 2009). However, the mechanism of this effect remains uncertain, since linaclotide is non-absorbed and appears to be released and degraded principally in the duodenum (Kessler et al., 2008), while has been presumed that IBS pain originates in the lower GI tract.

6.2 Opioid-induced constipation

A number of peripherally acting μ-opiate antagonists are currently being investigated for the treatment of opioid-induced constipation (OIC). These drugs are designed not to penetrate or cross the blood brain barrier or adversely impact the efficacy of concomitant analgesic therapy. Methylnaltrexone bromide (Relistor®) has been approved for the treatment of opiate-induced constipation in patients with advanced illness (Thomas et al., 2008). The drug is administered subcutaneously and appears to have onset of effect within four hours. Oral bioavailability has been a challenge, although a new formulation has recently entered Phase 3 trials.

Alvimopan is an orally administered peripherally-acting μ-opioid antagonist approved for the treatment of postoperative ileus (Delaney et al., 2008). In one controlled study in 522 patients on opioids for chronic non-cancer pain, alvimopan in doses of 0.5 mg BID to 2 mg BID was superior to placebo in inducing spontaneous bowel movements and reducing constipation-associated symptoms without antagonism of opioid analgesia (Jansen J.P. et al., 2011; Paulson et al., 2005; Webster et al., 2008), although one of the two pivotal trial failed to meet statistical significance (Irving et al., 2011). This could have resulted from loss of statistical power due to use of SBM rather than CSBM as a primary endpoint, and a placebo response exceeding 50%. Development of alvimopan for OIC was discontinued in 2008 because of a numeric imbalance in myocardial infarction, neoplasm, and bone fracture adverse events that appeared in a long-term safety study.

Several other peripherally-acting μ-opioid antagonists are currently in development for OIC, including TD-1211, NKTR-118, and ALKS-37. One of the challenges will be the development of combination drugs that permit co-administration of opioid with opioid antagonists as a means to prevent constipation from occurring. It is worth noting that opioid antagonists are not expected to cause an increase in the frequency of bowel movements in healthy volunteers or patients with constipation associated with other causes rather than opioid. In contrast, prokinetic agents are likely to improve constipation associated with opioid usage. Lubiprostone and prucalopride are also being studies for the treatment of opioid-induced constipation.

7. Conclusions

Prokinetic agents and secretagogues in development will most likely assume a position on formularies with other constipation therapies, including prucalopride and lubiprostone, and OTC agents. Based on current data, it is unlikely that one agent or class of compounds will suffice for most patients. The challenge will be to integrate different mechanisms into treatment algorithms that optimize safety, cost-effectiveness and therapeutic response. This information will be established in future therapeutic trials.

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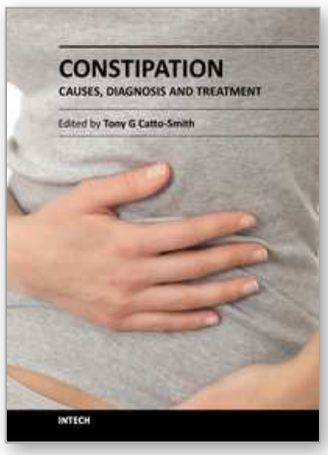

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Constipation is common in both adults and children. Estimates would suggest a median prevalence of around 12-16% in the general population. While regarded as a minor nuisance in some cases, its consequences can be severe, with a substantial impact on quality of life. Secondary faecal soiling has a profound psychological effect at all ages. This book provides contributions from authors with a range of backgrounds which clarify the pathogenesis, diagnosis, and therapy of constipation for the general population and also for certain high risk groups.

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