EU Risk Management Plan for Linaclotide

AbbVie Inc. (AbbVie)

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Summary of significant changes in the RMP: A summary of significant changes is included in RMP Annex 8.

Administrative Information on the RMP

Part Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
Part 1: Product(s) Overview	27 Oct 2017	8.0
Part II: Safety Specification		
SI – Epidemiology of the Indication(s) and Target Population(s)	11 Mar 2019	9.0
SII – Non-Clinical Part of the Safety Specification	27 Oct 2017	8.0
SIII – Clinical Trial Exposure	01 Feb 2017	7.1
SIV – Populations Not Studied in Clinical Trials	27 Oct 2017	8.0
SV – Post-Authorization Experience	01 Nov 2016	7.0
SVI – Additional EU Requirements for the Safety Specification	27 Oct 2017	8.0
SVII – Identified and Potential Risks	07 Aug 2020	10.1
SVIII – Summary of the Safety Concerns	11 Mar 2019	9.0
Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies)	07 Aug 2020	10.1
Part IV: Plan for Post-Authorization Efficacy Studies		Not applicable
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	11 Mar 2019	9.0
Part VI: Summary of the Risk Management Plan	11 Mar 2019	9.0
Part VII: Annexes		
Annex 2 – Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	15 Jun 2020	10.0
Annex 3 – Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	07 Aug 2020	10.1
Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms	27 Oct 2017	8.0
Annex 5 – Protocols for Proposed and Ongoing Studies in RMP Part IV		Not applicable
Annex 6 – Details of Proposed Additional Risk Minimization Activities (If Applicable)		Not applicable
Annex 7 – Other Supporting Data (Including Referenced Material)		Not applicable

Part	Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
	Annex 8 – Summary of Changes to the Risk Management Plan Over Time	07 Aug 2020	10.1
	Annex 9 – Local Currently-Approved Country Labeling		Not applicable
	Annex 10 – Local Risk Management/Mitigation Plan		Not applicable

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List of Abbreviations

#E	number of cases
ADR	adverse drug reaction
AE	adverse event
ATC	anatomical therapeutic chemical
BSFS	Bristol Stool Form Scale
BM	bowel movement
CCSI	Company Core Safety Information
CFTR	cystic fibrosis transmembrane conductance regulator
cGMP	cyclic guanosine monophosphate
CIC	chronic idiopathic constipation
ClC-2	chloride channel type 2
cRMP	core Risk Management Plan
CSR	clinical study report
CV	cardiovascular
DLP	data lock point
DUS	drug utilization study
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FDA	Food Drug Administration
GI	gastrointestinal
GC-C	guanylate cyclase c
GD	gallstone disorders
GVP	good pharmacovigilance practices
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IBS C	irritable bowel syndrome with constipation
IBS D	irritable bowel syndrome with diarrhea
IBS M	irritable bowel syndrome mixed type
ICSR	individual case safety report
INN	International Non-proprietary name
ISD	Ironwood Safety Database
LTSS	long-term safety study(ies)
MAA	marketing authorisation application

MedDRA	medical dictionary for drug regulatory activities
NSAIDs	non-steroidal anti-inflammatory drugs
OLE	open-label extension
OR	odds ratio
OTC	over the counter
PASS	Post authorization Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PK	pharmacokinetic
PL	patient leaflet
PPI	proton pump inhibitors
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
QOL	quality of life
RMP	Risk Management Plan
RW	randomised withdrawal
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
TEAE	treatment-emergent adverse event

Part I: Product(s) Overview

Table 1. Product Overview

Active substance(s) (INN or common name)	Linaclotide
Pharmacotherapeutic group(s) (ATC Code)	Other drugs for constipation (A06AX04)
Marketing Authorization	AbbVie Deutschland GmbH & Co. KG
Medicinal products to which this RMP refers	Linaclotide
Invented name(s) in the European Economic Area (EEA)	Constella
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Linaclotide is a GC-C receptor agonist with visceral analgesic and secretory activities. Linaclotide is a 14-amino acid synthetic peptide structurally related to the endogenous guanylin peptide family.
	Summary of mode of action: In the GI tract, linaclotide is metabolized to a primary active metabolite, des-tyrosine, which is a 13 amino acid peptide lacking the C-terminal tyrosine present in linaclotide. Both linaclotide and the des tyrosine metabolite bind to and activate the GC-C receptor on the luminal surface of the intestinal epithelium. Through its action at GC-C, linaclotide has been shown to reduce visceral pain and increase GI secretion and transit in humans and animal models. Activation of GC-C results in an increase in concentrations of cyclic guanosine monophosphate, both extracellularly and intracellularly. Extracellular cGMP modulates the activity of local afferent nerve fibres, which is hypothesised to result in reduced visceral pain. Intracellular cGMP triggers a signal transduction cascade activating the CFTR within intestinal epithelial cells. This activation causes secretion of chloride and bicarbonate into the intestinal lumen, resulting in increased fluid secretion and acceleration of intestinal transit. Linaclotide is minimally absorbed and therefore no major systemic AEs are expected.
	Important information about its composition: Nil of relevance

Hyperlink to the Product Information	Latest approved Product Information
Indication(s) in the EEA	Current (if applicable): Constella is indicated for the symptomatic treatment of moderate to severe IBS-C in adults.
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current (if applicable): The recommended dose is 1 capsule (290 µg) once daily. Physicians should periodically assess the need for continued treatment. The efficacy of linaclotide has been established in double-blind placebo-controlled studies for up to 6 months. If patients have not experienced improvement in their symptoms after 4 weeks of treatment, the patient should be re-examined and the benefit and risks of continuing treatment reconsidered. Oral use. The capsule should be taken at least 30 minutes before a meal. Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Hard capsules white-to-off white-orange opaque, marked "290" with grey ink, containing linaclotide 290 µg.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

Module SI Epidemiology of the Indication(s) and Target Population(s)

Indication #1: The symptomatic treatment of moderate to severe IBS-C in adults

Incidence: IBS-C: 0.03%-0.12% (annual) (Lovell 2012a)

Prevalence: IBS-C: 0.5%-9.8% (Lovell 2012a), Women: 5.6%; Men 1.9% (Lovell 2012b), Moderate to severe IBS-C is 60% of IBS-C population (Drossman 2011)

Demographics of the target population: Occurs between ages 15-65 years, age of first presentation to a physician: 30-50 years (Drossman 2002, worldgastroenterology.org 2009); Similar prevalence among all age groups (Lovell 2012a); Female: Male = 2:1 - 3:1 (Drossman 2002, Ford 2008, Guilera 2005, Herman 2010, Hungin 2003, Jones 2006, Muller-Lissner 2001, Mykletun 2010); similar prevalence in Caucasians and African Americans (Drossman 2002); similar across socioeconomic status groups (Lovell 2012a).

Risk Factors: Psychosocial factors such as sexual/physical abuse, stress, anger and low QOL (Agrawal 2009, Balboa 2006, Beesley 2010, Drossman 1993, Guthrie 2003).

The main treatment options:

OTC fibre supplements and laxatives are frequently recommended to treat IBS-C but are indicated only for the relief of occasional constipation. In addition, these treatments have not been shown to provide relief of abdominal pain, and can be associated with increased bloating, abdominal distension, and flatulence (Quigley 2006). The abdominal symptoms of IBS are treated with a variety of agents including tricyclic antidepressants, selective serotonin reuptake inhibitors, anticholinergic agents, narcotics, and NSAIDs. The level of evidence supporting the effectiveness of these agents for the treatment of abdominal symptoms in IBS is variable, and these agents are not specifically indicated for the treatment of IBS (Saad 2011, Tack 2006). Tegaserod (Zelnorm®), a 5-hydroxytryptamine (serotonin) receptor 4 (5-HT4) partial agonist approved by the FDA for the short-term treatment of IBS-C in women.

A MAA submitted via the Centralised Procedure was rejected in December 2005. This decision was confirmed by a Committee for Medicinal Products for Human Use majority decision on re-examination in March 2006. Lubiprostone (Amitiza®), a prostanoid that activates the ClC-2 It is not approved anywhere in the EU. Thus, there are no products specifically approved for the treatment of IBS-C in the EU.

Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity:

Symptoms experienced by patients with IBS fluctuate over time. Over short periods of time, as some patients experience resolution of symptoms, others develop new ones, meaning the prevalence of symptomatic IBS remains stable over 1–2 years follow-up. In the first 3 months following diagnosis, patients experience four distinct episodes of symptoms per month on average. The longest of these episodes lasts around 5 days, and most patients experience symptoms on more than half of the days. However, 1 year after initial diagnosis 30%–45% of patients will have prolonged periods that are symptom free, potentially in remission. After 10 years, 50%–70% of patients report persistent symptoms. In patients who do report IBS symptom resolution, 45% will subsequently experience other functional GI symptoms. Up to two-thirds of IBS patients experience functional dyspepsia, the prevalence of which in patients with IBS is up to seven times higher than in controls.

If all GI symptoms resolve, then many develop symptoms of other functional diseases. Those with lower QOL and higher levels of anxiety are more likely to suffer with other functional comorbid conditions (Canavan 2014).

IBS is not known to be associated with increased mortality (worldgastroenterology.org 2009). As a result, there is currently limited literature regarding IBS-specific mortality rates related to subtype.

Important co-morbidities:

Although little is known about factors influencing IBS, psychological and social factors seem to be significantly related with the development of the condition. Studies describing comorbidities in target population are shown in Table 2.

Table 2. Co-morbidity in Target Population

Indication/Target population	**Psychological Disorders such as depression, mood and anxiety disorders**
Prevalence in target population	30-94% (Whitehead 2002)
Main co-prescribed medicinal products	Antidepressants, antipsychotics and mood stabilizers
Indication/Target population	**Fibromyalgia**
Prevalence in target population	15-65% (Riedl 2008, Whitehead 2002)
Main co-prescribed medicinal products	Antidepressants, muscle relaxants, serotonin norepinephrine reuptake inhibitors (SNRIs), NSAIDs
Indication/Target population	**Chronic fatigue syndrome**
Prevalence in target population	14-20% (Riedl 2008, Whitehead 2002, Whitehead 2007)
Main co-prescribed medicinal products	SNRIs, central nervous system (CNS) stimulants
Indication/Target population	**Chronic pelvic pain**
Prevalence in target population	8.6% (overall) (Whitehead 2007), 35% (among women) (Riedl 2008, Whitehead 2002)
Main co-prescribed medicinal pro	Analgesics, muscle relaxants
Indication/Target population	**Faecal incontinence**
Prevalence in target population	1-21% (Whitehead 2002, Whitehead 2007)
Main co-prescribed medicinal products	Fibre products, anti-diarrhoeal agents
Indication/Target population	**Headache/migraine**
Prevalence in target population	23-45% (Hillilä 2007, Riedl 2008, Whitehead 2002, Whitehead 2007)
Main co-prescribed medicinal products	Analgesics, anti-migraine agents, NSAIDs, muscle relaxants
Indication/Target population	**Back pain**
Prevalence in target population	27-81% (Hillilä 2007, Riedl 2008, Whitehead 2002, Whitehead 2007)
Main co-prescribed medicinal products	NSAIDs, analgesics

Indication/Target population	**Dyspepsia**
Prevalence in target population	17-87% (Whitehead 2002, Whitehead 2007)
Main co-prescribed medicinal products	Antacids, histamine H_2 antagonists, proton pump inhibitors (PPIs)
Indication/Target population	**Acid reflux**
Prevalence in target population	19-47% estimates (Riedl 2008, Whitehead 2002, Whitehead 2007)
Main co-prescribed medicinal products	Antacids, H_2 antagonists, PPIs
Indication/Target population	**Gallstone disorders (GD)**
Incidence in target population	24 cases/354 GD-free female subjects followed for 7.8 ± 1.0 years; 9 cases/241 GD-free male subjects followed for 7.8 ± 1.0 years (Corazziari 2008)
Prevalence in target population	33% in females; 7% in males (Corazziari 2008)
Main co-prescribed medicinal products	Gallstone solubilising agents
Indication/Target population	**Diverticular disease**
Prevalence in target population	5% (Whitehead 2007)
Main co-prescribed medicinal products	Stool softeners, pain medications
Indication/Target population	**Suicidal Behaviour and Ideations**
Prevalence of condition	4-38% (Miller 2004)
Main co-prescribed medicinal products	Antidepressants, antipsychotics and mood stabilizers

Module SII Non-Clinical Part of the Safety Specification

Key Safety Findings (from Non-Clinical Studies)	**Relevance To Human Usage**
Toxicity	
Single and repeat dose toxicity • Orally and intravenously administered linaclotide given as repeated daily doses was, in general, well tolerated across all species (tests conducted in mice [up to 26 weeks], rats [up to 13 weeks], and monkeys [up to 39 weeks]), with the primary effects observed related to reversible stool consistency changes in monkeys (at a dose level of 15 mg/kg/day,	Linaclotide has the potential to cause diarrhoea in humans due its pharmacological action of increasing fluid secretion and accelerating intestinal transit time. Diarrhoea will be considered **Important Identified Risk**. Immune related microscopic findings were not observed unless there was a general debilitation and a stress response in moribund animals; therefore, the findings were not considered to be directly

intravenous) and consistent with the pharmacological effects of linaclotide expected at high doses. • In monkeys, diarrhoea was observed at high dose levels in single dose administration. In repeated dose studies, diarrhoea was observed at all dose levels, although these were reversible findings. • Linaclotide-related microscopic findings in the GI tract were observed in monkeys (caecum, colon and rectum) and mice (stomach and caecum) at dose levels that produced mortality. None of the linaclotide-related microscopic findings (affecting GI tract, heart, kidney, and lymphoid system) observed in the 13-week study in mice were observed in the 26-week study. Although dose levels were higher in the 13-week study, mortality was produced at the high dose levels in both studies. Additionally, these microscopic findings were not observed in the 2-year carcinogenicity studies in rodents. There were no adverse effects of intravenous linaclotide on CV or respiratory parameters in a study using dogs.	related to linaclotide administration and are unlikely to be of relevance to human use.
Reproductive toxicity • Reproductive toxicology studies conducted in male and female rats demonstrated that linaclotide had no effects on fertility or reproductive performance. A developmental toxicology study conducted in mice demonstrated no adverse maternal or foetal effects at a dose of 5 mg/kg/day of linaclotide (1,000-fold greater than the highest clinical dose in Phase 3 trials). At higher dose levels (40-100 mg/kg/day) that were 8000- to 20,000-fold the highest clinical dose in Phase 3 trials maternal mortality and lower mean body weight	Direct toxicity to the foetus is not expected due to the low systemic bioavailability of linaclotide and its metabolites. However, as with any drug, the benefit to the mother compared with the risk to the child should always be considered if linaclotide will be used in pregnant or lactating women. Use in pregnancy will be considered **Missing information**.

gains were observed at doses ≥ 40 mg/kg/day (between 8,000 and 20,000-hold the highest clinical dose in Phase 3 trials). Reduced foetal weights, reduced gravid uterine weights, and effects on foetal morphology were observed at maternally toxic doses ≥ 40 mg/kg/day. Additional developmental toxicology studies conducted in rats and rabbits demonstrated no maternal toxicity or effects on embryo-foetal development at doses of up to 100 mg/kg/day (rat) or 40 mg/kg/day (rabbit). In a pre- and postnatal development study in the rat, the administration of linaclotide at doses of up to 100 mg/kg/day was not associated with any maternal toxicity and there was no evidence of any toxic effects on the development of pups and their survival, behaviour, and reproductive performance.	
Juvenile Animal Studies • Studies in juvenile mice revealed that younger animals were more sensitive to linaclotide-related mortality. In the 9-week repeated-dose oral toxicity study in juvenile mice initiated on Day 7 post-partum, there was an increase in mortality after administration of 1 or 2 doses of linaclotide at 10 µg/kg/day to Day 9 post-partum. However, the 10 µg/kg/day dose level was well tolerated after Day 9 post-partum for the remaining treatment period in surviving juvenile mice, with no linaclotide-related adverse effects or microscopic findings and no effects on the physical development or neurobehavioral assessments. Based on the mortality observed, the No-Observed Adverse Effect Level (NOAEL) was determined to be 3 µg/kg/day in juvenile mice	Based on these nonclinical data, very young paediatric patients may be sensitive to the effects of orally administered linaclotide and the sensitivity may decrease with age. However, as linaclotide is not currently indicated for use in children and adolescents, this is not expected to be of relevance, but has to be taken into consideration in the event of off-label paediatric use. Study MCP-103-311 (postmarket requirement (PMR) 2825-1) was conducted to measure GC-C messenger ribonucleic acid (mRNA) levels in duodenal and colonic mucosal tissue samples obtained from children 0 to < 18 years of age undergoing indicated endoscopy or colonoscopy. Four age groups were evaluated – Birth to < 24 months, 24 months to < 6 years, 6 Years to < 12 Years, and 12 Years to < 18 Years. The key findings from this study were that GC-C mRNA expression was greater in duodenum tissue samples compared with colonic tissue samples. Within each GI region evaluated, there was limited variation in GC-C mRNA levels across the 4 age groups measured. Mean expression

administered linaclotide orally once daily for 9 weeks. The increased sensitivity of juvenile mice to linaclotide may be related to the increased expression of intestinal GC-C receptors in young animals, (Al-Majali 1999, Cohen 1986) or possibly other factors such as those related to an immature GI system (Heller 1951, Walthall 2005). • The Sponsor considered that the deaths observed after linaclotide administration in neonatal mice were likely the consequence of GC-C agonist pharmacology, specifically from the significant fluid secretion into the immature intestines of neonatal mice leading to severe dehydration. • In order to test the hypothesis and fulfil the FDA Commitment 1915-1, additional studies in juvenile animals were conducted to explore the mechanism of mortality in neonatal mice and to assess the tolerability in 4 weeks old mice treated with linaclotide by oral route for 7 days. The following studies have been completed and summary of results is provided below: • The objective of Study MDP-103-089-PHR-01 was to determine the mechanism of linaclotide induced mortality in neonatal mice on Day 7 post-partum and to test the hypothesis that the mortality observed in linaclotide-treated neonatal mice is a consequence of GC-C activation by linaclotide which stimulates a significant fluid shift from the systemic circulation into the intestine leading to dehydration in neonatal mice known to have functionally immature intestinal tracts, higher GC-C agonist affinity, and higher sensitivity to the effects of GC-C agonism (Al-Majali 1999, Dean 1972, Pácha 2000). The results from	levels in duodenal tissue samples ranged from 2.21 to 2.46 across age groups and were 2.36 overall. Mean expression levels in colonic tissue samples ranged from 1.27 to 1.91 across age groups (excluding the birth to < 24-months age group which includes only two samples) and were 1.56 overall (based on all colonic samples collected). A linear piecewise regression model employed to assess the relationship between expression levels and age showed no trend toward an increase or decrease in GC-C mRNA levels based on age in either duodenal or colonic samples.

this study demonstrate that linaclotide administered at 20 μg/kg to neonatal mice on Day 7 post-partum produces a significant fluid shift from the intravascular compartment into the intestines (as evidenced by diarrhoea, an increase in gut/carcass ratio, intestinal fluid volume, pH and osmolality) resulting in a rapid and severe dehydration (as measured by elevation of haematocrit and total plasma protein) which precedes mortality. The administration of supplemental fluids (0.45% sodium chloride in water) completely prevented mortality in linaclotide-treated neonatal mice, without affecting the pharmacological effect (i.e., diarrhoea) related to GC-C agonism. • The objective of Study MNP-103-078-TXR-01 was to determine the effect of the administration of supplemental fluid on survival after a single oral gavage dose of linaclotide, which produces mortality in neonatal mice and to confirm the observations in MDP-103-089-PHR-01 in a good laboratory practice (GLP) compliant study. This study confirmed that the administration of supplemental fluids (0.45% NaCl in water) prevented mortality and resulted in 100% survival of 7-day-old mice administered linaclotide at 20 μg/kg. • The objective of Study MNP-103-074-TXR-01 was to determine the tolerability of linaclotide when given by daily oral gavage to 4-week-old juvenile mice for 7 days starting on Day 28 followed by a 7-day recovery period. This study demonstrated that linaclotide administered daily for 7 days to 4-week-old juvenile mice was well tolerated at doses up to 1.0 mg/kg/day, 200-fold higher than	

the maximum approved therapeutic adult dose of linaclotide (5 μg/kg). • In summary, the cause for deaths observed in neonatal mice treated with linaclotide is dehydration, a consequence of GC-C agonist pharmacology in these immature animals, and involving significant fluid shifts from the vascular compartment into the intestine. The administration of supplemental fluids completely prevented mortality thereby confirming that deaths were due to severe dehydration in linaclotide-treated mice. During the first few weeks of life in mice as intestinal function develops and GC-C agonist affinity and expression decreases, the tolerability to linaclotide increases markedly. • Notwithstanding the observations in the toxicology studies, the Sponsor does not believe that there is a risk of death from severe dehydration in human infants as observed in neonatal mice treated with linaclotide. It is well documented in the scientific literature (Montgomery 1999, Pácha 2000) that neonatal mice have immature (both structurally and functionally) GI tracts, equivalent to mid-gestational human foetuses and this makes them highly susceptible to life threatening dehydration.	
Nephrotoxicity/Hepatotoxicity • In vitro studies indicate that the primary clearance mechanism for linaclotide is rapid digestion in the GI tract.	Changes in hepatic or renal function in patients would not be expected to alter linaclotide metabolism or clearance. Although linaclotide has not been studied in patients with renal and hepatic impairment, it is rarely detectable in the plasma and, therefore, renal and hepatic impairment would not be expected to affect the metabolism or clearance of the parent drug or its metabolite.

Carcinogenicity & Genotoxicity • In 2-year carcinogenicity studies, linaclotide, administered at doses of up to 3,500 µg/kg/day (rats) and 6,000 µg/kg/day (mice), did not produce any evidence of carcinogenicity. The results from in vitro bacterial reverse mutation (Ames Assay) and human lymphocyte chromosomal aberrations assays indicated that linaclotide is not mutagenic, genotoxic or clastogenic.	No safety concern relevant to human use has arisen from these non-clinical data.
Pharmacology Studies • The PK of linaclotide could not be evaluated in humans due to extremely low plasma concentrations at clinical doses.	Bioanalytical measurements were conducted in a total of seven studies, including enrolled healthy volunteers (Studies MCP-103-001, MCP-103-002, and MCP-103-103), patients with IBS-C (Studies MCP-103-302 and LIN MD-31), and patients with CIC (Studies LIN-MD-01 and MCP-103-303). Generally, neither linaclotide nor its metabolite was detectable in human plasma at the proposed commercial doses of linaclotide. Of the 465 linaclotide-dosed patients whose plasma was analysed, only two had quantifiable concentrations of linaclotide (< 0.5 ng/mL). When the highest proposed commercial dose was increased 10 fold, concentrations of linaclotide were quantifiable in only two of 18 subjects and remained below 1 ng/mL in each case (Study MCP-103-103-CSR-01). The active metabolite was not detected in any of the plasma study samples. Systemic exposure to linaclotide remained undetectable in > 99% of linaclotide-dosed subjects and patients whose plasma was analysed. Although no definitive conclusions can be drawn given the lack of quantifiable drug concentrations in the plasma, age, gender, and race factors are not expected to affect the PK of linaclotide. Based on the low concentrations of linaclotide and MM-419447 in systemic circulation following oral dosing in clinical studies, specific clinical investigations to assess the effects of renal or hepatic impairment on the PK of linaclotide would not be informative and were, therefore, not conducted. Furthermore, in vitro studies indicate that the primary clearance mechanism for linaclotide is rapid digestion in the

	GI tract and, thus, changes in hepatic or renal function in patients would not be expected to alter linaclotide metabolism or clearance.
General Safety Pharmacology	
Cardiovascular • None	Not applicable
Mechanisms for drug interactions • In vivo drug-drug interaction studies were not conducted with linaclotide due to the generally undetectable concentrations of linaclotide in human plasma at the therapeutic dose levels and the observed lack of interaction of linaclotide with cytochrome P450 enzymes, which is typical of peptides. Despite the low probability of drug-drug interactions, the potential for linaclotide and its primary metabolite to inhibit a series of efflux and uptake transporters was tested in vitro. Additionally, the in vitro inhibition and induction potential of linaclotide and its primary active metabolite, MM-419447 (des-tyrosine), were determined for several drug-metabolizing P450 enzymes. The results of these studies indicate that linaclotide and MM-419447 do not inhibit common intestinal, liver, or kidney transporters at clinically relevant concentrations. Furthermore, neither linaclotide nor MM-419447 was an inhibitor or inducer of the tested P450 enzymes.	No potential for drug-drug interactions in humans
Other toxicity-related information or data • None	

Non-Clinical Safety Findings that are Included as Safety Concerns

Safety Concerns	
Important identified risks	Diarrhoea
Important potential risks	None
Missing information	Use in pregnancy

Based on the above it is evaluated that there are no safety issues that should warrant additional non-clinical studies.

Module SIII Clinical Trial Exposure

The following account of clinical trial exposure reflects exposure as stated in RMP Version 7.1 of 29 August 2016.

Table 3. Duration of Exposure: IBS-C

	Double Blind Studies						LTSS			TOTAL
	72 µg	97 µg	145 µg	290 µg	> 290 µg	LIN total	145 µg	290 µg	LIN total	LIN total
	(n = 79)	(N = 12)	(N = 82)	(N = 1223)	(N = 100)	(N = 1496)	(N = 656)	(N = 2141)	(N = 2147)	(N = 2753)
Treatment duration	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	72 (91.1)	0	75 (91.5)	855 (69.9)	78 (78.0)	1080 (72.2)	545 (83.1)	1703 (79.5)	1977 (92.1)	2440 (88.6)
≥ 3 months (≥ 90 days)	5 (6.3)	0	2 (2.4)	487 (39.8)	6 (6.0)	500 (33.4)	427 (65.1)	1443 (67.4)	1762 (82.1)	1916 (69.6)
≥ 6 months (≥ 180 days)	0	0	0	272 (22.2)	0	272 (18.2)	341 (52.0)	1235 (57.7)	1553 (72.3)	1670 (60.7)
≥ 12 months (≥ 360 days)	0	0	0	0	0	0	231 (35.2)	979 (45.7)	1278 (59.5)	1330 (48.3)
Patient-year of exposure	16.3	0.2	17.0	300.8	17.9	352.1	446.3	1709.0	2155.3	2507.4

Linaclotide-treated patients from IBS-C studies (LIN-MD-31, MCP-103-005, MCP-103-202, MCP-103-302), and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Total = Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

Table 4. Duration of Exposure: CIC

	Double Blind Studies						LTSS			TOTAL
	72 µg	97 µg	145 µg	290 µg	> 290 µg	LIN total	145 µg	290 µg	LIN total	LIN total
	(N = 469)	(N = 12)	(N = 1050)	(N = 830)	(N = 73)	(N = 2434)	(N = 318)	(N = 1123)	(N = 1129)	(N = 2762)
Treatment duration	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	400 (85.3)	0	933 (88.9)	568 (68.4)	6 (8.2)	1907 (78.3)	276 (86.8)	924 (82.3)	1064 (94.2)	2397 (86.8)
≥ 3 months (≥ 90 days)	28 (6.0)	0	133 (12.7)	105 (12.7)	0	266 (10.9)	220 (69.2)	798 (71.1)	952 (84.3)	1135 (41.1)
≥ 6 months (≥ 180 days)	0	0	0	0	0	0	171 (53.8)	694 (61.8)	850 (75.3)	907 (32.9)
≥ 12 months (≥ 360 days)	0	0	0	0	0	0	118 (37.1)	566 (50.4)	720 (63.8)	750 (27.2)
Patient-year of exposure	94.5	0.4	221.7	145.5	4.8	466.9	228.8	946.1	1174.9	1641.8

Linaclotide-treated patients from CIC studies (LIN-MD-01, LIN-MD-04, MCP-103-004, MCP-103-201, MCP-103-303, MCP-103-309) and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Total = Double-Blind + LTSS patients; patients enrolled in >1 Group 4 study are counted once across indications, as well as aggregate counts.

Table 5. Duration of Exposure (Totals)

	Double Blind Studies						LTSS			TOTAL
	72 µg	97 µg	145 µg	290 µg	> 290 µg	LIN total	145 µg	290 µg	LIN total	LIN total
	(N = 548)	(N = 24)	(N = 1132)	(N = 2049)	(N = 172)	(N = 3925)	(N = 974)	(N = 3259)	(N = 3271)	(N = 5505)
Treatment duration, n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	472 (86.1)	0	1008 (89.0)	1421 (69.4)	83 (48.3)	2984 (76.0)	821 (84.3)	2622 (80.5)	3036 (92.8)	4828 (87.7)
≥ 3 months (≥ 90 days)	33 (6.0)	0	135 (11.9)	590 (28.8)	6 (3.5)	764 (19.5)	647 (66.4)	2236 (68.6)	2709 (82.8)	3044 (55.3)
≥ 6 months (≥ 180 days)	0	0	0	271 (13.2)	0	271 (6.9)	512 (52.6)	1927 (59.1)	2401 (73.4)	2573 (46.7)
≥ 12 months (≥ 360 days)	0	0	0	0	0	0	349 (35.8)	1545 (47.4)	1998 (61.1)	2080 (37.8)
Patient-year of exposure	110.8	0.6	238.8	445.4	22.4	817.9	675.1	2652.7	3327.8	4144.9

Linaclotide-treated patients from CIC studies (LIN-MD-01, LIN-MD-04, MCP-103-004, MCP-103-201, MCP-103-303, MCP-103-309), IBS-C studies (LIN-MD-31, MCP-103-005, MCP-103-202, MCP-103-302), and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Total = Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

Table 6. By Dose: IBS-C

Indication: IBS-C			
	72 µg	**145 µg**	**290 µg**
	(N = 79)	**(N = 730)**	**(N = 2551)**
Treatment duration	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	72 (91.1)	612 (83.8)	2101 (82.4)
≥ 3 months (≥ 90 days)	5 (6.3)	429 (58.8)	1637 (64.2)
≥ 6 months (≥ 180 days)	0	341 (46.7)	1381 (54.1)
≥ 12 months (≥ 360 days)	0	231 (31.6)	1030 (40.4)
Patient-year of exposure	16.3	463.3	2009.8

Linaclotide-treated patients from IBS-C studies (LIN-MD-31, MCP-103-005, MCP-103-202, MCP-103-302), and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Includes Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

Table 7. By Dose: CIC

Indication: CIC			
	72 µg	**145 µg**	**290 µg**
	(N = 469)	**(N = 1286)**	**(N = 1508)**
Treatment duration	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	400 (85.3)	1139 (88.6)	1263 (83.8)
≥ 3 months (≥ 90 days)	28 (6.0)	350 (27.2)	894 (59.3)
≥ 6 months (≥ 180 days)	0	182 (14.2)	727 (48.2)
≥ 12 months (≥ 360 days)	0	128 (10.0)	577 (38.3)
Patient-year of exposure	94.5	450.5	1091.6

Linaclotide-treated patients from CIC studies (LIN-MD-01, LIN-MD-04, MCP-103-004, MCP-103-201, MCP-103-303, MCP-103-309) and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Includes Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

Table 8. By Dose: Totals

Totals			
	72 µg	**145 µg**	**290 µg**
	(N = 548)	**(N = 2016)**	**(N = 4050)**
Treatment duration	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	472 (86.1)	1751 (86.9)	3356 (82.9)
≥ 3 months (≥ 90 days)	33 (6.0)	779 (38.6)	2524 (62.3)
≥ 6 months (≥ 180 days)	0	523 (25.9)	2104 (52.0)
≥ 12 months (≥ 360 days)	0	359 (17.8)	1607 (39.7)
Patient-year of exposure	110.8	913.8	3097.3

Linaclotide-treated patients from CIC studies (LIN-MD-01, LIN-MD-04, MCP-103-004, MCP-103-201, MCP-103-303, MCP-103-309), IBS-C studies (LIN-MD-31, MCP-103-005, MCP-103-202, MCP-103-302), and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Includes Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

Table 9. By Age Group and Gender: IBS-C/Male

Indication: IBS-C Sex: Male				
	< 65 years	**65 ≤ Age < 75**	**Age ≥ 75**	**Total**
	(N = 194)	**(N = 28)**	**(N = 21)**	**(N = 243)**
Treatment duration	n (%)	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	168 (86.6)	25 (89.3)	17 (81.0)	210 (86.4)
≥ 3 months (≥ 90 days)	135 (69.6)	19 (67.9)	12 (57.1)	166 (68.3)
≥ 6 months (≥ 180 days)	119 (61.3)	17 (60.7)	12 (57.1)	148 (60.9)
≥ 12 months (≥ 360 days)	89 (45.9)	13 (46.4)	9 (42.9)	111 (45.7)
Patient-year of exposure	170.7	24.6	16.7	212.0

Linaclotide-treated patients from IBS-C studies (LIN-MD-31, MCP-103-005, MCP-103-202, MCP-103-302), and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Includes Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

Table 10. By Age Group and Gender: IBS-C/Female

Indication: IBS-C Sex: Female				
	< 65 years	**65 ≤ Age < 75**	**Age ≥ 75**	**Total**
	(N = 2364)	**(N = 118)**	**(N = 28)**	**(N = 2510)**
Treatment duration	n (%)	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	2098 (88.7)	105 (89.0)	27 (96.4)	2230 (88.8)
≥ 3 months (≥ 90 days)	1649 (69.8)	78 (66.1)	23 (82.1)	1750 (69.7)
≥ 6 months (≥ 180 days)	1431 (60.5)	71 (60.2)	20 (71.4)	1522 (60.6)
≥ 12 months (≥ 360 days)	1150 (48.6)	59 (50.0)	10 (35.7)	1219 (48.6)
Patient-year of exposure	2166.0	105.8	23.7	2295.5

Linaclotide-treated patients from IBS-C studies (LIN-MD-31, MCP-103-005, MCP-103-202, MCP-103-302), and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Includes Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

Table 11. By Age Group and Gender: CIC/Male

Indication: CIC Sex: Male				
	< 65 years	**65 ≤ Age < 75**	**Age ≥ 75**	**Total**
	(N = 314)	**(N = 63)**	**(N = 30)**	**(N = 407)**
Treatment duration	n (%)	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	283 (90.1)	55 (87.3)	24 (80.0)	362 (88.9)
≥ 3 months (≥ 90 days)	105 (33.4)	28 (44.4)	7 (23.3)	140 (34.4)
≥ 6 months (≥ 180 days)	80 (25.5)	20 (31.7)	7 (23.3)	107 (26.3)
≥ 12 months (≥ 360 days)	75 (23.9)	18 (28.6)	7 (23.3)	100 (24.6)
Patient-year of exposure	168.7	38.6	15.1	222.4

Linaclotide-treated patients from CIC studies (LIN-MD-01, LIN-MD-04, MCP-103-004, MCP-103-201, MCP-103-303, MCP-103-309) and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Includes Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

Table 12. By Age Group and Gender: CIC/Female

Indication: CIC Sex: Female				
	< 65 years	**65 ≤ Age < 75**	**Age ≥ 75**	**Total**
	(N = 2149)	**(N = 172)**	**(N = 34)**	**(N = 2355)**
Treatment duration	n (%)	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	1864 (86.7)	141 (82.0)	30 (88.2)	2035 (86.4)
≥ 3 months (≥ 90 days)	909 (42.3)	67 (39.0)	19 (55.9)	995 (42.3)
≥ 6 months (≥ 180 days)	736 (34.2)	51 (29.7)	13 (38.2)	800 (34.0)
≥ 12 months (≥ 360 days)	596 (27.7)	43 (25.0)	11 (32.4)	650 (27.6)
Patient-year of exposure	1299.8	95.6	23.9	1419.4

Linaclotide-treated patients from CIC studies (LIN-MD-01, LIN-MD-04, MCP-103-004, MCP-103-201, MCP-103-303, MCP-103-309) and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Includes Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

Table 13. By Age Group and Gender: Totals Male

Totals Sex: Male				
	< 65 years	**65 ≤ Age < 75**	**Age ≥ 75**	**Total**
	(N = 506)	**(N = 91)**	**(N = 51)**	**(N = 648)**
Treatment duration	n (%)	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	449 (88.7)	80 (87.9)	41 (80.4)	570 (88.0)
≥ 3 months (≥ 90 days)	238 (47.0)	47 (51.6)	19 (37.3)	304 (46.9)
≥ 6 months (≥ 180 days)	198 (39.1)	37 (40.7)	19 (37.3)	254 (39.2)
≥ 12 months (≥ 3 60 days)	164 (32.4)	31 (34.1)	16 (31.4)	211 (32.6)
Patient-year of exposure	338.5	63.2	31.8	433.5

Linaclotide-treated patients from CIC studies (LIN-MD-01, LIN-MD-04, MCP-103-004, MCP-103-201, MCP-103-303, MCP-103-309), IBS-C studies (LIN-MD-31, MCP-103-005, MCP-103-202, MCP-103-302), and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Includes Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

Table 14. By Age Group and Gender: Totals Female

Totals Sex: Female				
	< 65 years	**65 ≤ Age < 75**	**Age ≥ 75**	**Total**
	(N = 4505)	**(N = 290)**	**(N = 62)**	**(N = 4857)**
Treatment duration	n (%)	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	3955 (87.8)	246 (84.8)	57 (91.9)	4258 (87.7)
≥ 3 months (≥ 90 days)	2553 (56.7)	145 (50.0)	42 (67.7)	2740 (56.4)
≥ 6 months (≥ 180 days)	2164 (48.0)	122 (42.1)	33 (53.2)	2319 (47.7)
≥ 12 months (≥ 360 days)	1746 (38.8)	102 (35.2)	21 (33.9)	1869 (38.5)
Patient-year of exposure	3462.3	201.4	47.6	3711.3

Linaclotide-treated patients from CIC studies (LIN-MD-01, LIN-MD-04, MCP-103-004, MCP-103-201, MCP-103-303, MCP-103-309), IBS-C studies (LIN-MD-31, MCP-103-005, MCP-103-202, MCP-103-302), and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Includes Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

Table 15. By Ethnic or Racial Origin: IBS-C

Indication: IBS-C			
	White	**All Other Races**	**Total**
	(N = 2139)	**(N = 614)**	**(N = 2753)**
Treatment duration	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	1886 (88.2)	554 (90.2)	2440 (88.6)
≥ 3 months (≥ 90 days)	1482 (69.3)	434 (70.7)	1916 (69.6)
≥ 6 months (≥ 180 days)	1297 (60.6)	373 (60.7)	1670 (60.7)
≥ 12 months (≥ 360 days)	1047 (48.9)	283 (46.1)	1330 (48.3)
Patient-year of exposure	1963.5	543.9	2507.4

Linaclotide-treated patients from IBS-C studies (LIN-MD-31, MCP-103-005, MCP-103-202, MCP-103-302), and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Includes Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

Table 16. By Ethnic or Racial Origin: CIC

Indication: CIC			
	White	**All Other Races**	**Total**
	(N = 2050)	**(N = 711)**	**(N = 2761)**
Treatment duration	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	1759 (85.8)	638 (89.7)	2397 (86.8)
≥ 3 months (≥ 90 days)	853 (41.6)	282 (39.7)	1135 (41.1)
≥ 6 months (≥ 180 days)	688 (33.6)	219 (30.8)	907 (32.9)
≥ 12 months (≥ 360 days)	588 (28.7)	162 (22.8)	750 (27.2)
Patient-year of exposure	1248.9	392.8	1641.7

Linaclotide-treated patients from CIC studies (LIN-MD-01, LIN-MD-04, MCP-103-004, MCP-103-201, MCP-103-303, MCP-103-309) and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Includes Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

Table 17. By Ethnic or Racial Origin: Totals

Totals			
	White	**All Other Races**	**Total**
	(N = 4184)	**(N = 1320)**	**(N = 5504)**
Treatment duration	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	3640 (87.0)	1188 (90.0)	4828 (87.7)
≥ 3 months (≥ 90 days)	2332 (55.7)	712 (53.9)	3044 (55.3)
≥ 6 months (≥ 180 days)	1982 (47.4)	591 (44.8)	2573 (46.7)
≥ 12 months (≥ 360 days)	1635 (39.1)	445 (33.7)	2080 (37.8)
Patient-year of exposure	3210.0	934.8	4144.8

Linaclotide-treated patients from CIC studies (LIN-MD-01, LIN-MD-04, MCP-103-004, MCP-103-201, MCP-103-303, MCP-103-309), IBS-C studies (LIN-MD-31, MCP-103-005, MCP-103-202, MCP-103-302), and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Includes Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

Table 18. Special Populations: IBS-C

Indication: IBS-C				
	Renal Impairment	**Hepatic Impairment**	**Cardiac Impairment**	**Immuno-Compromised**
	(N = 23)	**(N = 127)**	**(N = 134)**	**(N = 111)**
Treatment duration	n (%)	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	19 (82.6)	119 (93.7)	121 (90.3)	100 (90.1)
≥ 3 months (≥ 90 days)	17 (73.9)	104 (81.9)	102 (76.1)	81 (73.0)
≥ 6 months (≥ 180 days)	15 (65.2)	94 (74.0)	94 (70.1)	74 (66.7)
≥ 12 months (≥ 360 days)	13 (56.5)	78 (61.4)	82 (61.2)	62 (55.9)
Patient-year of exposure	22.7	141.6	144.3	113.3

Linaclotide-treated patients from IBS-C studies (LIN-MD-31, MCP-103-005, MCP-103-202, MCP-103-302), and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Includes Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

No medical history information for patients in studies MCP-103-201, MCP-103-004, MCP-103-202, and MCP-103-005 who did not continue into studies LIN-MD-02 or MCP-103-305.

Table 19. Special Populations: CIC

Indication: CIC				
	Renal Impairment	**Hepatic Impairment**	**Cardiac Impairment**	**Immuno-Compromised**
	(N = 30)	**(N = 203)**	**(N = 218)**	**(N = 151)**
Treatment duration	n (%)	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	27 (90.0)	188 (92.6)	197 (90.4)	141 (93.4)
≥ 3 months (≥ 90 days)	11 (36.7)	68 (33.5)	117 (53.7)	72 (47.7)
≥ 6 months (≥ 180 days)	9 (30.0)	56 (27.6)	92 (42.2)	55 (36.4)
≥ 12 months (≥ 360 days)	8 (26.7)	51 (25.1)	76 (34.9)	49 (32.5)
Patient-year of exposure	18.2	113.6	156.2	103.8

Linaclotide-treated patients from CIC studies (LIN-MD-01, LIN-MD-04, MCP-103-004, MCP-103-201, MCP-103-303, MCP-103-309) and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Includes Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

No medical history information for patients in MCP-103-201, MCP-103-004, MCP-103-202, and MCP-103-005 who did not continue into LIN-MD-02 or MCP-103-305.

Table 20. Special Populations: Totals

Totals				
	Renal Impairment	**Hepatic Impairment**	**Cardiac Impairment**	**Immuno-Compromised**
	(N = 53)	**(N = 330)**	**(N = 352)**	**(N = 262)**
Treatment duration	n (%)	n (%)	n (%)	n (%)
≥ 1 month (≥ 30 days)	46 (86.8)	307 (93.0)	318 (90.3)	241 (92.0)
≥ 3 months (≥ 90 days)	28 (52.8)	172 (52.1)	219 (62.2)	153 (58.4)
≥ 6 months (≥ 180 days)	24 (45.3)	150 (45.5)	186 (52.8)	129 (49.2)
≥ 12 months (≥ 360 days)	21 (39.6)	129 (39.1)	158 (44.9)	111 (42.4)
Patient-year of exposure	40.8	255.1	300.6	217.1

Linaclotide-treated patients from CIC studies (LIN-MD-01, LIN-MD-04, MCP-103-004, MCP-103-201, MCP-103-303, MCP-103-309), IBS-C studies (LIN-MD-31, MCP-103-005, MCP-103-202, MCP-103-302), and LTSS studies (LIN-MD-02, MCP-103-305).

Includes linaclotide treatment periods only (including RW period).

Treatment duration (Treatment Period) = treatment end date - treatment start date + 1, within the Treatment Period.

Treatment duration (RW Period) = treatment end date - treatment start date + 1, within the RW Period.

Treatment duration (Double-Blind) = treatment duration (Treatment Period) + treatment duration (RW Period).

Treatment duration (LTSS) = treatment end date - treatment start date - number of days of temporary dosing suspension + 1, within the LTSS open-label Treatment Period.

Includes Double-Blind + LTSS patients; patients enrolled in > 1 Group 4 study are counted once across indications, as well as aggregate counts.

No medical history information for patients in studies MCP-103-201, MCP-103-004, MCP-103-202, and MCP-103-005 who did not continue into studies LIN-MD-02 or MCP-103-305.

Study ICP-103-307

A total of 417 patients were exposed to linaclotide of which the majority were < 65 years (95.9%), female (79.9%) and Asian (81.1%).

Table 21. Study 103-307 Demographics

Demographic characteristic	Linaclotide (n = 417)
Age group n (%)	
< 65 years	400 (95.9)
> 65 years	17 (4.1)
Sex n (%)	
Female	333 (79.9)
Male	84 (20.1)
Race n (%)	
Asian	338 (81.1)
Caucasian	64 (15.3)
Black/African American	15 (3.6)
Other	0

Study 0456-CL-1021

In this Phase 2 study, 302 Japanese patients were treated with linaclotide.

Study 0456-CL-0031

In this Phase 3 study, 250 Japanese patients were treated with linaclotide.

Phase 1 studies in healthy volunteers

In Phase 1 studies, 93 healthy volunteers were exposed to linaclotide.

In completed studies, as of 29 August 2016, a total of 6,057 patients (5,505+302+250) were exposed to linaclotide and 93 healthy volunteers. With the inclusion of ongoing studies in addition to completed studies, at 29 August 2016, 8,791 patients were exposed.

Module SIV Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Clinical Development Program

Criterion 1: Patients with known or suspected mechanical GI obstruction
Reason for exclusion: The use of linaclotide in patients with this condition can be harmful since linaclotide has no effect on constipation due to mechanical obstruction possibly due to serious conditions.
Is it considered to be included as missing information?: No
Rationale: Contraindication.

Criterion 2: Patient reports loose (mushy) or watery stools (BSFS score of 6 or 7) in the absence of any laxative, suppository, enema, or prohibited medicine for > 25% of bowel movements during the 12 weeks before the Screening Visit.
Reason for exclusion: Minimize potential harm to vulnerable subjects as BSFS score of 6 or 7 indicate patients tending towards diarrhea. Minimize potential impact on the efficacy and safety evaluation of the treatment.
Is it considered to be included as missing information?: No
Rationale: Diarrhea is an important identified risk.

Criterion 3: Patient has ever had a diagnosis of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, or any other form of familial colorectal cancer. Patient has a family history of familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer or other familial form of colorectal cancer.
Reason for exclusion: The reason to include these criteria in the protocol is to define the IBS-C population (exclude other diseases that may mimic the symptoms).
Is it considered to be included as missing information?: No
Rationale: Use in this population is not predicted to be associated with additional risks of clinical significance.

Criterion 4: Patient has ever had a diagnosis of IBD.
Reason for exclusion: The reason to include this criterion in the protocol is to define the IBS-C population (exclude other diseases that may mimic the symptoms).
Is it considered to be included as missing information?: No
Rationale: The SmPC states that linaclotide has not been studied in patients with chronic inflammatory conditions of the intestinal tract, such as Crohn's disease and ulcerative colitis and therefore it is not recommended for use in these patients.

Criterion 5: Patient currently has both unexplained and clinically significant alarm symptoms (lower GI bleeding [rectal bleeding or haem-positive stool], iron deficiency anaemia or any unexplained anaemia, or weight loss) or systemic signs of infection or colitis.
Reason for exclusion: These symptoms may suggest a more relevant underlying condition.
Is it considered to be included as missing information?: No
Rationale: Lower GI haemorrhage is an important identified risk

Criterion 6: Patient currently has active peptic ulcer disease (i.e., disease that is not adequately treated or stable with therapy).
Reason for exclusion: These symptoms may suggest a medically relevant underlying condition.
Is it considered to be included as missing information?: No
Rationale: Use in this population is not predicted to be associated with additional risks of clinical significance.

Criterion 7: Patient has a history of diverticulitis or a history of any chronic condition (e.g., chronic pancreatitis, polycystic kidney disease, ovarian cysts, endometriosis, or lactose intolerance).
Reason for exclusion: The reason to include these criteria in the protocol is to define the IBS-C population (exclude other disease that may mimic the symptoms).
Is it considered to be included as missing information?: No
Rationale: Use in this population is not predicted to be associated with additional risks of clinical significance.

Criterion 8: Patient has a potential central nervous system cause of constipation (e.g., Parkinson's disease, spinal cord injury, and multiple sclerosis.)
Reason for exclusion: The reason to include these criteria in the protocol is to define the IBS-C population (exclude other disease that may mimic the symptoms). Effects of linaclotide in these patients may mask other conditions that require different treatment.
Is it considered to be included as missing information?: No
Rationale: Use in this population is not predicted to be associated with additional risks of clinical significance.

Criterion 9: Patient has ever had any of the following diseases or conditions that can be associated with constipation: pseudo-obstruction, colon inertia, megacolon, megarectum, bowel obstruction, descending perineum syndrome, solitary rectal ulcer syndrome, or systemic sclerosis.
Reason for exclusion: Effects of linaclotide in these patients may mask other conditions that require different treatment.
Is it considered to be included as missing information?: No
Rationale: Use in this population is not predicted to be associated with additional risks of clinical significance.

Criterion 10: Patient has ever had a fecal impaction that required hospitalization or emergency room treatment, or has a history of cathartic colon, laxative or enema abuse, ischemic colitis, or pelvic floor dysfunction (unless successful treatment has been documented by a normal balloon expulsion test).
Reason for exclusion: For ethical reasons, these patients may be at high risk of experiencing adverse effects.
Is it considered to be included as missing information?: No
Rationale: Use in this population is not predicted to be associated with additional risks of clinical significance. Abuse/excessive use is considered an important potential risk.

Criterion 11: Patient has had surgery that meets any of the following criteria: **a) Bariatric surgery for treatment of obesity, or surgery to remove a segment of the GI tract at any time before the Screening Visit;** **b) Surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit;** **c) An appendectomy or cholecystectomy during the 60 days before the Screening Visit;** **Other major surgery during the 30 days before the Screening Visit.**
Reason for exclusion: For ethical reasons, to protect patients during development phase.
Is it considered to be included as missing information?: No
Rationale: Use in this population is not predicted to be associated with additional risks of clinical significance.

Criterion 12: Patient has a history of cancer other than treated basal cell or squamous cell carcinoma of the skin. (Note: Patients with a history of cancer are allowed provided that the malignancy has been in a complete remission for at least 5 years before the Randomization Visit. A complete remission is defined as the disappearance of all signs of cancer in response to treatment).
Reason for exclusion: For ethical reasons.
Is it considered to be included as missing information?: No
Rationale: Use in this population is not predicted to be associated with additional risks of clinical significance.

Criterion 13: Patient has a history of diabetic neuropathy.
Reason for exclusion: Neurological diseases such as diabetic neuropathy further increase the likelihood of orthostatic hypotension.
Is it considered to be included as missing information?: No
Rationale: Orthostatic hypotension (as a result of severe diarrhea) is a potential risk.

Criterion 14: Patient has been treated for hypothyroidism for which the dose of thyroid hormone has not been stable for at least 6 weeks at the time of the Screening Visit.
Reason for exclusion: To avoid confounding factors that can interfere on result interpretation.
Is it considered to be included as missing information?: No
Rationale: Use in this population is not predicted to be associated with additional risks of clinical significance.

Criterion 15: Patient has a recent history (during the 12 months before the Randomization Visit) of drug or alcohol abuse. (Note: Patients with a history of drug or alcohol abuse that was diagnosed greater than 12 months before the Randomization Visit may be enrolled as long as they have exhibited no actual abuse during the 12 months before the Randomization Visit).
Reason for exclusion: For ethical reasons, to protect patients with such conditions during development phase.
Is it considered to be included as missing information?: No
Rationale: Use in this population is not predicted to be associated with additional risks of clinical significance.

Criterion 16: Patient used Rescue Medicine (bisacodyl tablet or suppository) or any other laxative, suppository, or enema on the calendar day before or the calendar day of the start of the Treatment Period (i.e., before the Randomisation Visit).
Reason for exclusion: The medicine taken by the patients may interfere on result interpretation.
Is it considered to be included as missing information?: No
Rationale: These concomitant medications may increase the risk of diarrhea however, diarrhea is considered an important identified risk and alterations of electrolytes, dehydration and orthostatic hypotension (as a result of severe diarrhea) are considered important potential risks and hence safety data in patients receiving concomitant medications will not be considered as missing information.

Criterion 17: Patient reported using a Prohibited Medicine (excluding laxatives, suppositories, and enemas) during the Pre-treatment Period or is not willing or able to abide by the restrictions regarding use of Prohibited Medicines (Note: The use of fibre, bulk laxatives, or stool softeners [such as docusate] is acceptable provided the patient has been on a stable dose during the 30 days before the Screening Visit and plans to continue on a stable dose throughout the trial).
Reason for exclusion: The medicine taken by the patients may interfere on result interpretation.
Is it considered to be included as missing information?: No
Rationale: These concomitant medications may increase the risk of diarrhea however, diarrhea is considered an important identified risk and alterations of electrolytes, dehydration and orthostatic hypotension (as a result of severe diarrhea) are considered important potential risks and hence safety data in patients receiving concomitant medications will not be considered as missing information.

Criterion 18: Patient has been hospitalized for a psychiatric condition or has made a suicide attempt during the two years before the Randomization Visit.
Reason for exclusion: For ethical reasons, to protect patients with such conditions during development phase. These patients are not reliable due to their condition.
Is it considered to be included as missing information?: No
Rationale: Use in this population is not predicted to be associated with additional risks of clinical significance.

Criterion 19: Patient has received an investigational drug during the 30 days before the Screening Visit or is planning to receive an investigational drug (other than that administered during this trial) or use an investigational device at any time during the trial.
Reason for exclusion: Ethical reasons. Patient may still develop AEs related to the other investigational drug/device.
Is it considered to be included as missing information?: No
Rationale: Use in this population is not predicted to be associated with additional risks of clinical significance.

Criterion 20: Patient has an acute or chronic condition that, in the investigator's opinion, would limit the patient's ability to complete or participate in this clinical trial.
Reason for exclusion: For ethical reasons, to protect patients with such conditions during development phase.
Is it considered to be included as missing information?: No
Rationale: Use in this population is not predicted to be associated with additional risks of clinical significance but this needs to be assessed individually based on coexisting condition.

Criterion 21: Pregnancy
Reason for exclusion: Limited amount of data in humans.
Is it considered to be included as missing information?: Yes
Rationale: not applicable

SIV.2 Limitations to Detect Adverse Reactions in the Clinical Development Program

From the clinical development program, ADRs with a frequency greater than 1 in 2,019 would be detected if there were no background incidence.

A total of 2,080 patients completed 12 months of treatment with linaclotide. During this period, there were no specific events associated with prolonged exposure.

SIV.3 Limitations in Respect to Populations Typically Under Represented in Clinical Development Program

Table 22. Exposure of Special Populations Included or Not in the Clinical Development Program (as of 29 August 2016 RMP Version 7.1)

Type of special population	Exposure
Paediatric population	Not included in the clinical development programme described in module SIII. Paediatric studies are ongoing.
Elderly	Out of the 5,505 patients that were exposed to linaclotide in the completed studies described in Module SIII there were 494 patients (9%) that were 65 years of age or older; 113 (2%) were 75 years of age or older.
Pregnant women	A small number of pregnancies have been reported as of 29 August 2016 in linaclotide clinical trials and, conception during linaclotide exposure was not associated with any untoward outcomes in mother, pregnancy or offspring. However, the dataset is very limited and there are no specific, adequate and well-controlled studies of linaclotide use in pregnant women.
Breastfeeding women	Not included in the clinical development programme
Patients with hepatic impairment	Out of the 5,505 patients that were exposed to linaclotide in the completed studies described in Module SIII there were 330 patients with hepatic impairment (6%).
Patients with renal impairment	Out of the 5,505 patients that were exposed to linaclotide in the completed studies described in Module SIII there were 53 patients with renal impairment (1%).
Safety data in male patients	Out of the 5,505 patients that were exposed to linaclotide in the completed studies described in Module SIII there were 648 males (11.8%).
Patients or different racial and/or ethnic origin	Out of the 5,505 patients that were exposed to linaclotide in the completed studies described in Module SIII there 76% Caucasians.

Module SV Post-Authorization Experience

SV.1 Post-Authorization Exposure

SV.1.1 Method Used to Calculate Exposure

In the absence of an alternative data source, worldwide sales data has been used in the calculation of the postmarketing exposure below. The total number of capsules/tablets sold

divided by the number of days in a year gives the total number of patient-years. The formula used to calculate exposure is:

Estimated patient exposure (patient-years) = total number of capsules/365

Cumulative sales data is presented below, from launch until DLP of 29 August 2023.

SV.1.2 Exposure

Cumulatively since the International Birthdate until DLP of 29 August 2023, worldwide linaclotide exposure from marketing experience is estimated to be 5,382,092 patient-years.

Table 23. Cumulative Estimated Exposure from Marketing Experience for Linaclotide

Country (Dose)	New Cumulative Patient-years
US (72 µg)	
US (145 µg)	
US (290 µg)	
Austria	
Belgium	
Canada (72 µg)	
Canada (145 µg)	
Canada (290 µg)	
Denmark	
Finland	
Germany	
Iceland	
Italy	
Mexico	
Netherlands	
Norway	
Portugal	
Puerto Rico	
Spain	
Sweden	
Switzerland	
UK	
Vatican City	
China (Mainland)	
China (Hong Kong, Macau)	
Totals (ex-Japan)	
Japan[a]	
Overall Totals	**5,381,130**

a. Distributed as 250 µg tablets.

Note: Totals may not add up exactly due to rounding. Individual dose level provided where available.

Module SVI Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

The risk of dependence with linaclotide is extremely low due to the limited systemic bioavailability of the drug. Linaclotide is a novel product and first in its class, it is not structurally or pharmacologically related to any drug known to cause abuse or dependence. There have been no AEs during clinical development, or in animal studies, that are indicative of any abuse or dependence potential.

Potential for off-label use and abuse/excessive use is considered an Important Potential Risk.

Module SVII Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- GI disorders: Abdominal pain, Flatulence, Abdominal distension, Nausea, Vomiting
- Skin and subcutaneous disorders: Rash
- Metabolism and nutrition disorders: Decreased appetite
- Nervous system disorders: Dizziness

SVII.1.2 Risks/Missing Information Considered Important for Inclusion in the RMP

Important Identified Risks

Identified risk 1: Diarrhoea Reason for Inclusion: Diarrhoea was the most common ADR (19.8-33.4%). Although the rate of severe diarrhoea was low (1.9%), patients should be instructed to inform their physician if severe or prolonged diarrhoea occurs as it may result in severe outcomes (e.g., dehydration, electrolyte imbalance etc.) that will negatively impact the risk-benefit balance.
Identified risk 2: Lower GI haemorrhage Reason for Inclusion: Lower GI haemorrhage events were uncommon and most were mild to moderate. Patients should be instructed to inform their physician if lower GI bleeding occurs as severe cases might negatively impact the risk-benefit balance.

Important Potential Risks

Potential risk 1: Potential for off-label use and abuse/excessive use

Reason for Inclusion: There were no reports of off-label use and abuse/excessive use during clinical development as linaclotide is not a habit-forming drug. Similarly to other laxative abuse, off-label use and abuse/excessive use of linaclotide is likely to require medical treatment. This risk will be assessed from routine pharmacovigilance activities.

Potential risk 2: Alterations of electrolytes (as a result of severe diarrhoea)

Reason for Inclusion: Alterations of electrolytes (as a result of severe diarrhoea) events were uncommon and most were mild to moderate. Prolonged or severe diarrhoea may lead to a disturbance of water or electrolyte balance that could be more consequential in elderly, patients with CV diseases, diabetes, or hypertension. Limiting the risk of diarrhoea is required to minimise the risk of electrolytes disturbances in order to ensure an acceptable risk-benefit balance. The safety profile will be derived from routine pharmacovigilance activities and a post-authorisation safety study (PASS) (Study EVM-18888-00).

Potential risk 3: Dehydration (as a result of severe diarrhoea)

Reason for Inclusion: Dehydration (as a result of severe diarrhoea) events were uncommon and most of the cases were mild to moderate. Prolonged or severe diarrhoea may lead to dehydration. Limiting the risk of diarrhoea is required to minimise the risk of dehydration and to ensure an acceptable risk-benefit balance. The safety profile will be derived from routine pharmacovigilance activities and a PASS (Study EVM-18888-00).

Potential risk 4: Orthostatic hypotension (as a result of severe diarrhoea)

Reason for Inclusion: Orthostatic hypotension (as a result of severe diarrhoea) events were uncommon and most of the cases were mild to moderate. Prolonged or severe diarrhoea may lead to orthostatic hypotension. Limiting the risk of diarrhoea is required to minimise the risk of orthostatic hypotension and in order to ensure an acceptable risk-benefit balance. The safety profile will be derived from routine pharmacovigilance activities and a PASS (Study EVM-18888-00).

Potential risk 5: Viral gastroenteritis

Reason for Inclusion: Viral gastroenteritis events were common and most of the cases were mild to moderate. The safety profile will be derived from routine pharmacovigilance activities.

Missing information

Information 1: Safety data in pregnancy

Reason for Inclusion: Pregnant women were excluded from enrollment in the clinical development program. Throughout the clinical development program, a small number of pregnancies have been reported to date in linaclotide clinical trials. Conception during linaclotide exposure was not associated with any untoward outcomes in mother, pregnancy or offspring. However, the dataset is very limited and there are no specific, adequate and well-controlled studies of linaclotide use in pregnant women.

Data to be Collected Post-Authorization: The safety profile in pregnancy will be derived from routine pharmacovigilance activities.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk 1: Diarrhea

MedDRA Terms: PT: Diarrhoea, Diarrhoea haemorrhagic, Diarrhoea infectious, Antidiarrheal supportive care, Bacterial diarrhoea, Post procedural diarrhoea, Prophylaxis against diarrhoea, Viral diarrhoea.

Potential Mechanisms:

The mechanism of action is consistent with the pharmacology of linaclotide whereby increased intestinal fluid secretion and decreased intestinal transit time may result in diarrhoea in a subset of patients.

Evidence Source(s) and Strength of Evidence:

Linaclotide and the des tyrosine metabolite bind to and activate the GC-C receptor on the luminal surface of the intestinal epithelium. This activation causes secretion of chloride and bicarbonate into the intestinal lumen, resulting in increased fluid secretion and acceleration of intestinal transit. Clinical trials showed elevated incidence rate of diarrhoea compared to placebo. Diarrhoea is considered an important identified risk as severe diarrhoea for a prolonged duration can be a serious condition that if left untreated may lead to further complications and hospitalisation.

Characterization of the Risk:

Frequency

Phase 3 double-blind placebo-controlled studies (LIN-MD-31 and MCP-103-302)

Diarrhoea was the most common TEAE reported during Phase 3 linaclotide clinical trials:

	Linaclotide (N = 807) N (%)	**Placebo (N = 798) N (%)**
Diarrhoea	160 (19.8%)	24 (3.0%)
OR (95% CI)	7.96 (5.12, 12.38)	

There were no fatalities and no events of diarrhoea were reported as serious, or had serious clinical relevant consequences or manifestations.

In the phase 3 double-blind placebo-controlled trials, diarrhoea was the TEAE most commonly associated with withdrawal of treatment - 43 (5.3%) of linaclotide-treated IBS-C patients compared to 3 (0.40%) placebo.

LTSS (LIN-MD-02 and MCP-103-305)

	LIN-MD-02 (N = 1032) N (%)	**MCP-103-305 (N = 1119) N (%)**
Diarrhoea	345 (33.4)	358 (32.0)

There were no SAEs of diarrhoea.

ICP-103-307

Diarrhoea was reported by 39 patients (9.4%) in the linaclotide group and 5 patients (1.2%) in the placebo group. Diarrhoea was the most common AE leading to discontinuation of study drug in the linaclotide group, leading to the discontinuation of 3 patients (0.7%) in the linaclotide group and one patient (0.2%) in the placebo group.

There were no SAEs of diarrhoea.

0456-CL-0031

Randomised, double-blind, placebo-controlled phase

	Linaclotide (N = 249) n (%), #E	**Placebo (N = 251) n (%), #E**
Diarrhoea	24 (9.6%), 43	1 (0.4%), 1

Open-label extension phase

	Linaclotide (N = 164) n (%), #E	**Placebo (N = 160) n (%), #E**
Diarrhoea	22 (13.4%), 46	25 (15.6%), 51

There were no SAEs of diarrhoea.

0456-CL-1021

	Linaclotide 0.0625 mg (N = 82) n (%) #E	**Linaclotide 0.125 mg (N = 71) n (%) #E**	**Linaclotide 0.25 mg (N = 73) n (%) #E**	**Linaclotide 0.5 mg (N = 76) n (%) #E**	**Placebo (N = 80) n (%), #E**
Diarrhoea	6 (7.3%) 8	3 (4.2%) 3	6 (8.2%) 8	3 (3.9%) 3	0

There was one SAE of diarrhoea that was possibly related to study drug.

Postmarketing

Cumulatively until DLP, there have been 4,192 reports of diarrhoea of which 93 were serious.

Severity

Phase 3 double-blind placebo-controlled studies (LIN-MD-31 and MCP-103-302)

The severity of the reported diarrhoea varied from mild to severe, with the majority being mild to moderate.

In 15 patients (1.9%) treated with linaclotide, diarrhoea was severe and in 43 patients (5.3%) diarrhoea led to discontinuation of treatment.

Diarrhoea	**Linaclotide (N = 807) N (%)**	**Placebo (N = 798) N (%)**
Mild	70 (8.7%)	18 (2.3%)
Moderate	75 (9.3%)	5 (0.6%)
Severe	15 (1.9%)	1 (0.1%)
Discontinued due to diarrhoea	43 (5.3%)	3 (0.4%)

Of the 160 patients who reported diarrhoea with linaclotide, 45 (28.1%) experienced the onset of diarrhoea during the first day of the treatment.

Mean time to onset was 20.7 days (standard deviation (SD) 31.7) with a median of 7.5 days and a range of 1-175 days.

LTSS (LIN-MD-02 and MCP-103-305)

	LIN-MD-02 (N = 1032) N (%)	**MCP-103-305 (N = 1119) N (%)**
Mild	111 (10.8)	154 (13.8)
Moderate	211 (20.4)	162 (14.5)
Severe	23 (2.2)	42 (3.8)
Diarrhoea resulting in discontinuation	68 (6.6)	59 (5.3)

ICP-103-307

	Linaclotide (N = 416) N (%)	**Placebo (N = 419) N (%)**
Mild	21 (5.0)	4 (1.0)
Moderate	16 (3.8)	1 (0.2)
Severe	2 (0.5)	0
Diarrhoea resulting in discontinuation	3 (0.7)	1 (0.2)

0456-CL-0031

Randomised, double-blind, placebo-controlled phase

	Linaclotide (N = 249) n (%), #E	**Placebo (N = 251) n (%), #E**
Diarrhoea		
Mild	21 (8.4%), 40	0
Moderate	3 (1.2%), 3	1 (0.4%), 1

Open-label extension phase

	Linaclotide (N = 164) n (%), #E	**Placebo (N = 160) n (%), #E**
Diarrhoea		
Mild	18 (11.0%), 42	25 (15.6%), 51
Moderate	4 (2.4%), 4	0

0456-CL-1021

	Linaclotide 0.0625 mg (N = 82) n (%), #E	**Linaclotide 0.125 mg (N = 71) n (%), #E**	**Linaclotide 0.25 mg (N = 73) n (%), #E**	**Linaclotide 0.5 mg (N = 76) n (%), #E**	**Placebo (N = 80) n (%), #E**
Diarrhoea					
Mild	5 (6.1%), 6	2 (2.8%), 2	6 (8.2%), 8	3 (3.9%), 3	0
Moderate	1 (1.2%), 2	1 (1.4%), 1	0	0	0

Postmarketing

Severity was not reported in all cases.

Impact on quality of life

Depending on the severity of diarrhoea, the impact could range from discomfort to potentially serious condition that can require hospitalisation.

Risk Factors and Risk Groups:

Risk groups include those patients at risk of volume depletion or electrolyte disturbances following a diarrhea episode and patients more likely to experience clinical consequences of such changes:

- Elderly patients
- Patients with hypertension, diabetes and CV disease
- Patients with co-existing psychiatric/anxiety disorders (who may be considered less likely to be able to cope with the onset of sudden diarrhea)

Most IBS patients presenting in medical clinics and 18% of IBS patients in the community have 1 or more psychiatric disorders, (Whitehead 2002) with depression, panic disorder and anxiety disorder being more prevalent in IBS versus IBD population (Walker 1990).

It should be noted that no pattern of diarrhea leading to clinically relevant dehydration or electrolyte disturbances, or any other potentially serious adverse clinical sequelae was identified during Phase 3 linaclotide trials.

Risk factors that may increase the risk of diarrhea include:

- Co-administration with food
- Concomitant treatment with PPIs and laxatives
- IBS-C patients with only a mild constipation
- Patients with a tendency to switch between IBS-C subtypes
- Patients with infections
- Patients receiving cytostatic agents
- Patients with hypersensitivity (Nematode infestation, food allergy, milk protein hypersensitivity, eosinophilic gastroenteritis)
- Patients with autoimmune disorders (lymphoma, graft versus host disease, Crohn's disease, ulcerative colitis or proctitis)

Concomitant medications that may increase the risk of diarrhea: NSAIDs, simvastatin, ticlopidine, cimetidine, lansoprazole, gold (Aurolin), cyclosporine, methyldopa; and many others. Additional 'at risk populations:' Transitional IBS-C/IBS-D Patients.

In addition, 'at risk' patients should be considered as those with alternating or mixed IBS, (Longstreth 2006) in whom IBS-C may transition into IBS-D subtype. In this subtype of patients, onset of diarrhea may shift the patient into subtype IBS-D and these patients might need to be monitored by their healthcare provider.

Subdividing IBS based on the predominant symptom pattern is attempted commonly, but few data are available on IBS prevalence by symptom subgroup. Moreover, it is unclear if those with 1 predominant symptom – diarrhea or constipation – if followed long enough, eventually develop the other, i.e., constipation in patients with IBS-D or diarrhea in patients with IBS-C. Some data from primary care support this contention.

Definitions of IBS subgroups remain arbitrary, and different definitions have been used in different studies (Drossman 2006, Kruis 1984, Manning 1978). In a study of 317 patients recruited for a clinical trial, at baseline 36% had IBS-D, 34% had IBS-C, and 31% IBS-M (both diarrhea and constipation symptoms occurred); more than 75% switched type over a year of follow-up, usually to and from IBS M pattern, but less than a third changed from IBS-C to IBS-D or vice versa.

Preventability:

Patients should be aware of the possible occurrence of diarrhoea during treatment. They should be instructed to inform their physician if severe or prolonged diarrhoea. Should prolonged (e.g., more than 1 week) or severe diarrhoea occur, medical advice should be sought and temporary discontinuation of linaclotide until diarrhoea episode is resolved may be considered. Additional caution should be exercised in patients who are prone to a disturbance of water or electrolyte balance (e.g., elderly, patients with CV diseases, diabetes, hypertension), and electrolyte control should be considered.

Impact on the Risk-Benefit Balance of the Product: Pharmacovigilance activities will further characterise the risk of diarrhoea with respect to number of reports, seriousness, outcome, and risk factors. As of DLP of 29 August 2017, postmarketing data is consistent with the information already known for this risk. No additional intervention to manage the risk or allow for a reduction in the chance of the risk occurring is warranted at this stage. As of the DLP, the risk-benefit of linaclotide remains unchanged.
Public Health Impact: The prevalence of IBS-C in the EU is estimated to range from 0.5-11.1% thus the size of the target population is around 2.6-56.6 million assuming the EU population is 510 million. Diarrhoea is expected in 19.8-33.4% of the patients treated with linaclotide and therefore the number of affected individuals is expected to be 0.5-18.9 million patients.

Important Identified Risk 2: Lower GI haemorrhage **MedDRA Terms**: Modified GI haemorrhage standardised MedDRA queries (SMQ) includes the following PTs: Anal haemorrhage, Anal ulcer haemorrhage, Anastomotic ulcer haemorrhage, Anastomotic haemorrhage, Anorectal varices haemorrhage, Chronic GI bleeding, Colonic haematoma, Diarrhoea haemorrhagic, Diverticulitis intestinal haemorrhagic, Diverticulum intestinal haemorrhagic, Enterocolitis haemorrhagic, GI anastomotic leak, GI angiectasia, GI angiodysplasia haemorrhagic, GI haemorrhage, GI polyp haemorrhage, GI ulcer haemorrhage, Haematochezia, Haemorrhoidal haemorrhage, Intestinal haematoma, Intestinal haemorrhage, Intestinal varices haemorrhage, Intra-abdominal haematoma, Large intestinal haemorrhage, Large intestinal ulcer haemorrhage, Lower GI haemorrhage, Melaena, Melaena neonatal, Mesenteric haemorrhage, Neonatal GI haemorrhage, Occult blood positive, Proctitis haemorrhagic, Rectal haemorrhage, Rectal ulcer haemorrhage, Small intestinal haemorrhage, Small intestinal ulcer haemorrhage, Ulcer haemorrhage.
Potential Mechanisms: Increasing BMs may increase the mechanical load and shearing force on the lower gut wall by pressing stool through an already strained intestinal wall. Thereby small injury of the gut wall or the thin wall of haemorrhoid vessels may cause bleeding. Bleeding in constipated patients or patients with haemorrhoids is associated with BMs and defaecation procedure. By increasing BMs and frequency of defaecation, linaclotide increases the risk for bleeding.
Evidence Source(s) and Strength of Evidence: Linaclotide increase BMs and frequency of defaecation that may lead to lower GI bleeding. Clinical trials showed very modest elevated incidence rate of lower GI bleeding events compared to placebo. Lower GI haemorrhage is considered an important identified risk as mild cases may have an impact on the patient's QOL and moderate to severe cases may necessitate medical intervention.

Characterization of the Risk:

Frequency

Phase 3 double-blind placebo-controlled studies (Studies LIN-MD-31 and MCP-103-302)

	Linaclotide (N = 807) N (%)	**Placebo (N = 798) N (%)**
Rectal haemorrhage	2 (0.2)	3 (0.4%)
OR (95% CI)	0.66 (0.11, 3.95)	
Occult blood positive	0	1 (0.1)
Haemorrhoidal haemorrhage	2 (0.2)	1 (0.1)
OR (95% CI)	1.98 (0.18, 21.62)	
Haematochezia	1 (0.1)	0

There were no SAEs of lower GI haemorrhage.

LTSS (Studies LIN-MD-02 and MCP-103-305)

PT	**LIN-MD-02 (N = 1032) N (%)**	**MCP-103-305 (N = 1119) N (%)**
Rectal haemorrhage	6 (0.6)	9 (0.8%)
Haemorrhoidal haemorrhage	1 (< 0.1)	3 (0.3)
Haematochezia	7 (0.7)	3 (0.3)

There were no SAEs of lower GI haemorrhage.

Study ICP-103-307

PT	**Linaclotide (N = 416) n (%)**	**Placebo (N = 419) n (%)**
Haematochezia	2 (0.5)	1 (0.2)

There were no SAEs of lower GI haemorrhage.

Study 0456-CL-0031

Randomised, double-blind, placebo-controlled phase

PT	**Linaclotide (N =249) n (%), #E**	**Placebo (N = 251) n (%), #E**
Haematochezia	0	1 (0.4%), 1

OLE phase

PT	Linaclotide (N = 164) n (%), #E	Placebo (N = 160) n (%), #E
Haematochezia	0	1 (0.6%), 1
Anal haemorrhage	1 (0.6%), 1	0
Occult blood positive	0	1 (0.6%), 1

There were no SAEs of lower GI haemorrhage.

Study 0456-CL-1021

PT	Linaclotide 0.0625 mg (N = 82) n (%), #E	Linaclotide 0.125 mg (N = 71) n (%), #E	Linaclotide 0.25 mg (N = 73) n (%), #E	Linaclotide 0.5 mg (N = 76) n (%), #E	Placebo (N = 80) n (%), #E
Anal haemorrhage	0	0	0	0	1 (1.3%), 1

There were no SAEs of lower GI haemorrhage.

Post-marketing experience

Cumulatively until DLP, there have been 117 cases of GI bleeding of which 98 were serious.

Severity

Phase 3 double-blind placebo-controlled studies (Studies LIN-MD-31 and MCP-103-302)

	Linaclotide (N = 807) N (%)	**Placebo (N = 798) N (%)**
Rectal haemorrhage		
Mild	1 (0.1)	3 (0.4)
Moderate	1 (0.1)	0
Severe	0	0
Occult blood positive		
Mild	0	0
Moderate	0	1 (0.1)
Severe	0	0
Haemorrhoidal haemorrhage		
Mild	2 (0.2)	1 (0.1)
Moderate	0	0
Severe	0	0
Haematochezia		
Mild	1 (0.1)	0
Moderate	0	0
Severe	0	0

LTSS (Studies LIN-MD-02 and MCP-103-305)

	LIN-MD-02 (N = 1032) N (%)	**MCP-103-305 (N = 1119) N (%)**
Rectal haemorrhage		
Mild	4 (0.4)	6 (0.5)
Moderate	2 (0.2)	3 (0.3)
Severe	0	0
Haemorrhoidal haemorrhage		
Mild	1 (< 0.1)	0
Moderate	0	3 (0.3)
Severe	0	0
Haematochezia		
Mild	6 (0.6)	3 (0.3)
Moderate	1 (< 0.1)	0
Severe	0	0

Study ICP-103-307

Not available

Study 0456-CL-0031

Randomised, double-blind, placebo-controlled phase

	Linaclotide (N = 249) n (%), #E	**Placebo (N = 251) n (%), #E**
Haematochezia		
Mild	0	1 (0.4%), 1
Moderate	0	0

Open-label extension phase

	Linaclotide (N = 164) n (%), #E	**Placebo (N = 160) n (%), #E**
Haematochezia		
Mild	0	1 (0.6%), 1
Moderate	0	0
Anal haemorrhage		
Mild	1 (0.6%), 1	0
Moderate	0	0
Occult blood positive		
Mild	0	1 (0.6%), 1
Moderate	0	0

Study 0456-CL-1021

The 1 mild case of anal haemorrhage was in the placebo group.

Postmarketing

Severity was not reported in all cases.

Impact on quality of life

Lower GI haemorrhage can be distressing and lead to medical consultation.

Risk Factors and Risk Groups:

Patient factors

Chronic constipation and straining may lead to hemorrhoids, which are the main cause of low GI bleeding.

Preventability:

Patients should be aware of the possible occurrence of diarrhea and lower GI bleeding during treatment.

Impact on the Risk-Benefit Balance of the Product:

Pharmacovigilance activities will further characterise the risk of lower GI haemorrhage with respect to number of reports, seriousness, outcome, and risk factors. As of DLP of 29 August 2017, post-marketing data is consistent with the information already known for this risk. No additional intervention to manage the risk or allow for a reduction in the chance of the risk occurring is warranted at this stage. As of the DLP, the risk-benefit of linaclotide remains unchanged.

Public Health Impact:

The potential public health impact of lower GI haemorrhage is considered low.

Important Potential Risk 1: Potential for off-label use and abuse/excessive use

MedDRA Terms: PTs: Off label use, Intentional product misuse, Intentional product use issue, Prescribed overdose, Intentional overdose, Accidental overdose, Overdose

High level term (HLT): Overdoses

Potential Mechanisms:

There may be a limited potential for abuse of linaclotide as a stimulant laxative due to its pharmacological actions. Both linaclotide and its metabolite bind to and activate GC-C locally, on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in concentrations of cGMP, both extracellularly and intracellularly. Intracellular cGMP causes secretion of chloride and bicarbonate into the intestinal lumen, through activation of the CFTR, which results in increased intestinal luminal fluid and accelerated transit.

Evidence Source (s) and Strength of Evidence:

There were no reports of off-label use and abuse/excessive use during clinical development.

Characterization of the Risk:

Frequency

Clinical development

There have been no AEs during clinical development that are indicative of abuse.

There was one SAE of intentional product misuse, overdose and intentional overdose each. In addition, there were two SAEs of off-label use.

Postmarketing

Cumulatively until DLP, there have been 1,365 cases of off-label use, 63 cases of overdose and 636 cases of intentional product misuse of which 3, 6 and 2 cases were serious, respectively. These cases are not mutually exclusive.

Risk Factors and Risk Groups:

Additive or synergistic factors

Stimulant laxatives are the more frequent type of laxative used in the eating disorder population. Also, the presence of laxative abuse has been reported to be associated with greater psychopathology by some, but not all, investigators.

Preventability:

None proposed

Impact on the Risk-Benefit Balance of the Product:

Pharmacovigilance activities will further characterise the risk of off-label use and abuse/excessive use with respect to number of reports, seriousness, outcome, and risk factors. As of DLP of 29 August 2017, post-marketing data is consistent with the information already known for this risk. No additional intervention to manage the risk or allow for a reduction in the chance of the risk occurring is warranted at this stage. As of the DLP, the risk-benefit of linaclotide remains unchanged.

Public Health Impact:

Minimal impact

Important Potential Risk 2: Alterations of electrolytes (as a result of severe diarrhea)

MedDRA Terms: Diarrhoea search (as described for the important identified risk of diarrhoea above) plus PTs: Hypokalaemia, Hyponatraemia, Blood potassium decreased, Blood sodium decreased, Blood chloride decreased, Blood bicarbonate decreased, Hyperkalaemia, Hypernatraemia, Hyperchloraemia, Hypochloraemia, Blood potassium increased, Blood chloride increased, Blood sodium increased, Weight increased, Hypertension, Polyuria. HLTs: Antidiuretic hormone related conditions, Chloride imbalance, Electrolyte imbalance Not Elsewhere Classified (NEC), Fluid intake decreased, Fluid intake increased, Potassium imbalance, Sodium imbalance, Total fluid volume decreased, Total fluid volume increased, Mineral and electrolyte analyses, Water and electrolyte analyses NEC

Potential Mechanisms:

The mechanism of action of linaclotide is by causing secretion of chloride and bicarbonate into the intestinal lumen to increase intestinal fluid secretion and accelerate transit. This situation may lead to an electrolyte imbalance.

Evidence Source(s) and Strength of Evidence:

Prolonged or severe diarrhoea may lead to electrolyte imbalance. Clinical trials showed very modest elevated incidence rate of alterations of electrolytes compared to placebo. Alterations of electrolytes (as a result of severe diarrhoea) is considered an important potential risk as it can be a serious condition that if left untreated may lead to further complications and hospitalisation.

Characterization of the Risk:

Frequency

Phase 3 double-blind placebo-controlled studies (LIN-MD-31 and MCP-103-302)

PT	**Linaclotide 290 µg (N = 807) N (%)**	**Placebo (N = 798) N (%)**
Blood potassium decreased	2 (0.2)	3 (0.4)
OR (95% CI)	0.66 (0.11, 3.96)	
Hypokalaemia	0	3 (0.4)
Blood potassium increased	4 (0.5)	1 (0.1)
OR (95% CI)	4.04 (0.45, 36.31)	
Hyperkalaemia	1 (0.10)	0
Blood bicarbonate decreased	1 (0.1)	0

One case of hypokalaemia in the Phase 3 open label study for IBS-C was serious. The outcome of this event is resolved with no sequelae.

LTSS (LIN-MD-02 and MCP-103-305)

PT	LIN-MD-02 (N = 1032) N (%)	MCP-103-305 (N = 1119) N (%)
Blood potassium decreased	7 (0.7)	13 (1.2)
Hypokalaemia	9 (0.9)	12 (1.1)
Blood potassium increased	4 (0.4)	6 (0.5)
Hyperkalaemia	0	2 (0.2)
Blood sodium decreased	0	2 (0.2)
Hyponatremia	1 (< 0.1)	0
Hypernatremia	0	1 (0.1)
Blood magnesium decreased	0	2 (0.2)

ICP-103-307

There were no cases of electrolytes alterations in the linaclotide arm. In the placebo arm, there was one report of blood potassium increased and one report of hypokalaemia.

0456-CL-0031

Randomised, double-blind, placebo-controlled phase

There were no cases of electrolytes alterations in either arm.

Open-label extension phase

PT	Linaclotide (N = 164) n (%), #E	Placebo (N = 160) n (%), #E
Blood bicarbonate decreased	0	1 (0.6%), 1
Blood potassium increased	0	1 (0.6%), 1

0456-CL-1021

PT	Linaclotide 0.0625 mg (N = 82) n (%), #E	Linaclotide 0.125 mg (N = 71) n (%), #E	Linaclotide 0.25 mg (N = 73) n (%), #E	Linaclotide 0.5 mg (N = 76) n (%), #E	Placebo (N = 80) n (%), #E
Blood potassium increased	1 (1.2%), 1	0	0	1 (1.3%), 1	1 (1.3%), 1

There was one serious case of hyperkalaemia in the placebo arm.

Postmarketing

Cumulatively until DLP, there have been 30 cases of which 3 were serious.

Severity

In the Phase 3 double-blind placebo-controlled and open label studies, severity of the alterations of electrolytes was reported as mild or moderate in all the events, except from the serious case of hypokalaemia in IBS-C which was reported as severe.

ICP-103-307

Not applicable

0456-CL-0031

The two reports in the placebo arm of blood bicarbonate decreased and blood potassium increased were mild.

0456-CL-1021

The three reports of blood potassium increased were mild.

Postmarketing

The severity of the post-marketing events is not known.

Impact on quality of life

Alteration of electrolytes may lead to medical consultation and treatment. For some patients such as the elderly, patients with CV diseases, diabetes, or hypertension, alteration of electrolytes may be serious and can require hospitalisation.

Risk Factors and Risk Groups:

Patient factors

Patients with CV diseases, diabetes, hypertension and elderly patients have higher risk of experiencing alterations of electrolytes.

Preventability:

Additional caution should be exercised in patients who are prone to a disturbance of water or electrolyte balance (e.g., elderly, patients with CV diseases, diabetes, hypertension), and electrolyte control should be considered. Patients are advised to drink plenty of fluids to replace the water and electrolytes like potassium lost from the diarrhoea.

Impact on the Risk-Benefit Balance of the Product:

Pharmacovigilance activities will further characterise the risk of alterations of electrolytes (as a result of severe diarrhoea) with respect to number of reports, seriousness, outcome, and risk factors. As of DLP of 29 August 2017, post-marketing data is consistent with the information already known for this risk. No additional intervention to manage the risk or allow for a reduction in the chance of the risk occurring is warranted at this stage. As of the DLP, the risk-benefit of linaclotide remains unchanged.

Public Health Impact:

Minimal impact

Important Potential Risk 3: Dehydration (as a result of severe diarrhea)

MedDRA Terms: Diarrhoea search (as described for the important identified risk of diarrhoea above) plus PT: Dehydration

Potential Mechanisms:

The mechanism of action of linaclotide is by causing secretion of chloride and bicarbonate into the intestinal lumen to increase intestinal fluid secretion and accelerate transit. This situation may lead to an electrolyte imbalance.

Evidence Source(s) and Strength of Evidence:

Prolonged or severe diarrhoea may lead to dehydration. Clinical trials showed some events of dehydration. Dehydration (as a result of severe diarrhoea) is considered an important potential risk as it can be a serious condition that if left untreated may lead to further complications and hospitalisation.

Characterization of the Risk:

Frequency

Phase 3 double-blind placebo-controlled studies (LIN-MD-31 and MCP-103-302)

PT	**Linaclotide 290 µg (N = 807) N (%)**	**Placebo (N = 798) N (%)**
Dehydration	2 (0.2)	2 (0.3)
OR (95% CI)	0.99 (0.14, 6.97)	

There were no SAEs of dehydration.

LTSS (LIN-MD-02 and MCP-103-305)

	LIN-MD-02 (N = 1032) N (%)	**MCP-103-305 (N = 1119) N (%)**
Dehydration	4 (0.4)	2 (0.2)

There were no SAEs of dehydration.

ICP-103-307

There were no cases of dehydration.

There were no SAEs of dehydration.

0456-CL-0031

There were no cases of dehydration.

There were no SAEs of dehydration.

0456-CL-1021

There were no cases of dehydration.

There were no SAEs of dehydration.

Postmarketing

Cumulatively until DLP, there have been 25 cases of dehydration associated with severe diarrhoea of which 5 were serious.

Severity

Phase 3 double-blind placebo-controlled studies (LIN-MD-31 and MCP-103-302)

Dehydration	**Linaclotide (N = 807) N (%)**	**Placebo (N = 798) N (%)**
Mild	1 (0.1)	1 (0.1)
Moderate	0	0
Severe	1 (0.1)	1 (0.1)

LTSS (LIN-MD-02 and MCP-103-305)

Dehydration	**LIN-MD-02 (N = 1032) N (%)**	**MCP-103-305 (N = 1119) N (%)**
Mild	1 (0.1)	1 (0.1)
Moderate	3 (0.3)	1 (0.1)
Severe	0	0
Dehydration resulting in discontinuation	0	0

ICP-103-307

Not applicable

0456-CL-0031

Not applicable

0456-CL-1021

Not applicable

Postmarketing

Severity was not reported in all cases.

Impact on quality of life

Dehydration may lead to medical consultation and treatment. For some patients such as the elderly, dehydration may be serious and can require hospitalisation.

Risk Factors and Risk Groups:

Patient factors

Patients with CV diseases, diabetes, hypertension and elderly patients have more risk of experiencing dehydration particularly during the hot summers.

Preventability:

Patients are advised to drink plenty of fluids to replace the water lost from the diarrhoea.

Impact on the Risk-Benefit Balance of the Product:

Pharmacovigilance activities will further characterise the risk of dehydration (as a result of severe diarrhoea) with respect to number of reports, seriousness, outcome, and risk factors. As of DLP of 29 August 2017, post-marketing data is consistent with the information already known for this risk. No additional intervention to manage the risk or allow for a reduction in the chance of the risk occurring is warranted at this stage. As of the DLP, the risk-benefit of linaclotide remains unchanged.

Public Health Impact:

Minimal impact

Important Potential Risk 4: Orthostatic hypotension (as a result of severe diarrhea)
MedDRA Terms: Diarrhoea search (as described for the important identified risk of diarrhoea above) plus PTs: Fatigue, Asthenia, Malaise, Muscular weakness, Blood pressure decreased, Blood pressure orthostatic decreased, Blood pressure abnormal, Blood pressure diastolic abnormal, Blood pressure diastolic decreased, Blood pressure systolic abnormal, Blood pressure systolic decreased, Dizziness, Heart rate increased, Tachycardia, Syncope, Hypotension, Orthostatic hypotension, Fall, Gait disturbance, Loss of consciousness.

Potential Mechanisms:

The mechanism of action of linaclotide is by causing secretion of chloride and bicarbonate into the intestinal lumen to increase intestinal fluid secretion and accelerate transit. This situation may lead to an electrolyte imbalance.

Evidence Source(s) and Strength of Evidence:

Prolonged or severe diarrhoea may lead to orthostatic hypotension. During clinical development, there were a few events of orthostatic hypotension. Orthostatic hypotension (as a result of severe diarrhoea) is considered an important potential risk as if serious may require medical intervention especially in sensitive populations such as the elderly.

Characterization of the Risk:

Frequency

Phase 3 double-blind placebo-controlled studies (LIN-MD-31 and MCP-103-302)

In the Phase 3 placebo-controlled IBS-C trials orthostatic hypotension was not reported as an AE.

One case was reported as SAE in the open label study.

No cases of discontinuation from the study due to orthostatic hypotension were reported.

LTSS (LIN-MD-02 and MCP-103-305)

	LIN-MD-02 (N = 1032) N (%)	**MCP-103-305 (N = 1119) N (%)**
Orthostatic hypotension	0	2 (0.2)

There were no SAEs.

ICP-103-307

None

0456-CL-0031

None

0456-CL-1021

None

Postmarketing

Cumulatively until DLP, there have been 31 cases of orthostatic hypotension and severe diarrhoea of which 8 were serious.

Severity

Phase 3 double-blind placebo-controlled studies (LIN-MD-31 and MCP-103-302)

Severity available for two cases was reported as moderate.

LTSS (LIN-MD-02 and MCP-103-305)

	LIN-MD-02 (N = 1032) N (%)	**MCP-103-305 (N = 1119) N (%)**
Orthostatic hypotension		
Mild	0	0
Moderate	0	2 (0.2)
Severe	0	0

ICP-103-307

Not applicable

0456-CL-0031

Not applicable

0456-CL-1021

Not applicable

Postmarketing

Severity was not reported in all cases.

Impact on quality of life

Orthostatic hypotension may lead to medical consultation and treatment. For some patients such as the elderly, orthostatic hypotension may be serious and can require hospitalisation.

Risk Factors and Risk Groups:

Patient factors

Patients who normally have low blood pressure and elderly patients have more risk of experiencing orthostatic hypotension.

Preventability:

In the "Undesirable effects" section of the summary of product characteristics (SmPC) it is stated that in severe cases of diarrhoea may lead to orthostatic hypotension.

Impact on the Risk-Benefit Balance of the Product:

Pharmacovigilance activities will further characterise the risk of orthostatic hypotension (as a result of severe diarrhoea) with respect to number of reports, seriousness, outcome, and risk factors. As of DLP of 29 August 2017, post-marketing data is consistent with the information already known for this risk. No additional intervention to manage the risk or allow for a reduction in the chance of the risk occurring is warranted at this stage. As of the DLP, the risk-benefit of linaclotide remains unchanged.

Public Health Impact:

Minimal impact.

Important Potential Risk 5: Viral gastroenteritis

MedDRA Terms: Abdominal and GI infections, Gastric and gastroenteric infections, Gastroenteritis viral

Potential Mechanisms:

From the known mechanism of action of linaclotide, there is no data to suggest any pathophysiological mechanism that could increase the virus penetration or invasion of the GI tract.

Evidence Source(s) and Strength of Evidence:

During clinical development, there were a few events of Viral Gastroenteritis. Viral Gastroenteritis is considered an important potential risk as if serious may require medical intervention.

Characterization of the Risk:

Frequency

Phase 3 double-blind placebo-controlled studies (Studies LIN-MD-31 and MCP-103-302)

In the Phase 3 IBS-C placebo-controlled trials, gastroenteritis viral was defined a common TEAE numerically more frequent with linaclotide than with placebo in IBS-C pivotal trials: linaclotide 2.6% (21/807) vs. placebo 1.4% (11/798).

PT	**Linaclotide 290 μg (N = 807) N (%)**	**Placebo (N = 798) N (%)**
Viral Gastroenteritis	21 (2.6 %)	11 (1.4 %)
OR (95% CI)	1.93 (0.92, 4.04)	

None of the events of viral gastroenteritis was considered serious. Only 2 cases were considered possibly related to the study drug by the investigator in double blind conditions. The result after unblinding showed that one patient was on placebo and another on linaclotide.

LTSS (Studies LIN-MD-02 and MCP-103-305)

PT	**LIN-MD-02 (N = 1032) N (%)**	**MCP-103-305 (N = 1119) N (%)**
Gastroenteritis viral	26 (2.5)	28 (2.5)

There was one serious report of viral gastroenteritis in LIN-MD-02.

Study ICP-103-307

None

Study 0456-CL-0031

There was one case of viral gastroenteritis in the open-label extension part of the study (Part 2).

Study 0456-CL-1021

None

Postmarketing

Cumulatively until DLP, there have been 29 reports of viral gastroenteritis of which one was serious.

Severity

Phase 3 double-blind placebo-controlled studies (Studies LIN-MD-31 and MCP-103-302)

Viral gastroenteritis	**Linaclotide (N = 807) N (%)**	**Placebo (N = 798) N (%)**
Mild	6 (0.8)	10 (1.2)
Moderate	5 (0.6)	9 (1.1)
Severe	0	2 (0.2)

LTSS (Studies LIN-MD-02 and MCP-103-305)

Viral gastroenteritis	**LIN-MD-02 (N = 1032) N (%)**	**MCP-103-305 (N = 1119) N (%)**
Mild	9 (0.9)	11 (10)
Moderate	15 (1.5)	15 (1.3)
Severe	2 (0.29)	2 (0.2)
Viral gastroenteritis resulting in discontinuation	0	0

Study ICP-103-307

None

Study 0456-CL-0031

There 1 case of viral gastroenteritis was mild.

Study 0456-CL-1021

None

Postmarketing

Severity was not reported in all cases.

Impact on quality of life

Viral gastroenteritis can lead to medical consultation and treatment since if symptoms are severe can result in a disturbance of water or electrolyte balance. Thus, it is important that certain risk groups such as the elderly, patients with CV diseases, diabetes, and hypertension should be monitored and electrolyte control should be considered.

Risk Factors and Risk Groups:

Immunocompromised patients

Elderly patients

Patients who live with young children

Risk groups include those patients at risk of volume depletion or electrolyte disturbances following a viral gastroenteritis and patients more likely to experience clinical consequences of such an infection:

- Patients with an underlying GI infection
- Patients with an underlying GI condition that may be worsened by such events, e.g., Crohn's Disease, ulcerative colitis, proctitis
- Immunocompromised patients
- Elderly patients
- Patients with hypertension, diabetes and CV disease
- Patients with co-existing psychiatric/anxiety disorders (who may be considered less likely to be able to cope with the onset of a gastric virus)

Risk factors include patients receiving concurrent medications that may cause diarrhoea and exacerbate the condition.

Preventability:

In the "Undesirable effects" section of the SmPC it is stated that viral gastroenteritis is common.

Impact on the Risk-Benefit Balance of the Product:

Pharmacovigilance activities will further characterise the risk of viral gastroenteritis with respect to number of reports, seriousness, outcome, and risk factors. As of DLP of 29 August 2017, post-marketing data is consistent with the information already known for this risk. No additional intervention to manage the risk or allow for a reduction in the chance of the risk occurring is warranted at this stage. As of the DLP, the risk-benefit of linaclotide remains unchanged.

Public Health Impact:

The potential public health impact of viral gastroenteritis is considered low.

SVII.3.2 Presentation of the Missing Information

Missing information 1: Safety data in Pregnancy
Evidence source: Pregnant women were excluded from enrollment in the clinical development program. A small number of pregnancies have been reported to date in linaclotide clinical trials. Conception during linaclotide exposure was not associated with any untoward outcomes in mother, pregnancy or offspring. However, the dataset is very limited and there are no specific, adequate and well-controlled studies of linaclotide use in pregnant women. Animal studies did not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. At the highest dose levels, some maternal toxicity and fetal effects were noted in mice. No effects on the embryonal/fetal/newborn/infant are anticipated since the systemic exposure to linaclotide is minimal. Population in need of further characterization: The risks of use in pregnancy cannot be defined based on available evidence and thus the safety profile in this population will be derived from routine pharmacovigilance activities.

Module SVIII Summary of the Safety Concerns

Table 24. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Diarrhea Lower GI haemorrhage
Important potential risks	Potential for off-label use and abuse/excessive use
	Alterations of electrolytes (as a result of severe diarrhea)
	Dehydration (as a result of severe diarrhea)
	Orthostatic hypotension (as a result of severe diarrhea)
	Viral gastroenteritis
Missing information	Safety data in pregnancy

Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Description	Purpose
Specific ADR follow-up questionnaires for serious events of diarrhea. This questionnaire should also be used for reports of fecal incontinence, defecation urgency, dehydration, electrolyte disturbance and orthostatic hypotension if the patient experienced diarrhea at the same time	Targeted follow-up questionnaires will be utilized as follow-up to an ADR report to determine indication, diarrhea description, complications, patient characteristics, risk factors for diarrhea, and risk factors for complications.

III.2 Additional Pharmacovigilance Activities

Study Short Name and Title: Post-Authorization Safety Study (PASS) (Study EVM-18888-00): Linaclotide Safety Study for the Assessment of Diarrhea-Complications and Associated Risk Factors in Selected European Populations with IBS-C.

Rationale and Study Objectives: Linaclotide, a GC-C receptor agonist with visceral analgesic and secretory activities, is the first medicine authorized for the symptomatic treatment of moderate to severe IBS-C in adults in the EU. Therefore, this study is planned to assess the safety of linaclotide in terms of the risk of SCD during treatment and other risk factors among patients with IBS-C.

The specific research questions and objectives for this study are to:

- Estimate the risk (case-control odds ratio (OR)) of SCD (case) among patients with IBS-C (source population) who received linaclotide prescriptions vs. those who did not, controlling for other potential SCD risk factors (socio-demographics, comorbidities [up to 15], co-medications [up to 15] and other potential variables of interest [up to 10])
- Investigate potential risk factors associated to SCD in patients with IBS-C
- Describe the crude incidence of diarrhea among patients with IBS-C

If allowed by the results of the cases and controls validation as discussed below, two additional objectives will be addressed:

- Describe the crude incidence of SCD among patients with IBS-C (source population) prescribed linaclotide (first-time users)

- Describe the crude incidence of SCD among patients with IBS-C (source population) prescribed linaclotide (first-time users) who are at increased risk of SCD:
  - Patients ≥ 65 years
  - Patients with hypertension, diabetes, or CV disease diagnostic codes

Study Design: Retrospective case-control nested in a cohort of patients with IBS-C (cases will be patients suffering from SCD).

Study Population: This study will use observational data from three different countries: the UK, Sweden, and Spain. The study population will be a cohort of IBS-C patients. Patients with less than 12 months of computerized records prior to IBS-C cohort entry date or no follow-up time will not be included.

Milestones: The start of data collection was in February 2013 in Sweden, May 2013 in the UK, and September 2014 in Spain. The end of data collection will be defined based on the linaclotide uptake.

Study end: Quarter 3 (Q3) 2024.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 25. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 3 - Required additional pharmacovigilance activities				
Study EVM-18888-00 (PASS): Linaclotide Safety Study for the Assessment of Diarrhea-Complications and Associated Risk Factors in Selected European Populations with IBS-C	Estimate the risk of SCD among patients with IBS-C who received linaclotide prescriptions vs. those who did not, controlling for other potential SCD risk factors Investigate potential risk factors associated to SCD in patients with IBS-C Describe the crude incidence of diarrhea among patients with IBS-C	Alterations of electrolytes (as a result of severe diarrhea) Dehydration (as a result of severe diarrhea) Orthostatic hypotension (as a result of severe diarrhea)	Final report	Q3 2024

Part IV: Plans for Post-Authorization Efficacy Studies

Not applicable

Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 26. Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Diarrhoea (Identified risk)	Routine risk communication: *SmPC section: 4.4, 4.8* *Patient Leaflet (PL) section: Warnings and precautions, Possible side effects* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*
Lower GI haemorrhage (Identified risk)	Routine risk communication: *SmPC section: 4.4, 4.8* *PL section: Warnings and precautions, Possible side effects* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*
Potential for off-label use and abuse/excessive use (Potential risk)	Routine risk communication: *SmPC section: 4.2* *PL section: If you take more Constella than you should* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*

Safety Concern	Routine Risk Minimization Activities
Alterations of electrolytes (as a result of severe diarrhoea) (Potential risk)	Routine risk communication: *SmPC section: 4.4, 4.8* *PL section: Warnings and precautions, Possible side effects* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*
Dehydration (as a result of severe diarrhoea) (Potential risk)	Routine risk communication: *SmPC section: 4.8* *PL: Warnings and precautions, Possible side effects* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*
Orthostatic hypotension (as a result of severe diarrhoea) (Potential risk)	Routine risk communication: *SmPC section: 4.8* *PL: Warnings and precautions, Possible side effects* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*
Viral gastroenteritis (Potential risk)	Routine risk communication: *SmPC section: 4.8* *PL section: Possible side effects* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*

Safety Concern	Routine Risk Minimization Activities
Use in pregnancy (Missing information)	Routine risk communication: *SmPC section: 4.6* *PL: Pregnancy and breast-feeding* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*

V.2 Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the product.

V.3 Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table 27. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Diarrhoea (Identified risk)	Routine risk communication: *SmPC section: 4.4, 4.8* *Patient Leaflet (PL) section: Warnings and precautions, Possible side effects* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Specific ADR follow-up questionnaires* Additional pharmacovigilance activities: *None*

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Lower GI haemorrhage (Identified risk)	Routine risk communication: *SmPC section: 4.4, 4.8* *PL section: Warnings and precautions, Possible side effects* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Potential for off-label use and abuse/excessive use (Potential risk)	Routine risk communication: *SmPC section: 4.2* *PL section: If you take more Constella than you should* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Alterations of electrolytes (as a result of severe diarrhoea) (Potential risk)	Routine risk communication: *SmPC section: 4.4, 4.8* *PL section: Warnings and precautions, Possible side effects* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Specific ADR follow-up questionnaires* Additional pharmacovigilance activities: *PASS (Study EVM-18888-00)*

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Dehydration (as a result of severe diarrhoea) (Potential risk)	Routine risk communication: *SmPC section: 4.8* *PL: Warnings and precautions, Possible side effects* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Specific ADR follow-up questionnaires* Additional pharmacovigilance activities: *PASS (Study EVM-18888-00)*
Orthostatic hypotension (as a result of severe diarrhoea) (Potential risk)	Routine risk communication: *SmPC section: 4.8* *PL: Warnings and precautions, Possible side effects* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Specific ADR follow-up questionnaires* Additional pharmacovigilance activities: *PASS (Study EVM-18888-00)*
Viral gastroenteritis (Potential risk)	Routine risk communication: *SmPC section: 4.8* *PL section: Possible side effects* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in pregnancy (Missing information)	Routine risk communication: *SmPC section: 4.6* *PL: Pregnancy and breast-feeding* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for Constella

This is a summary of the risk management plan (RMP) for Constella. The RMP details important risks of Constella, how these risks can be minimized, and how more information will be obtained about Constella's risks and uncertainties (missing information).

Constella's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Constella should be used.

This summary of the RMP for Constella should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Constella's RMP.

I The Medicine and What it Is Used For

Constella is authorised for treatment of irritable bowel syndrome with constipation (IBS-C) in adults (see SmPC for the full indication). It contains linaclotide as the active substance and it is given by oral administration.

Further information about the evaluation of Constella's benefits can be found in Constella's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage

(https://www.ema.europa.eu/en/medicines/human/EPAR/constella)

II Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Constella, together with measures to minimize such risks and the proposed studies for learning more about Constella's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Constella is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of Constella are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Constella. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Diarrhoea Lower GI haemorrhage
Important potential risks	Potential for off-label use and abuse/excessive use Alterations of electrolytes (as a result of severe diarrhoea) Dehydration (as a result of severe diarrhoea) Orthostatic hypotension Viral Gastroenteritis
Missing information	Safety data in pregnancy

II.B Summary of Important Risks

Important identified risk 1: Diarrhea	
Evidence for linking the risk to the medicine	Linaclotide and the des tyrosine metabolite bind to and activate the GC-C receptor on the luminal surface of the intestinal epithelium. This activation causes secretion of chloride and bicarbonate into the intestinal lumen, resulting in increased fluid secretion and acceleration of intestinal transit. Clinical trials showed elevated incidence rate of diarrhoea compared to placebo. Diarrhoea is considered an important identified risk as severe diarrhoea for a prolonged duration can be a serious condition that if left untreated may lead to further complications and hospitalisation.
Risk factors and risk groups	Risk groups include those patients at risk of volume depletion or electrolyte disturbances following a diarrhoeal episode and patients more likely to experience clinical consequences of such changes: • Elderly patients • Patients with hypertension, diabetes and CV disease. • Patients with co-existing psychiatric/anxiety disorders (who may be considered less likely to be able to cope with the onset of sudden diarrhoea) Most IBS patients presenting in medical clinics and 18% of IBS patients in the community have 1 or more psychiatric disorders, (Whitehead 2002) with depression, panic disorder and anxiety disorder being more prevalent in IBS versus IBD population (Walker 1990). It should be noted that no pattern of diarrhoea leading to clinically relevant dehydration or electrolyte disturbances, or any other potentially serious adverse clinical sequelae was identified during Phase 3 linaclotide trials. Risk factors that may increase the risk of diarrhoea include: • Co-administration with food • Concomitant treatment with PPIs and laxatives

Important identified risk 1: Diarrhea	
	• IBS-C patients with only a mild constipation • Patients with a tendency to switch between IBS-C subtypes • Patients with infections • Patients receiving cytostatic agents • Patients with hypersensitivity (nematode infestation, food allergy, milk protein hypersensitivity, eosinophilic gastroenteritis) • Patients with autoimmune disorders (lymphoma, graft versus host disease, Crohn's disease, ulcerative colitis or proctitis) Concomitant medications that may increase the risk of diarrhoea: NSAIDs, simvastatin, ticlopidine, cimetidine, lansoprazole, gold (Aurolin), cyclosporine, methyldopa; and many others. Additional 'at risk' populations: Transitional IBS-C/IBS-D Patients In addition, 'at risk' patients should be considered as those with alternating or mixed IBS, (Longstreth 2006) in whom IBS-C may transition into IBS-D subtype. In this subtype of patients, onset of diarrhoea may shift the patient into subtype IBS-D and these patients might need to be monitored by their healthcare provider. Subdividing IBS based on the predominant symptom pattern is attempted commonly, but few data are available on IBS prevalence by symptom subgroup. Moreover, it is unclear if those with 1 predominant symptom – diarrhoea or constipation – if followed long enough, eventually develop the other, i.e., constipation in patients with IBS-D or diarrhoea in patients with IBS-C. Some data from primary care support this contention. Definitions of IBS subgroups remain arbitrary, and different definitions have been used in different studies (Drossman 2006, Kruis 1984, Manning 1978). In a study of 317 patients recruited for a clinical trial, at baseline 36% had IBS-D, 34% had IBS-C, and 31% IBS-M (both diarrhoea and constipation symptoms occurred); more than 75% switched type over a year of follow-up, usually to and from IBS-M pattern, but less than a third changed from IBS-C to IBS-D or vice versa.
Risk minimisation measures	**Routine risk minimisation measures:** *SmPC section: 4.4, 4.8* *PL section: Warnings and precautions, Possible side effects* *Prescription only medicine* **Additional risk minimisation measures:** *None*

Important identified risk 2: Lower GI haemorrhage	
Evidence for linking the risk to the medicine	Linaclotide increase BMs and frequency of defaecation that may lead to lower GI bleeding. Clinical trials showed very modest elevated incidence rate of lower GI bleeding events compared to placebo. Lower GI haemorrhage is considered an important identified risk as mild cases may have an impact on the patient's QOL and moderate to severe cases may necessitate medical intervention.
Risk factors and risk groups	***Patient factors*** Chronic constipation and straining may lead to haemorrhoids, which are the main cause of low GI bleeding.
Risk minimisation measures	**Routine risk minimisation measures:** *SmPC section: 4.4, 4.8* *PL section: Warnings and precautions, Possible side effects* *Prescription only medicine* **Additional risk minimisation measures:** *None*

Important potential risk 1: Potential for off-label use and abuse/excessive use	
Evidence for linking the risk to the medicine	There were no reports of off-label use and abuse/excessive use during clinical development.
Risk factors and risk groups	***Additive or synergistic factors*** Stimulant laxatives are the more frequent type of laxative used in the eating disorder population. Also, the presence of laxative abuse has been reported to be associated with greater psychopathology by some, but not all, investigators.
Risk minimisation measures	**Routine risk minimisation measures:** *SmPC section: 4.2* *PL section: If you take more Constella than you should* *Prescription only medicine* **Additional risk minimisation measures:** *None*

Important potential risk 2: Alterations of electrolytes (as a result of severe diarrhoea)	
Evidence for linking the risk to the medicine	Prolonged or severe diarrhoea may lead to electrolyte imbalance. Clinical trials showed very modest elevated incidence rate of alterations of electrolytes compared to placebo. Alterations of electrolytes (as a result of severe diarrhoea) is considered an important potential risk as it can be a serious condition that if left untreated may lead to further complications and hospitalisation.
Risk factors and risk groups	***Patient factors*** Patients with CV diseases, diabetes, hypertension and elderly patients have higher risk of experiencing alterations of electrolytes.
Risk minimisation measures	**Routine risk minimisation measures:** *SmPC section: 4.4, 4.8* *PL section: Warnings and precautions, Possible side effects* *Prescription only medicine* **Additional risk minimisation measures:** *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** *PASS (EVM-18888-00)*

Important potential risk 3: Dehydration (as a result of severe diarrhoea)	
Evidence for linking the risk to the medicine	Prolonged or severe diarrhoea may lead to dehydration. Clinical trials showed some events of dehydration. Dehydration (as a result of severe diarrhoea) is considered an important potential risk as it can be a serious condition that if left untreated may lead to further complications and hospitalisation.
Risk factors and risk groups	***Patient factors*** Patients with CV diseases, diabetes, hypertension and elderly patients have more risk of experiencing dehydration particularly during the hot summers.
Risk minimisation measures	**Routine risk minimisation measures:** *SmPC section: 4.4, 4.8* *PL section: Warnings and precautions, Possible side effects* *Prescription only medicine* **Additional risk minimisation measures:** *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** *PASS (Study EVM-18888-00)*

Important potential risk 4: Orthostatic hypotension (as a result of severe diarrhoea)	
Evidence for linking the risk to the medicine	Prolonged or severe diarrhoea may lead to orthostatic hypotension. During clinical development, there were a few events of orthostatic hypotension. Orthostatic hypotension (as a result of severe diarrhoea) is considered an important potential risk as if serious may require medical intervention especially in sensitive populations such as the elderly.
Risk factors and risk groups	***Patient factors*** Patients who normally have low blood pressure and elderly patients have more risk of experiencing orthostatic hypotension.
Risk minimisation measures	**Routine risk minimisation measures:** *SmPC section: 4.8* *PL section: Warnings and precautions, Possible side effects* *Prescription only medicine* **Additional risk minimisation measures:** *None*
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** *PASS (Study EVM-18888-00)*

Important potential risk 5: Viral gastroenteritis	
Evidence for linking the risk to the medicine	During clinical development, there were a few events of Viral Gastroenteritis. Viral Gastroenteritis is considered an important potential risk as if serious may require medical intervention.
Risk factors and risk groups	Immunocompromised patients Elderly patients Patients who live with young children Risk groups include those patients at risk of volume depletion or electrolyte disturbances following a viral gastroenteritis and patients more likely to experience clinical consequences of such an infection: • Patients with an underlying GI infection • Patients with an underlying GI condition that may be worsened by such events, e.g., Crohn's Disease, ulcerative colitis, proctitis; • Immunocompromised patients • Elderly patients • Patients with hypertension, diabetes and CV disease. • Patients with co-existing psychiatric/anxiety disorders (who may be considered less likely to be able to cope with the onset of a gastric virus) Risk factors include patients receiving concurrent medications that may cause diarrhoea and exacerbate the condition.
Risk minimisation measures	**Routine risk minimisation measures:** *SmPC section: 4.8* *PL section: Possible side effects* *Prescription only medicine* **Additional risk minimisation measures:** *None*

Missing information 1: Safety data in pregnancy	
Risk minimisation measures	**Routine risk minimisation measures:** *SmPC section: 4.6* *PL section: Pregnancy and breast-feeding* *Prescription only medicine* **Additional risk minimisation measures:** *None*

II.C Post-Authorization Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Constella.

II.C.2 Other Studies in Post-Authorization Development Plan

PASS (Study EVM-18888-00): Linaclotide Safety Study for the Assessment of Diarrhoea-Complications and Associated Risk Factors in Selected European Populations with IBS-C.

Purpose of the study: To estimate the risk of SCD among patients with IBS-C who received linaclotide prescriptions or vs. those who did not, controlling for other potential SCD risk factors; to investigate potential risk factors associated to SCD in patients with IBS-C; to describe the crude incidence of diarrhoea among patients with IBS-C.

Part VII: Annexes

Annex 4. Specific Adverse Drug Reaction Follow-Up Forms

We are requesting more information regarding the adverse event that your patient experienced *to help us ensure the safety and effectiveness of our medications for all individuals using them.*

Patient Information

Reference Numbers

Name:	Initials:	Patient ID:	AER #
Address:	City, State:	Zip:	Affiliate Ref #
Height: _____ cm ☐ in ☐	Weight: _____ kg ☐ lb ☐	Race/Ethnicity:	Other reference #:
Sex: M ☐ F ☐	Date of Birth: ___/____/___(d/m/y)	Age at Time of Event:	Age group^:

^ Age group codes: Neonate (Day 0 to Day 27), Infant (28 days to 23 months), Child (2 years to 11 years), Adolescent (12 years to 17 years), Adult (18 years to 64 years), Elderly (65 years and over)

Patient Medical History

Include family history, pregnancy, risk factors, HIV, weight, height, tobacco history:

Additionally specify:

Has the patient previously experienced diarrhea as part of the IBS-C? ☐ Yes ☐ No ☐ Not known

Does the patient have hypertension, diabetes or cardiovascular disease?

☐ Yes

If yes, specify

☐ No

☐ Not known

Does the patient have inflammatory bowel disease (Crohn's disease; ulcerative colitis)

☐ Yes

If yes, specify

☐ No

☐ Not known

If applicable, has the patient had previous episodes of fecal incontinence/defecation urgency/dehydration/electrolyte disturbances/ orthostatic hypotension before linaclotide treatment?

☐ Yes

If yes, specify

☐ No

☐ Not known

For patients experiencing fecal incontinence or defecation urgency: (Please provide information on gynecologic and obstetric disorder(s) and surgery(ies) and childbirth(s)

Adverse Event Details

Provide detailed event information including symptoms the patient experienced leading up to the events:

Select one of the following codes to answer the questions designated with numbers 1-3.

1. Event Criteria Codes: Serious (Death, Hospitalization, Prolonged Hospitalization, Congenital anomaly, Life-threatening, Medically Important, Persistent or Significant Disability) or Non-serious
2. Causality Code: Reasonable Possibility, No Reasonable Possibility, Non-Assessable
3. Outcome Codes: Death, Recovered, Not recovered, Recovering, Worsened, Unknown, or Recovered with Sequela (provide Sequela if available)

Adverse Event(s)	Event Onset (d/m/y)	End Date (d/m/y)	Event Criteria[1]	Was this caused by suspect?[2]	Outcome[3]

Additionally specify:
Severity of diarrhea:

Was the diarrhea continuous or episodic? ☐ Continuous, ☐ Episodic, ☐Not Known

On an average how many diarrhea episodes did the patient experience in a day? _____ ☐Not Known

Indicate if patient experienced any of these complications:

Fecal incontinence or defecation urgency	☐ Yes ☐ No ☐ Not known If yes; how many times/how often did it occur?
Was the patient absent from work/school?	☐ Yes ☐ No ☐ Not known
Dehydration	☐ Yes ☐ No ☐ Not known If yes; provide relevant laboratory values in the section below
Electrolyte disturbance	☐ Yes ☐ No ☐ Not known If yes; which type? If yes; provide relevant laboratory values in the section below
Orthostatic hypotension	☐ Yes ☐ No ☐ Not known If yes; specify severity
Any other complication occur in relation to the diarrhea	☐ Yes ☐ No ☐ Not known If yes; specify

Suspected AbbVie Medication(s)

Name	Dose	Form	Frequency	Route	Start date (d/m/y)	End Date (d/m/y)	Indication	If stopped, did event abate? *If yes, provide date*

AbbVie Medication Lot Number (*If unable to provide lot number,* indicate reason below): Expiration Date (d/m/y):

Discarded ☐ Not Accessible to Physician ☐ Not on Patient's File ☐ Didn't Receive in Original Package ☐ Not Legible on Package ☐

Additionally specify:
If the indication was IBS-C, what was the severity of IBS-C?

Did the patient take linaclotide with food? ☐ Yes ☐ No ☐ Not known

Did the patient receive treatment for diarrhea and/or related adverse events listed above? If yes, complete the "Treatment Medication" table below. ☐ Yes ☐ No ☐ Not known

Treatment Medication(s) (*attach additional pages as needed*)

List any treatments provided for diarrhea and/or related adverse events above (provide medications, electrolyte, fluids etc.)

Name	Dose	Form	Frequency	Route	Start date	End Date	Indication
					___/___/_____	___/___/_____	
					___/___/_____	___/___/_____	
					___/___/_____	___/___/_____	
					___/___/_____	___/___/_____	
					___/___/_____	___/___/_____	

Concomitant or Past Medication(s) (*attach additional pages as needed*)

Indicate Concomitant (active at time of event) (C)or Past (P). Include herbal, OTC medications, and supplements

Name	C, P or	Dose	Form	Frequency	Route	Start date	End Date	Indication
						___/___/_____	___/___/_____	
						___/___/_____	___/___/_____	
						___/___/_____	___/___/_____	
						___/___/_____	___/___/_____	
						___/___/_____	___/___/_____	

Additionally specify if the patient use/used laxatives, PPIs or NSAIDs

Laboratory Test

Name	Date(d/m/y) (prior to Abbvie product)	Result (include units of measure)	Date(d/m/y) (Peak during treatment)	Results (include units of measure)	Date (when event improved/resolved) (d/m/y)	Reference Range

Diagnostic Test

Name	Date(d/m/y)	Result (include units of measure)

Contact Information

Does the reporter agree to have HCP/MD contacted? Yes ☐ No ☐ Not Applicable ☐		
Physician/HCP Name:		
Street Address:		
City:	State:	Postal Code:
Phone Number:		

Person completing form *if different from Physician/HCP*		
Name:		
Street Address:		
City:	State:	Postal Code:
Phone Number:		

Annex 6. Details of Proposed Additional Risk Minimization Activities (If Applicable)

Not applicable