20 September 2012
EMA/CHMP/60979/2012
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Constella

International non-proprietary name**: linaclotide**

Procedure No. **EMEA/H/C/002490**

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Executive Summary

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterised by intestinal pain or discomfort together with alteration of bowel habit, abdominal distension, bloating, constipation or diarrhoea[1]. Symptoms usually wax and wane for many years, often resulting in reduced quality of life and work productivity. The pathophysiology of IBS is incompletely understood.

Despite affecting 5 to 20% of the Western population, no medicines are authorised in the European Union (EU) specifically for the treatment of IBS. Patients and prescribers are limited to general symptomatic treatments such as laxatives, antidiarrhoeals and antispasmodics, which are recommended in current guidelines but on the basis of weak evidence. Alternatively, they may use unapproved treatments such as antidepressants and non-absorbable antibiotics when lifestyle modifications such as reducing stress, altering diet or psychological interventions prove ineffective.

In September 2012, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended the authorisation of Constella (linaclotide) to offer a new option for adults with moderate to severe IBS with constipation (IBS-C), a common subtype of the disease. The recommended dose is one capsule (290 micrograms) once daily, to be taken at least 30 minutes before a meal. Linaclotide, a synthetic 14-amino-acid peptide, is a new oral compound that works by increasing intestinal fluid secretion and accelerated transit. It stimulates guanylate-cyclase-subtype-C (GC-C) receptors on the luminal surface of the intestinal epithelium, leading to increased intra- and extracellular levels of cyclic guanosine monophosphate (cGMP). The increase in intracellular cGMP in turn activates the cystic fibrosis transmembrane conductance regulator (CFTR), leading to secretion of chloride and bicarbonate into the intestinal lumen. The increase in extracellular (basolateral) cGMP increases the threshold for colonic nociception and is believed to thereby reduce sensation of pain.

In the two main clinical studies provided to support its authorisation[2], linaclotide showed superiority over placebo, with statistically significant improvements in abdominal pain and discomfort as well as considerable or complete relief from symptoms after 12 weeks. Both studies employed randomised, double-blind, parallel-group designs in a total of approximately 1600 patients who met criteria that correspond to a moderate to severe IBS population. Around 38% of the patients treated with linaclotide showed a 'relief response', defined as considerable or complete relief of symptoms for six out of 12 treatment weeks as measured on a seven-point Likert scale. This compared with around 18% of the patients treated with placebo. In addition, around 54% of the patients treated with linaclotide showed an at least 30% improvement in their abdominal pain or discomfort score for six out of 12 treatment weeks, compared with around 40% of those receiving placebo.

The Committee judged these results to be clinically relevant, because the primary endpoints met a 14% to 20% margin of superiority over placebo, and because the results were consistent across the main trials. Nonetheless, it noted that around half of the patients in the main studies did not sufficiently respond to linaclotide, leading to the recommendation that prescribers should assess patients regularly and reconsider treatment if there is no improvement in symptoms after four weeks.

Although linaclotide is intended for long-term continuous use, only study MCP-103-302 evaluated the effects of the medicine for six months; this is the duration of treatment required by the Agency's guidelines for chronic IBS treatments. For both endpoints, the effect over placebo in this study after 26 weeks was statistically significant: 37% and 54% of the patients treated with linaclotide showed response to IBS degree of relief and to abdominal pain or discomfort, respectively, compared with 17% and 36% of those receiving placebo. These results were supported by additional justification from the

[1] Currently the Rome III criteria are widely accepted as the gold standard for the diagnosis and classification of IBS.
[2] LIN-MD-31 and MCP-103-302.

applicant concerning the medicine's mode of action, the patient population studied and the consistency of its effects across sub-populations and a variety of endpoints.

No rebound effect was seen in study LIN-MD-31, which included a randomised withdrawal period of four weeks after three months of treatment. Although there are no data after longer treatment periods, the Agency accepted that these three-month withdrawal data could be extrapolated to later time points because the medicine showed sustained efficacy and in the absence of a biologically plausible reason for why withdrawal effects would differ after longer treatment duration.

Because diarrhoea was the most common adverse event seen, the Agency warns that patients with severe or prolonged diarrhoea should be monitored closely and that linaclotide should be used with caution in patients prone to a water or electrolyte-balance disturbances. Diarrhoea was reported in 160 (20%) of the linaclotide-treated patients but only 24 (3%) of those receiving placebo, with this being moderate or severe in 91 and 6 patients, respectively. In linaclotide patients, diarrhoea lasted more than 28 days in half of those affected, but less than a week in a third. Rarely, potentially more serious consequences of diarrhoea were seen, such as serum bicarbonate and potassium level changes, dehydration, dizziness, and syncope.

Only 5% of the study participants were above 65 years of age. The Committee noted that diarrhoea appeared to be more common in the elderly, leading to its recommendation that prescribers should afford special attention to older patients and assess the medicine's benefits and risks carefully before and during treatment in this age group. To further elucidate the safety profile of the medicine in this population, the Agency has requested a post-authorisation safety study that specifically includes elderly patients. Regarding children and adolescents, the absence of data led the Agency to restrict its recommended use of linaclotide to adults, especially since GC-C receptor is overexpressed in young children. Specific studies will need to be conducted before a conclusion on safe and effective use in the paediatric population can be made.

Linaclotide is expected to offer a useful treatment option for patients with moderate or severe IBS with constipation, once organic diseases have been ruled out and a diagnosis of IBS-C has been established. The Committee's conclusion that the medicine's benefits outweigh its risks is based on the medicine's robust superiority over placebo, clear clinical relevance, and acceptable safety profile. The Committee awaits the final results of the long-term safety study, and the data from the post-authorisation safety study, concentrating in particular on complications of diarrhoea in patients with associated risk factors as well as the medicine's risks in older patients, and will make further recommendations on its use in line with these and any other information that becomes available after the medicine is in use.

Table of contents

List of abbreviations

AAA	Amino acid analysis
ACE	angiotensin-converting enzyme
ADO	Adverse Event Dropout
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve to infinity
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BID	twice daily
BM	Bowel Movement
BMI	body-mass index
BRB	bilirubin
BSFS	Bristol Stool Form Scale
CC	Chronic Constipation
cGMP	Cyclic Guanosine Monophosphate
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CID	Clinically Important Difference
ClC-2	Chloride Channel type 2
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CrCl	creatinine clearance
CRF	Case Report Form
CSBM	Complete Spontaneous Bowel Movement
CSR	clinical study report
CT	computed tomography
CV	Coefficient of Variation
CYP	cytochrome P450
DB	Double Blind
DBP	Diastolic Blood Pressure
DMT	Deviation from the theoretical mean
DNA	deoxyribonucleic acid
DSC	differential scanning calorimetry
DVS	dynamic vapour sorption
ECG	Electrocardiogram
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EQ-5D	EuroQoL – 5 Dimensions
E-R	exposure-response
EU	European Union
FDA	Food and Drug Administration
FTIR	Fourier transform infrared
g	Gram
GC-C	Guanylate Cyclase receptor, subtype C
GI	Gastrointestinal
GIS	Global Improvement Scale
GLP	Good Laboratory Practice
HA	health authority
HMG-CoA	3-hydroxy-3-methyl-glutaryl CoA
HPLC	High-Performance Liquid Chromatography

IBS	Irritable Bowel Syndrome
IBS-C	Irritable Bowel Syndrome with Constipation
IBS-D	Irritable Bowel Syndrome with Diarrhoea
IBS-M	Irritable Bowel Syndrome Mixed
IBS-U	Irritable Bowel Syndrome Unsubtyped
ICAC	independent central adjudication committee
ICH	International Conference on Harmonisation
IMMPACT	Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
IR	Immediate Release
IS	Internal Standard
ISS	Integrated Summary of Safety (US)
ITT	Intent-To-Treat
IV	intravenous(ly)
IVRS	Interactive Voice Response System
K2EDTA	Dipotassium ethylenediaminetetraacetic acid
LC	Liquid Chromatography
LFT	liver function test
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LoQ	list of questions
LS	Least Squares
LSMD	Least Square Mean Difference
LTS	Long Term Safety
MCP	Multiple Comparisons Procedure
MD-1100	Acetate Ironwood Pharmaceuticals development designation for linaclotide
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
ml	milliliter
mM	millimolar
MM-420026	A stable isotope-labeled internal standard of linaclotide (15N13C9-linaclotide)
MS/MS	Tandem Mass Spectrometry
NDA	New Drug Application
NF	National Formulary
ng	nanogram
NLT	Not Less Than
NMR	Nuclear magnetic resonance
NOAEL	No Observed Adverse Effect Level
NRS	Numeric Rating Scale
OC	Observed Case
OLE	open-label extension
OR	Odds Ratio
OTC	Over The Counter
Pbo	Placebo
PCS	Potentially Clinically Significant
PD	pharmacodynamic(s)
PET	primary efficacy timepoint
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
PO	oral(ly)
Pop-PK	population pharmacokinetics
PP	Per Protocol
PPI	Proton Pump Inhibitor
Q	The amount of dissolved active ingredient, expressed as a percentage of the labeled content of the dosage unit.
QC	Quality Control
QD	once daily
QoL	Quality of Life
RE	Relative Error
RI	Randomization Ineligible
RMP	Risk Management Plan
RO	Rollover
ROW	rest of world

RSD	Relative Standard Deviation
RW	Randomized Withdrawal
SA	Scientific Advice
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAWP	Scientific Advice Working Party
SBM	Spontaneous Bowel Movement
SBP	Systolic Blood Pressure
SEC	size exclusion chromatography
SC	subcutaneous(ly)
SCE	Summary of Clinical Efficacy
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SPC	Summary of Product Characteristics
SPE	Solid-phase extraction
TEAE	Treatment Emergent Adverse Event
ULN	upper limit of normal
ULOQ	Upper Limit of Quantitation
US	United States
USP	United States Pharmacopeia
UV	Ultraviolet
Vc/F	apparent volume of distribution of the central compartment
µg	microgram
µl	microliter
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Almirall, S.A. submitted on 27 September 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Constella, through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP during its meeting on 13-16 December 2010.

The applicant applied for the following indication: Constella is indicated for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/110/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/110/2011 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance linaclotide contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 17 December 2009. The Scientific Advice pertained to insert quality, non-clinical and clinical aspects of the dossier.

Licensing status

Constella was not licensed in any country at the time of submission of the application.

The product (Linzess) has been given a Marketing Authorisation in the USA on 30 August 2012.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP and the evaluation team was:

Rapporteur: **Harald Enzmann**

- The application was received by the EMA on 27 September 2011.
- The procedure started on 19 October 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 6 January 2012 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 5 January 2012.
- During the meeting on 13-16 February 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 16 February 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 May 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 June 2012.
- During the CHMP meeting on 16-19 July 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 August 2012.
- During the meeting on 17 to 20 September 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Constella on 20 September 2012.

2. Scientific discussion

2.1. Introduction

Problem statement

The condition to be treated, Irritable Bowel Syndrome (IBS) is a chronic, relapsing gastrointestinal problem characterised primarily by intestinal pain and/or discomfort. In addition to pain and discomfort an association exists with alteration of defecation and/or bowel habit. Associations with other symptoms are also regularly present, such as abdominal distension, bloating, constipation, and/or diarrhoea. IBS is generally regarded to be a functional gastrointestinal disorder with the meaning that – by usual investigations and up to most recently – a disease specific correlate cannot be found. Moreover, IBS is frequently associated with other functional gastrointestinal (e.g. functional dyspepsia; GERD) or non-gastrointestinal (e.g. fibromyalgia, chronic pelvic pain, interstitial cystitis) disorders, as well as with co-existing psychological conditions. In about 10% of the adult patients, IBS-like symptoms develop after bacterial or viral enteric infections ("post-infectious IBS").

IBS is associated with a significantly impaired health-related quality of life and reduced work productivity, however, seems not to be associated with increased mortality. The impairment of quality of life has been evaluated to be similar as in diseases like depression and diabetes mellitus, and higher than, e.g. in patients with chronic renal failure.

IBS is regarded to be a common disorder, the prevalence of which has been estimated to be in the order of between 5 % and 20% of the general populations in Western Societies, depending on the method used for data collection, and on the methods used for the diagnosis. The prevalence of the conditions decreases with age, and is anticipated to be highest in the 4th decade. There is a clear female dominance in the prevalence of the disease with usually the ratio reported to be about 2:1. IBS is regarded to be a chronic stable disorder with so-called "waxing and waning" of symptoms for years.

The pathophysiology of IBS is still incompletely understood. Whereas more "traditional" markers of disease activity, such as altered motor dysfunction (including small intestinal motor abnormalities, altered colonic transit, etc), altered visceral sensitivity and sensory dysfunction, altered autonomic nervous system regulation (including brain-gut interaction), and stress in the form of severe life-time events such as physical and sexual abuse have long been implicated into the generation of the symptoms, more recent research have elucidated a role for factors like genetics, disturbed processing of bowel gas, and, most importantly, subclinical inflammation.

The diagnosis and classification of IBS has formerly based on the so-called Kruis, or the (later) Manning criteria, which have later been broadly superseded by the Rome criteria, of which the third version (Rome III) is currently regarded the standard of diagnosis and classification. Despite the limitations of all symptom-based diagnostic systems, the currently applicable Rome III criteria have been accepted and are regarded as the current Gold Standard by the wide variety of learned societies in different countries, especially for the research setting (e.g. UK and US).

The treatment of IBS is usually started with recommendations for a change in life-style ("reduce stress"), and dietary modifications, based on the evaluation of symptoms and history taking. Among patients diagnosed with IBS, a certain percentage of patients can indeed be identified to suffer from food allergies, and/or certain carbohydrate intolerances. Psychological therapies (cognitive behavioural therapy, hypnotherapy) have also shown to have some effect on the disease.

Current guidelines on the pharmacological treatment of IBS generally recommend the administration of traditional pharmaceuticals such as laxatives (e.g. psyllium), antidiarrhoeals and antispasmodics based on the evaluation of the symptoms. However, all of these above medications are considered to provide the lowest level of evidence only ("weak recommendation based on low-quality or very low-quality evidence"). Recommendations with a higher level of evidence, especially from the American consensus recommendations refer to medicinal products that are not available in the EU. The only further "higher level" recommendations are given for antidepressants (TCAs and SSRIs) and non-absorbable antibiotics (e.g. rifaximin), however, these medications are also not licensed for the indication IBS. Further recommendations refer to the use of herbal products and probiotics with the problem of high heterogeneity in the trials.

It is therefore acknowledged that there is a lack of documented reliable treatment options for the condition. The recommendations for the treatment of IBS are either not available in the EU, or mostly represent off-label use only. A clear unmet medical need exists for the condition IBS.

About the product

Linaclotide is a fully synthetic 14-amino-acid peptide proposed to act by stimulation of the guanylate cyclase subtype C (GC-C) receptor. GC-C receptors are present on the luminal surface of the intestinal

epithelium throughout the intestines. Linaclotide is structurally related to the endogenous guanylin peptide family. Linaclotide is proposed to act within the lumen of the intestine and has very low absolute oral bioavailability. The activation of the GC-C receptor increases cyclic guanosine monophosphate (cGMP), both intracellularly and extracellularly. The increase in intracellular cGMP causes secretion of chloride and bicarbonate into the intestinal lumen, through activation of the cystic fibrosis transmembrane conductance regulator (CFTR), which results in increased intestinal fluid secretion and accelerated transit. The increase in extracellular (basolateral) cGMP increases the threshold for colonic nociception and is believed to thereby reduce sensation of pain.

Linaclotide is intended for the symptomatic treatment of adult patients with a moderate to severe form of irritable bowel syndrome with constipation (IBS-C). The daily dose is 290 µg administered orally as a single dose on an empty stomach.

Type of Application and aspects on development

The application was made in accordance with Article 8 (3) (full application) of Directive 2001/83/EC, containing the results of pharmaceutical, nonclinical, and clinical tests.

The clinical trial programme conducted by the company includes seven completed clinical studies and two ongoing (open-label safety) studies, which were the basis for the application for treatment of IBS-C. In addition, data from studies in chronic constipation have been provided.

For the development of medicinal products for the treatment of IBS, a guidance document, the "Points to consider on the evaluation of medicinal products for the treatment of irritable bowel syndrome" (CPMP/EWP/785/97) applies. Generally, the guideline refers to two alternatives for drug development, referring to the nature of disease: Either a short-term intermittent treatment can be aimed at, for which it is required to elucidate several aspects of this mode of administration (dose-response, first use, repeated use, withdrawal and rebound effects), or the development for a long-term continuous use of the product, requiring the inclusion of patients with well-defined IBS into trials that should have a duration long enough to determine if any response will be sustained (6 months is given), and to evaluate a withdrawal effect. Linaclotide was developed for long-term continuous treatment.

The company received EMA/CHMP Scientific Advice as well as national scientific advice during the development programme. In general, the recommendations from the authorities were followed.

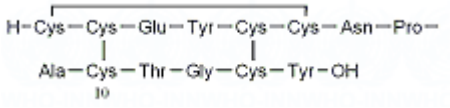
2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard gelatin capsules containing 290 microgram of linaclotide as active substance. The full composition is described in section 6.1 of the SmPC. The product is packed in a high density polyethylene (HDPE) bottle with polypropylene (PP) child-resistant screw cap. The bottle contains one or more desiccant canisters containing silica gel.

2.2.2. Active Substance

The international nonproprietary name (INN) of the active substance is linaclotide. The chemical name is: L-cysteinyl-L-cysteinyl-L-glutamyl-L-tyrosyl-L-cysteinyl-L-cysteinyl-L-asparaginyl-L-prolyl-L-alanyl-L-cysteinyl-L-threonyl-glycyl-L-cysteinyl-L-tyrosine, cyclic (1-6), (2-10),(5-13)-tris(disulfide). Linaclotide is a 14-amino acid synthetic peptide with 3 disulfide bonds. All chiral amino acid are of L-configuration. The structural formula is:



Linaclotide is a white to off-white hygroscopic powder and is sparingly soluble in 0.1 N HCl, slightly soluble in water and very slightly soluble in acetone and acetonitrile. The solubility in aqueous solutions over a pH range of 1.0 to 7.5 is > 100 µg/ml. Linaclotide exhibits stereoisomerism due to the presence of 14 chiral centers. Chiral identity is controlled routinely by specific optical rotation. Linaclotide is an amorphous peptide, no crystalline material has been observed in the x-ray powder diffractogram. The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture

Linaclotide is manufactured by a five step process. Linaclotide is supplied by two active substance manufacturers. Both suppliers provided adequate information on the active substance development, manufacturing process, control of starting materials, reagents and solvents, and control of critical steps and intermediates in the form of an active substance master file (ASMF). All relevant impurities, degradation products and residual solvents have been appropriately characterized.

The two suppliers manufacture linaclotide in a slightly different way. One supplies linaclotide as lyophilised powder, the other as a precipitated powder. Both processes have been adequately described and comparability between the active substances from the two manufacturers has been demonstrated. The manufacturing process does not include any aseptic processing or sterilisation, hence no description of process validation is provided. This is in accordance with ICH M4.

The applicant has confirmed the structure of linaclotide by MS, Edman degradation, NMR, GC-MS, FTIR, UV, AAA, specific optical rotation and bioidentity. The physical properties have been studied by DSC, DVS, XRPD, optical light microscopy, solubility profile and a particle size distribution test.

Specification

The applicant's active substance specification include tests as: appearance and solubility (visual), identity (AAA, HPLC, optical rotation), assay (HPLC), related substances (HPLC), multimers (SEC), acetic acid (HPLC), water (Ph.Eur.), trifluoroacetic acid (HPLC), residual organic solvents (GC) and mass balance.

The specifications and tests comply with the ICH guidelines and general requirements of Ph.Eur. and are adequate to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety. Batch analysis data have been provided by both active substance suppliers and confirm consistency and uniformity of the active substance manufacture.

Stability

The primary stability studies have been performed on six commercial scale batches (three from each supplier) packed in containers that are representative to the containers proposed for marketing. Up to 24 months stability data have been presented for the primary stability studies performed under long term (-20±5°C) conditions, and up to 18 months under accelerated (5±3°C) conditions. The specifications tested were appearance, assay, related substances, total disulfide-bonded multimer

content and water content. The stability results demonstrated that the stability of the active substance produced by the two suppliers is comparable and that the active substance is of adequate stability.

Forced degradation studies were performed to identify the likely degradation products and demonstrated that the analytical methods are stability indicating. Photostability studies, following ICH guidelines Q1B, were performed on two batches (one from each supplier) to demonstrate that the proposed primary containers adequately protect the active substance from light exposure. In conclusion, the stability data provided support the proposed retest period at the proposed packaging and storage conditions.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The applicant's objective was to develop an immediate release formulation containing 290 microgram linaclotide that has good long term stability at room temperature and uniform content. In view of the low doses of linaclotide, the applicant selected gelatin capsules filled with linaclotide-coated microcrystalline cellulose beads as the appropriate pharmaceutical form. Linaclotide was classified as a class III active substance per BCS (biopharmaceutical classification system). By selecting a process where linaclotide is dissolved and sprayed onto microcrystalline cellulose beads, the particle size distribution is not considered a critical quality attribute for the dissolution behaviour.

As a peptide, linaclotide is known to be chemically reactive towards aldehydes and ketones. Hence attention has been paid to the levels of formaldehyde present in excipients, packaging components and the manufacturing environment. The suitability of the excipients was determined with excipient compatibility studies. The list of excipients include: microcrystalline cellulose (diluent), hypromellose (binding agent), hydrochloric acid (acidifying agent), calcium chloride dihydrate and leucine (stabilising agents). The gelatin capsule consists of gelatin (shell matrix), titanium dioxide (opacifer), red iron oxide and yellow iron oxide (colourants). The excipients selected for Constella are commonly used in this type of formulation and comply with the Ph.Eur., except for some excipients in the capsule cap and printing ink for which adequate specifications (USP or NF) have been set. The full list of excipients can be found in section 6.1 of the SmPC.

The selection of the excipients has been extensively discussed in the dossier. Microcrystalline cellulose beads were selected as substrate in view of stability of the final finished product. The bead particle size was selected carefully to ensure efficiency and uniformity of coating, as well as stability. Hydrochloric acid was chosen as a spray coating solvent media due to its capability to dissolve linaclotide at high concentrations with acceptable stability characteristics thus enabling a time efficient spray coating process. Hypromellose was selected to support the adhesion of linaclotide to the microcrystalline bead surface. Additives were evaluated for their stabilising effect on the linaclotide degradation. Calcium chloride dihydrate and leucine were identified as effective stabilisers. A combination of these stabilisers in the formulation was shown to improve the stability of the product by controlling the major degradation pathways for linaclotide. A design of experiment (DOE) was conducted to determine the optimum levels of calcium chloride dihydrate and leucine as stabilisers and of hypromellose as binder.

Comparative dissolution data between the phase 3 and commercial batches have been provided to demonstrate that no significant differences exist in their dissolution behaviour. Because the composition of the drug layered beads used in the phase 3 formulation is identical to the proposed commercial formulation, no bioequivalence studies were considered necessary between the phase 3 and commercial formulation and comparative dissolution data were sufficient.

The primary packaging proposed is a high density polyethylene (HDPE) bottle with polypropylene (PP) child-resistant screw cap, containing one or more (depending on the pack-size) desiccant canisters with silica gel. The material complies with PhEur. requirements and applicable regulations and it is adequate to support the stability and use of the product.

Adventitious agents

Gelatin obtained from bovine/limed bone is used in the product. Valid TSE certificates granted by the EDQM have been provided and confirm, for each source of gelatin, compliance with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01). There are no novel excipients used in the manufacture of Constella.

Manufacture of the product

The manufacturing process consists of three main steps: i) dissolution of the active substance and the excipients in an acidic coating solution, ii) coating of this solution onto inert microcrystalline cellulose beads and iii) encapsulation of the appropriate amount of coated beads in hard gelatin capsules. A detailed manufacturing description and flow scheme have been provided. The manufacturing process is considered to be a non-standard process. Adequate in-process controls are performed to control the manufacturing process. The acceptance criteria and the test methods are adequately chosen to ensure that the finished product will comply with the specification limits. The manufacturing process involves no novel technology or procedures and the manufacturer has demonstrated to have experience with the technology used.

The manufacturing process has been validated on two production scale batches which have been manufactured with linaclotide from each active substance supplier. The validation will be completed before marketing of the finished product following an agreed validation scheme. The full-scale validation scheme proposed by the applicant was agreed with the Scientific Advice Working Party in Scientific Advice in October 2009. The proposed sampling plan, tests, acceptance criteria and methodology are considered adequate to validate the manufacturing process.

The validation results obtained so far indicate that the manufacturing process for Constella is capable of consistently producing hard capsules that meet the quality and release specifications as detailed in the finished product specifications.

Product Specification

The finished product release and shelf-life specification includes tests for appearance (visual), identity (HPLC) and assay of linaclotide (HPLC), degradation products (HPLC), titanium dioxide and iron oxide identity (in-house method), content uniformity (Ph.Eur), water content (Ph.Eur.), mulitmers (in-house method), dissolution (Ph.Eur.) and microbial control (Ph.Eur.). The finished product specifications are standard for hard gelatin capsules. The proposed test procedures and acceptance criteria comply with the requirements of the Ph.Eur. and ICH guidelines. All tests included in the specification have been satisfactorily described and validated. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. Batch analysis data are provided for two validation batches (one for each active substance supplier), six pilot scale batches and several other supporting batches. Batch analysis results comply with the predefined specifications and confirm consistency & uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability studies have been carried out under long term (25°C/60%RH), intermediate (30°C/65%RH) and accelerated (40°C/75%RH) conditions, on six pilot scale batches using the active substance from both active substance manufacturers. Up to 24, 12 and 6 months data have been provided, respectively. The parameters tested and analytical methods used are identical to those used for the release specifications, except for the content uniformity and identity tests which are not tested in the stability studies. The methods used for assay and related substances were proven to be stability indicating. Two production scale stability batches have been manufactured at the proposed finished product manufacturing site, according to the proposed process and using the active substance obtained from the two proposed active substance manufacturers. Stability tests have been carried out in the packaging proposed for marketing.

All results at long term and intermediate storage conditions were conform to the proposed end of the shelf-life specifications, and no differences in stability were observed between batches from the two active substance suppliers. However, the CHMP believes that the proposed end of shelf life specifications for specified and unspecified impurities and water content can be further tightened in view of the batch analysis data provided by the applicant. Hence, the CHMP has recommended the applicant to re-evaluate the limits of the finished product shelf-life specification once full-term stability data on three process validation batches are available, together with release and available stability data for at least ten more full-scale production batches.

A bracketing study design was proposed for the generation of stability data on the four proposed pack sizes. This approach was agreed with the SAWP in 2009. The bracketing strategy was also applied for in-use stability testing. Up to 18 months in-use stability data have been provided with the fresh manufactured finished product and up to 12 months with the aged product (stored during 9, 12 or 24 months). From the in-use stability studies was concluded that after first opening, all pack sizes of Constella are stable for up to 18 weeks under the normal conditions of use.

Photostability studies have been carried out in accordance with ICH Q1B and confirmed that the product is not photosensitive and the primary packaging affords adequate protection from light.

In conclusion, the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

The pharmaceutical part of the MAA dossier focused on the fact that Constella contains a low amount of active substance, and the fact that the active substance is a synthetic peptide. The CHMP considers that the applicant has an adequate manufacturing process and controls in place to ensure a good content uniformity, stability and overall quality of the finished product.

At the time of the CHMP opinion, there were no unresolved quality issues which could have an impact on the benefit/risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendation for future quality development

The CHMP recommends the applicant to re-evaluate the limits of the finished product shelf-life specification once full-term stability data on three process validation batches are available, together with release and available stability data for at least ten more full-scale production batches.

2.3. Non-clinical aspects

2.3.1. Introduction

A comprehensive non-clinical programme has been performed covering studies to investigate pharmacology including safety pharmacology, pharmacokinetics as well as toxicology including repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development. The studies have been performed in rats, mice, rabbits, dogs and cynomolgus monkeys. Drug administration was performed mainly per os, mimicking the human route of administration, or i.v..

Scientific advice was received from the European Medicines Agency on non clinical development, where issues about genotoxicity studies, safety pharmacology studies and general non clinical development were discussed. Other scientific advice on non-clinical development was received nationally.

The pivotal toxicology studies supporting the safety of linaclotide were conducted in compliance with Good Laboratory Practice (GLP) regulations and International Conference on Harmonization (ICH) guidelines, with the exception of a single dose toxicity study in monkeys.

2.3.2. Pharmacology

Linaclotide is a guanlylate cyclase-C (GC-C) receptor agonist. GC-C receptor is found in the luminal aspect of intestinal epithelium and dopamine neurons in the brain, and is a key receptor for heat-stable enterotoxins that are responsible for acute secretory diarrhea. Linaclotide is structurally related to the guanylin peptide family, which is involved in the regulation of intestinal fluid homeostasis and bowel function, and includes the hormones guanylin and uroguanlyin. Linaclotide, similarly to guanylin and uroguanylin, is able to increase intracellular concentrations of the second messenger cyclic guanosine monophosphate (cGMP) through activation of the GC-C receptor, located on the apical surface of epithelial cells throughout the intestine. The presence of intracellular cGMP triggers a signal transduction cascade that leads to the activation of the cystic fibrosis transmembrane conductance regulator (CFTR) through its cGMP-dependent phosphorylation by protein kinase G II (PKG II). CFTR activation causes secretion of chloride and bicarbonate into the intestinal lumen, causing an increase in fluid secretion and acceleration of GI transit. cGMP is also transported out of the cell into the intestinal lumen and submucosa, modulating the activity of local afferent nerve fibers and causing a reduced visceral pain. Linaclotide has one active metabolite (MM-419447) which is formed by the removal of one carboxy-terminal tyrosine. Linaclotide and MM-419447 are approximately equally potent in

activation of the GC-C receptor. MM-419447 is a metabolite in all species involved in the development program, including man.

Primary pharmacodynamic studies

The Applicant has performed several receptor binding studies in human T84 cells, freshly isolated rat intestinal epithelial cells, in wild-type and GC-C receptor KO mice, and in rat intestinal brush-border membranes to show linaclotide and linaclotide's active metabolite MM-419447 affinity to the GC-C-receptor. Linaclotide and MM-419447 were equally potent in binding to the GC-C-receptor with a Ki in the low nanomolecular range. The study on pH dependence [MDP-103-067-PHR-01] revealed no significant influence of the pH on the binding affinity, predicting that linaclotide will likely bind to the receptor even in the gastrointestinal environment.

Further studies performed with T84 and CaCo cells showed that linaclotide and its active metabolite MM-419447 stimulate an increase of cellular cGMP concentration and a cGMP efflux to the basolateral and apical side of the gastrointestinal cells. Although not directly shown the Applicants conclusion is reasonable, that this effect is mediated by an active transport process.

Linaclotide and MM-419447 ability to influence intestinal fluid secretion was further investigated in juvenile mice, rats and GC-C-receptor KO mice. Linaclotide and MM-419447 were shown to increase gastrointestinal fluid secretion in animals with functional GC-C receptors. The studies in mice, rats and GC-C KO mice show that linaclotide enhances gastrointestinal transit in GC-C-receptor competent animals and the occurrence of watery and non-formed faeces. The two conducted In Vivo studies in rats to evaluate the GI-transit after postoperative ileus and after opiate induced delay demonstrated that linaclotide has the ability to reverse on the one hand the surgically induced delayed GI transit and on the other hand the opiate induced constipation dose dependently. These pharmacological results can be expected for a selective agonistic ligand of the GC-C-receptor of the intestinal lumen, supported by a negative result for binding to opiate receptors tested in the receptor binding studies.

Further studies were performed in rats, mice and KO mice to investigate linaclotides effects in models of visceral pain. The studies show that linaclotide reduces visceral pain in inflammatory and stress induced pain models in GC-C receptor competent animals and that this effect is most likely mediated by the liberation of cGMP.

Secondary pharmacodynamic studies

To assess any further secondary effects by linaclotide one in vitro receptor screen and three in vivo pharmacodynamic studies have been performed.

In the receptor binding study 50 mammalian receptors and ion channels were tested. No significant effects were observed up to a concentration of 10 µM, compared to the respective specific ligand. The concentration at which these possible interactions have been tested is more than 1.000-fold higher than the predicted pharmacological concentration for linaclotide in humans.

Effects of linaclotide on the paracellular permeability of intestinal epithelium were not detected in an in-vivo study in rats by using radiolabeled EDTA for detection in the urine.

The Applicant has performed two studies to investigate linaclotide's potential activity on known substrate transporter P-gp. The Applicants conclusion, that linaclotide is not likely to be a target of the P-gp transporter is supported. Although linaclotide is shown to be an inhibitor of the OATP2B1 transporter in vitro and the active metabolite MM-419447 of BCRP and PEPT1, considering the very

short half-life of linaclotide and its active metabolite within the gastrointestinal lumen as shown in the animal studies the clinical relevance appears currently to be low.

Studies with linaclotide impurities or degradants revealed no noteworthy pharmacodynamic effects.

Safety pharmacology programme

The Applicant has performed in vitro and in vivo safety pharmacology studies to investigate potential effects on cardiovascular function. Effects on respiratory function were investigated in anesthetised dogs. Effects on the CNS were assessed during the repeated dose toxicity studies.

Linaclotide showed a very weak activity in the micro molar range in the hERG Assay, whereas MM-419447 was not tested. In the in vivo-studies in dogs some effects were noticed after intravenous administration of linaclotide, but were believed to be without biological significance. The active metabolite MM-419447 was not tested itself. Since linaclotide has a very low oral bioavailability and since no relevant plasma concentrations will be reached in the clinical use of the medicinal product the CHMP concluded that further studies on cardiovascular parameters are not required. No effects on respiratory parameters were observed. No separate studies on linaclotide's influence on central nervous parameters have been performed. However, no effects on neurobehaviour parameters have been observed during the repeated dose toxicity studies.

Pharmacodynamic drug interactions

No specific pharmacodynamic drug interaction studies were conducted, which is accepted. Non-clinical studies regarding food interaction are not required due to the available data in healthy subjects suggesting that food increases the pharmacodynamics of linaclotide

2.3.3. Pharmacokinetics

Absorption:

The applicant has performed studies in rat and mice to investigate linaclotide/MM-419447 absorption. The studies show clearly that systemic exposure after oral administration is low.

Distribution:

In line with linaclotide's low oral biovailability, no linaclotide or MM-419447 could be detected in the study on distribution. Placental transfer and excretion within milk was not specifically investigated. Since conventional radio-assays will not be very significant, further studies were not considered necessary.

Metabolism:

The metabolism of linaclotide was investigated in a set of experiments, predominantly in rodents. Linaclotide is metabolised in the intestine by immediate break down of the disulfide bridges which prone linaclotide to further digestion by the enzymes present in the gastrointestinal environment. Several breakdown products containing 3-13 amino acids have been identified. Only one metabolite, MM-419447, was shown to be pharmacodynamic active.

A second set of experiments investigated the effects of linaclotide on the human CYP450 systems without any evidence that linaclotide will inhibit the human cytochrome system. A similar result was obtained for MM-419447.

Excretion:

The applicant has performed one study in rats to investigate the faecal concentration of linaclotide and its metabolite MM-419447 after oral administration in rats. The recovery was below 1% of the dose applied. In a second study in normal and functional deficient rats it was shown that linaclotide and MM-4194467 are predominantly excreted by the kidney in the case of reaching systemic circulation; however other excretion pathways appear to be involved.

2.3.4. Toxicology

Single dose toxicity

Two single dose toxicity studies have been performed in rats and two studies in Cynomolgus Monkeys for evaluating NOAEL and MTD after oral or intravenous administration. No related effects for linaclotide after oral or intravenous administration in rats were observed in both sexes up to the maximal dose of 5.0 mg/kg; therefore a NOAEL was determined to be ≥5.0 mg/kg.

In Cynomolgus monkeys, changes in stool consistency (nonformed or liquid feces) effects could be observed at oral doses ≥1.5 mg/kg and are probably related to the pharmacological action of linaclotide. Single intravenous doses of linaclotide up to 15 mg/kg were well tolerated, associated with reversible stool consistency changes only. In an additional Phase 2, two male and two female monkeys were intravenously dosed for seven consecutive days with 15 mg/kg/day linaclotide. Plasma levels declined rapidly after administration down to the LLOQ of 3.0 ng/ml and mean t1/2 was approximately 1.5h on day 1 and 7 for both genders. Therefore, a NOAEL ≥5.0 mg/kg after oral administration and a MTD of ≥15.0 mg/kg after intravenous administration, respectively, were determined.

Repeat dose toxicity

Repeated dose toxicity studies have been performed in rodents and non-rodent species. Two studies have been performed in mice. One study of 13 weeks and one of 26 weeks with an additional recovery period of two weeks revealed an NOAEL of 20 mg/kg/day due to an increased mortality in the higher dosing groups. The cause of death in the higher dosing groups could not clearly be estimated, since no clear correlation could be found in the pathology investigations. No clear pharmacodynamic response is obtained in these studies, since the changes in stool consistency and defecation frequency are not in accordance with the proposed pharmacodynamic effect. However, linaclotide was shown to be pharmacodynamic active in the previous sections of this dossier.

Two studies of 2 weeks and 13 weeks with an additional recovery period have been performed in rats. The NOAEL was estimated to be above 100 mg/kg/day, which was the highest dose tested in this species.

Two studies of 2 and 13 weeks with an additional recovery of 2 weeks have been performed in cynomolgus monkeys. The NOAEL was estimated to be 5 mg/kg/day due to an exaggerated pharmacodynamic effect in the higher dosing groups. The studies in non-human primates are performed in small animal numbers for animal welfare reasons, and therefore the database for clinical observations and pathology is rather sparse. However, the use of cynomolgus monkeys was adequately justified by the Applicant.

There are some findings in the heart of the high dose group/recovery animals which are rather unexpected. In mice degeneration and necrosis of the heart, necrosis of the coronary artery and mineralization were observed, in rats there are mononuclear infiltrations and a decrease in heart weights; and in monkeys an increased incidence of inflammation processes were reported (MNP-103-021-TXR-01). However, ECG recordings which have been performed during the studies revealed no

effects on cardiac activity. All other findings are likely to be incidental in rats and monkeys and the tolerability of linaclotide is limited by the pharmacodynamic activity of linaclotide in these species. In addition, in the 13-week study in mice, mortality related to linaclotide was observed at dose levels ≥ 100 mg/kg/day, along with microscopic changes in the lymphoid system, GI tract, kidney and heart at doses ≥ 100 mg/kg/day. In the 13-week study in monkeys a male in the middle-dose group was euthanized with microscopic lymphoid lesions and bacterial and fungal colonization of the esophagus consistent with immunologic compromise. However, no similar findings were detected in other animals, and in the 39-week study in monkeys (MNP-103-028-TXR-01) the cause of the unscheduled termination of two animals seem to be an exaggerated pharmacological effect of linaclotide without apparent effects on the immune system. Therefore, it is considered that the changes observed in organs or tissues described in the 13-week mouse study and the 13-week monkey study are secondary to the exaggerated pharmacological effect of linaclotide or spontaneous, and they have no clinical relevance

Genotoxicity and Carcinogenicity

Linaclotide was tested in vitro for genotoxic effects and in life time bioassays in mouse and rat for carcinogenic effects. No treatment related effects were observed. It was noted though that no linaclotide was detected in plasma during the carcinogenicity studies, in contrast to the 26-week repeated toxicity study. However, it is acknowledged that these observations are likely to be caused by an improved methodology for plasma bioanalysis developed after the initiation of the carcinogenicity studies and used in the 26-week toxicity study in mice.

Reproduction Toxicity

The reproductive and developmental toxicity of linaclotide was evaluated in a fertility and embryo-foetal development study in rats, embryo-foetal development studies in rats, mice and rabbits and a peri- and post-natal development study in rats. The juvenile toxicity was evaluated in mice and rabbits. Doses for reproductive toxicity studies in rats, mice and rabbits were selected based dose range finding studies.

In the fertility and embryo-foetal development study in rats, linaclotide did not induce adverse effects on male and female fertility.

No treatment-related adverse effects were noted up to the highest dose of 100 mg/kg/day (3243-fold the maximum recommended human dose, adjusted for body surface). The slightly lower body weight gain and slightly lower body weights noted in the 10, 50 and 100 mg/kg/day groups reaching significant differences at 50 and 100 mg/kg/day had no effect on the reproductive parameters.

In the early embryo-foetal development study in mice test article-related mortality and moribundity were observed at dosage levels of 40 and 100/40 mg/kg/day. Due to clinical signs, mortality and moribundity noted in the 40 and 100 mg/kg/day the 100 mg/kg/day dosage level was reduced to 40 mg/kg/day. Developmental toxicity was evidenced in the 40 and 100 mg/kg/day groups by significant lower mean foetal body weights resulting in lower mean gravid uterine weight. In addition, test article-related increased mean litter proportions of open eyelid and reduced body weight was noted at 40 mg/kg/day and vertebral anomaly with or without associated rib anomaly were noted in the 40 and 100/40 mg/kg/day groups. In contrast to these findings no clinical signs up to the highest dose group of 80 mg/kg/day were noted in the dose range finding study.

Based on the clinical signs, mortality and moribundity, as well as effects on the body weight, intrauterine growth and foetal morphology, a dose level of 5 mg/kg/day (81-fold the maximum

recommended human dose, adjusted for body surface area) was determined to be the NOAEL for maternal and embryo-foetal developmental toxicity in mice.

In rats and rabbits embryo-foetal development studies, no effects were seen on body weight, body weight gain, and food consumption. There was no evidence of maternal toxicity, embryo lethality, foetal-toxicity or teratogenicity in the studies. The minor dose dependent increase of soft feaces and brown fur staining in the rabbits is consistent with the known pharmacologic activity of linaclotide. Toxicokinetic results indicated no accumulation of linaclotide after multiple administrations.

Exposure to linaclotide from implantation to weaning (prenatal and postnatal development study conducted with linaclotide in rats) did not induce maternal toxicity. Viability, growth, mating and fertility in the offspring were not affected by daily treatment with linaclotide.

Behavioural and reproductive development of the F1 adult generation and the viability and growth of the F2 generation pups were unaffected by linaclotide administration.

The placental transfer was not evaluated. The concentration of linaclotide in milk of lactating rats was not tested.

The NOAEL for the F0, F1 and F2 generations was determined to be ≥ 100 mg/kg/day.

Toxicity of linaclotide in the juvenile organism has been investigated in the rabbit and mice. No specific toxic effects specific for juvenile animals have been observed in juvenile animals in the dose ranging study in rabbits. In the studies in mice the juvenile animals were more sensitive than the adult mice. Higher dose levels of linaclotide were tolerated when animals were older. An increased sensitivity of juvenile mice to orally administered linaclotide may be related to the increased expression of intestinal GC-C receptors in young animals (Al-Majali et al. 1999; Cohen et al, 1986) or possibly other factors such as those related to an immature GI system.

Toxicokinetic data

The Applicant has performed toxicokinetic evaluation for the pivotal toxicity studies, which show a rather low animal exposure to linaclotide and MM-419447 at the respective NOAEL. This is in line with the metabolic degradation within the gastrointestinal environment. Therefore, the systemic half-life of the substance was not estimated in most of the studies. In humans exposed to therapeutic doses of linaclotide the systemic concentration was below the limit of detection. Therefore, no formal animal to human safety margin could be calculated by these parameters. The Applicant has therefore performed a safety assessment based on body surface area. These calculations revealed a safety margin greater than 300. In addition, it should be considered that the dose limiting factor in the monkey studies was due to exaggerated pharmacodynamic effects.

Local Tolerance

No specific local tolerance studies were performed, but effects on local tolerance were detected in the repeated-dose toxicity studies (p.o.): reversible erosions in stomach and cecum in mice, and in the pivotal study in monkeys, the two euthanized animals showed microscopic findings (degeneration/necrosis) in the mucosal glands and surface epithelium in the colon, cecum and rectum. In the single-dose toxicity studies where linaclotide was administered intravenously, no effects in the site of injection were found. The effects on local tolerance are not considered to have clinical relevance because they are reversible and the safety margin is sufficient. Linaclotide is orally-administered; therefore no sensitization studies are required.

Other toxicity studies

Regarding the multimer impurities, multiple linaclotide batches containing high levels of multimers were used in GLP toxicology studies. The batch PPL-MD11000501, with a 13.1% of multimers, was used in 13-week rat and monkey studies. No adverse findings were detected in these studies.

2.3.5. Ecotoxicity/environmental risk assessment

The active ingredient linaclotide is a peptide. A general exemption from an environmental risk assessment is granted for peptides in guideline (EMEA/CHMP/SWP/4447/00). This exemption is based on the assumptions that peptides are readily biodegradable, can only be administered in a parenteral way, are not excreted in an intact form and do not reach the environment.

These assumptions are not true for linaclotide. Linaclotide is a member of the guanylin peptide family, which includes the natural hormones uanylin and uroguanylin as well as the bacterial heat stable enterotoxin, STa. Like STa, linaclotide is stable across a broad pH range including low pH found in the stomach. Due to its exceptional stability (compared to other peptides), linaclotide may be administered orally. In the human intestinal tract the 14th amino acid, Tyrosin, is cleaved resulting in an equally bioactive metabolite MM 419447. The active ingredient and its active metabolite are excreted to up to 6 % and might reach the environment. Therefore no general exemption can be granted from an environmental risk assessment for linaclotide.

The environmental risk assessment at Phase I leads to a PEC surface water below 0.01 µg/L. According to EMEA/CHMP/SWP/4447/00 information on the octanol-water partitioning coefficient for the active ingredient is required in Phase I. However, the octanol/water partition coefficient that is normally used in Phase I to screen for potentially bioaccumulative substances is not a good predictor for this property for macromolecular compounds of the size of linaclotide. The applicant states that considering all available information (low LogKow, high solubility and low permeability into Caco-2 cells) suggest that bioaccumulation of linaclotide should be considered very unlikely. This was accepted by the CHMP. Therefore, a Phase II assessment has not been conducted.

Table 1. Summary of main study results

Substance (INN/Invented Name): linaclotide			
CAS-number (if available): 851199-59-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Custom method at pH 7.4	log D_{ow} below method quantification limit	logD_{ow} (pH 7.4) likely below -2
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	likely below -2 (see above)	not a good predictor for bioaccumulation for polymeric substances
	BCF		no data available
Persistence	DT50 or ready biodegradability		no data available
Toxicity	NOEC or CMR		no data available
PBT-statement :	A PBT assessment has not been conducted. The available information from the PBT screening step (low logDow, high solubility and low permeability into Caco-2 cells in virtro) suggests that bioaccumulation of linaclotide should be considered very unlikely.		

Substance (INN/Invented Name): linaclotide			
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.00145	µg/L	< 0.01 threshold
A Phase II assessment has not been conducted as PEC $_{surfacewater}$ is below the action limit of 10 ng/L.			

2.3.6. Discussion on non-clinical aspects

Linaclotide, a fully synthetic peptide, mimics the function of the endogenous hormones guanylin and uroguanlyin. Based on its mechanism of action it can be assumed that Linaclotide and its active metabolite effects on regulation of intestinal fluid homeostasis, bowel function and visceral pain are mediated by the linaclotide induced liberation of cGMP from gastrointestinal cells.

Secondary pharmacodynamics studies and demonstration of a very short half-life of linaclotide and its active metabolite within the gastrointestinal lumen reveal that non-specific interaction and effect on passive transport processes are very unlikely.

Linaclotide has a very low oral bioavailability and no relevant plasma concentrations will be reached in the clinical use of the medicinal product therefore taken together the core battery on safety pharmacology reveals no specific risks for the clinical use of linaclotide.

Phamacokinetic studies on Linaclotide reveal low exposure after oral administration and this is most probably caused by a low absorption and not by an enhanced degradation in the liver or an enterohepatic recirculation. The low absorption reflects in an absence of detection of Linaclotide in studies of distribution. Metabolism is due to digestion by enzymes present in the gastrointestinal environment and excretion of the Linaclotide and its metabolite is very low in the faeces.

Changes observed in organs or tissues described above in the 13-week repeat dose toxicity studies in mice and monkeys are considered secondary to the exaggerated pharmacological effect of linaclotide or spontaneous, and have no clinical relevance.

No treatment related effects were observed as genotoxic and/or carcinogenic.

Based on the reproductive and developmental toxicity studies the risk of reproductive or developmental toxicity in humans is considered to be low. However, because animal reproduction studies are not always predictive of human responses, the actual risk of linaclotide during pregnancy in humans remains uncertain. This is properly addressed in the SmPC.

Given the low oral bioavailability and low permeability coefficients of linaclotide, it is unlikely that measurable active peptide would be present in the milk of lactating women.

In the studies in mice the juvenile animals were more sensitive than the adult mice therefore based on these nonclinical data, very young paediatric patients may be extremely sensitive to the effects of orally administered linaclotide and the sensitivity may decrease with age. Therefore, Constella is not recommended for use in children and adolescents; this is reflected in the SmPC.

The performed safety assessment based on body surface area revealed a safety margin greater than 300. The Applicant's approach is acceptable under these conditions.

Regarding the multimer impurities no adverse findings were detected in these studies.

Available information on environmental risk assessment (low LogKow, high solubility and low permeability intoCaco-2 cells) suggest that bioaccumulation of linaclotide should be considered very

unlikely. In conclusion, PEC surfacewater for linaclotide is below the action limit of 0.01 µg/L and Linaclotide is not considered to possess PBT properties.

2.3.7. Conclusion on the non-clinical aspects

From the non-clinical point of view the Applicant has investigated the pharmacodynamic and pharmacokinetic properties and the toxicity of linaclotide to a sufficient extend to support the indication applied for. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development program included 7 completed randomized, well-controlled, clinical studies (3 phase I, 2 phase II and 2 phase III) and 2 ongoing open-label long-term safety (LTS) studies, with an overall exposed population to linaclotide of 2753 IBS-C patients and 75 healthy subjects. The 2 pivotal studies were randomized placebo-controlled double-blind clinical trials with a duration of 12 and 26 weeks, designed to assess the effects of linaclotide on the signs and symptoms of IBS-C that are most important to patients. The two long-term safety studies, MCP-103-305, and LIN-MD-02 are ongoing; initially submitted data with data lock October 2010 was during the evaluation updated with data lock June 2011.

For the development of medicinal products for the treatment of IBS, the "Points to consider on the evaluation of medicinal products for the treatment of irritable bowel syndrome" (CPMP/EWP/785/97) are relevant. Generally, the guideline refers to two alternatives for drug development, referring to the nature of disease: Either a short-term intermittent treatment can be aimed it, for which it is required to elucidate several aspects of this mode of administration (dose-response, first use, repeated use, withdrawal and rebound effects), or the development for a long-term continuous use of the product, requiring the inclusion of patients with well-defined IBS into trials that should have a duration long enough to determine if any response will be sustained (6 months is given), and to evaluate a withdrawal effect. Linaclotide has been developed for long-term continuous treatment.

The clinical development programme was subject to Scientific Advice by the EMA as well as several national competent authorities..

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Tabular overview of phase 1 and 2a studies:

Study number	Title of the study
MCP-103-103	A Randomized, Open-Label, Two-Period, Two-Sequence, Crossover Trial Of Oral Linaclotide Acetate Administered To Healthy Volunteers under Fed and Fasting Conditions.

Study number	Title of the study
MCP-103-001	Single Oral, Ascending Dose, Placebo-Controlled study in healthy males and postmenopausal females
MCP-103-002	A 7-Day, Oral, Multiple-Ascending Dose, Placebo-Controlled Study of MD-1100 Acetate in Healthy Subjects
MCP-103-005	A Phase 2 Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Pharmacodynamic Effects of Orally Administered 100 mcg and 1000 mcg QD MD-1100 Acetate on Gastrointestinal Transit in Patients with Constipation Predominant Irritable Bowel Syndrome (C-IBS).

The studies in healthy volunteers included 22 placebo- and 75 linaclotide-treated subjects altogether being treated for a maximum of 7 days. The phase 2a study included 36 patients randomised into three groups.

Table 2: Overview on phase 2b and phase 3 studies.

Study ID No. of study centres	Design Duration	Study Posology	Study Objective	Subjects by arm entered/ completers	Gender M/F Median Age	Primary Endpoint
MCP-103-202 92	randomized, placebo-controlled double-blind 3 months	72µg, 145 µg, 290 µg, 579 µg or placebo once daily	Evaluation of dose-ranging safety, efficacy and dose response	79/63 82/67 85/71 89/71 420 linaclotide 85/65 placebo	387 F/ 33 M Age: 45.0	Change in weekly CSBM rate from week 1 through 12
LIN-MD-31 118	randomized, placebo-controlled double-blind 3 months plus 4 weeks randomised withdrawal	290 µg or placebo once daily	Evaluation of safety and efficacy	406/312 lin 397/335 plc.	726 F/ 76 M Age: 43.5 (mean)	Co-primary: 12 week abdominal pain responder; 12 week IBS degree of relief responder
MCP-103-302 102	randomized, placebo-controlled double-blind 6 months	290 µg or placebo once daily	Evaluation of safety and efficacy	402/294 linaclotide 403/305 placebo.		Co-primary: 12 week abdominal pain responder; 12 week IBS degree of relief responder

In addition, data from the PK and safety data from the development of linaclotide for the treatment of chronic constipation (CC) was provided.

Three different formulations of linaclotide have been evaluated in the clinical studies: an oral aqueous solution of linaclotide (Formulation A), an oral hard gelatine capsule containing linaclotide (Formulation B) and an improved capsule formulation (Formulation C, proposed commercial formulation). Table 3 indicates which formulation has been used in the different studies.

Table 3: Linaclotide Formulations used in the Clinical studies. (PK studies are highlighted in bold).

Linaclotide Formulation	Description of Clinical Studies	Clinical Study Numbers
Formulation A (Oral Solution)	Phase 1 Safety and Tolerability Studies	**MCP-103-001, MCP-103-002**
	Phase 2a Studies	MCP-103-004, MCP-103-005
Formulation B (Oral Hard Gelatine Capsule)	Phase 1 Food Effect Study	**MCP-103-103**
	Phase 2b Studies	MCP-103-201, MCP-103-202
Formulation C (Oral Hard Gelatine Capsule)	Phase 3 Trials	**MCP-103-303, MCP-103-302, LIN-MD-01, LIN-MD-31**
Proposed Commercial Formulation	LTS Studies	MCP-103-305, LIN-MD-02

2.4.2. Pharmacokinetics

Linaclotide pharmacokinetics, have been assessed in three in-vivo studies in healthy volunteers, and in the two phase 3 studies in IBS-C in patients and in two such studies in CC patients. An overview on these studies, including the main results, is given in the following table.

Table 4: Summary of clinical PK results following oral dosing of linaclotide in humans:

Study Number	Linaclotide Doses (PK Subjects)	Plasma Collection Times	Linaclotide Plasma Concentrations	MM-419447 Plasma Concentrations
PK STUDIES IN HEALTHY VOLUNTEERS				
MCP-103-001	Single Placebo (6); 29 µg (4); 97 µg (8); 290 µg (4); 966 µg (4); 2897 µg (4)	0, 0.25, 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 36, and 48 h	All BQL (LLOQ = 3.00 ng/ml)	All BQL (LLOQ = 3.00 ng/ml)
MCP-103-002	QD x 7 days Placebo (16); 29 µg (8); 97 µg (8); 290 µg (8); 966 µg (8)	Day 1 & 7: 0.5, 1, 3, 6, 9, 12, and 24 h (pre-dose on Day 2)	All BQL (LLOQ = 3.00 ng/ml)	All BQL (LLOQ = 3.00 ng/ml)
MCP-103-103	QD x 7 days 290 µg (9 Fed)	Day 7 0, 0.5, 1, 2, 3, 4, 6, and 24 h	All BQL (LLOQ = 0.200 ng/ml)	All BQL (LLOQ = 2.00 ng/ml)
	QD x 7 days 290 µg (10 Fasted)		All BQL (LLOQ = 0.200 ng/ml)	All BQL (LLOQ = 2.00 ng/ml)

Study Number	Linaclotide Doses (PK Subjects)	Plasma Collection Times	Linaclotide Plasma Concentrations	MM-419447 Plasma Concentrations
	Single 2897 µg (9 Fed)	0, 0.5, 1, 2, 3, 4, 6, and 24 h	All BQL (LLOQ = 0.200 ng/ml)	All BQL (LLOQ = 2.00 ng/ml)
	Single 2897 µg (9 Fasted)		Subject 19 C_{max} = 0.212 ng/ml (0.5 h) Subject 12 C_{max} = 0.735 ng/ml (2 h) (LLOQ = 0.200 ng/ml)	All BQL (LLOQ = 2.00 ng/ml)
SPARSE-SAMPLING PK STUDIES IN PATIENTS WITH CC				
LIN-MD-01	QD x 12 weeks Placebo (40); 145 µg (51); 290 µg (53)	Day 1 2 h Day 29 (± 3 days) Single time point (varied among patients)	All BQL (LLOQ = 0.200 ng/ml)	All BQL (LLOQ = 2.00 ng/ml)
MCP-103-303	QD x 12 weeks Placebo (96); 145 µg (101); 290 µg (98)	Day 1 2 h Day 29 (± 3 days) Single time point (varied among patients)	All BQL (LLOQ = 0.200 ng/ml)	All BQL (LLOQ = 2.00 ng/ml)
SPARSE-SAMPLING PK STUDIES IN PATIENTS WITH IBS-C				
LIN-MD-31	QD x 12 weeks Placebo (72); 290 µg (64)	Day 1 2 h Day 29 (± 3 days) Single time point (varied among patients)	All BQL (LLOQ = 0.200 ng/ml)	All BQL (LLOQ = 2.00 ng/ml)
MCP-103-302	QD x 12 weeks Placebo (93); 290 µg (98)	Day 1 2 h Day 29 (± 3 days) Single time point (varied among patients)	Pt 07-2006 = 0.241 ng/ml (Day 1) Pt 49-2006 = 0.239 ng/ml (Day 1) (LLOQ = 0.200 ng/ml)	All BQL (LLOQ = 2.00 ng/ml)

The extent of the programme to explore the pharmacokinetics of linaclotide reflects that the substance, being a short, only 14-amino-acid peptide, is not relevantly taken up into systemic circulation. Three studies in healthy volunteers have only yielded measurable plasma concentrations in a minority of subjects treated with a 10-times supratherapeutic dose, and four studies in the clinical phase 3, with sparse PK sampling in 465 patients, have only resulted in measurable plasma concentrations in 2 subjects. Therefore, certain studies of a classical PK programme have not been conducted, e.g. a mass balance study, metabolism, and excretion of the drug, or studies in special populations (renally and hepatically impaired patients). This is considered to be acceptable.

For detection of linaclotide and MM-419447 in human plasma, only LC/MS/MS methods were applied. A initial LC/MS/MS method for the quantitation of linaclotide and MM-419447 in human plasma was developed and validated with a lower limit of quantitation (LLOQ) of 3 ng/mL for both parent and metabolite (method MNP-103-004). The LC/MS/MS bioanalytical method was refined (method MNP 103 043) and was validated with a 15-fold increase in sensitivity for linaclotide (LLOQ = 0.2 ng/ml) and a 1.5-fold increase for MM-419447 (LLOQ = 2.0 ng/ml). MNP-103-043 was used in the analysis of PK samples from the Phase 1 food-effect study (MCP-103-103) and the four Phase 3 trials (MCP-103-302, MCP-103-303, LIN-MD-01, and LIN-MD-31).

Absorption

The absorption 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 (MCP-103-001, MCP-103-002, and MCP-103-103), patients with IBS-C (MCP-103-302 and LIN-MD-31), and patients with CC (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. In the target population, only 2 of the 162 patients treated with linaclotide who underwent PK sampling in the two IBS-C Phase 3 trials had measurable concentrations of linaclotide which were just above the LLOQ (0.2 ng/ml). No samples collected after four weeks of dosing showed linaclotide concentrations greater than the LLOQ, and none of the plasma samples collected during the study had measurable concentrations of MM-419447 (LLOQ = 2 ng/ml) at either time point. Of the subset of PK patients in the two similarly conducted CC Phase 3 trials (n = 303), none of them had measurable concentrations of linaclotide or MM-419447 at either time point. These results suggest that systemic exposure to linaclotide and its active primary metabolite MM-419447 following oral administration is minimal. Further properties of the compound have been investigated in vitro, and it has been determined that – besides the degradation in the intestines – obviously also the low permeability in intestinal cells is responsible for the missing systemic availability.

With regard to the two different capsule formulations subject to the clinical development t programme, similar observations i.e no observed absorption and similar pharmacokinetics in the food effect studies with formulations B and C provide evidence that there is no relevant impact on bioavailability of linaclotide due to the excipients.

Distribution

Distribution of linaclotide and its active primary metabolite MM-419447 could not be studied in humans due to their minimal absorption following oral administration of linaclotide. In mice, linaclotide and its metabolite MM-419447 were not detectable in brain, liver, or adipose tissues.

Elimination

Excretion:

Nearly all orally dosed linaclotide is cleared via metabolism and degradation in the intestine, and only a small proportion is excreted as active peptide in the faeces of humans during a faecal recovery study in healthy subjects, which is consistent with results from non-clinical studies. The IV administration of linaclotide in rats identified the kidney as the primary clearance organ for any active peptide in systemic circulation, with biliary clearance likely serving as an additional clearance pathway.

Not more than 6% of a single dose is finally excreted in faeces, with no relevant influence of concomitant food intake on this rate of recovery of active substance.

Metabolism:

Pre-clinical in-vitro investigations have shown that linaclotide does not interact with cytochrome P450 enzymes and is not metabolized in vitro by human intestinal microsomes. Peptides are typically degraded by proteolytic enzymes in the GI tract, and thus the metabolism and degradation of linaclotide was elucidated through a series of nonclinical studies and in vitro studies using the intestinal contents of rodents and humans. Proteolytic cleavage of the C-terminal tyrosine of linaclotide in the intestine yields the only known active metabolite, MM-419447, a 13-amino acid GC-C agonist with similar pharmacological properties to linaclotide. There are no known genetic polymorphisms in the degradation of linaclotide to its metabolite MM-419447.

Dose proportionality and time dependencies

In light of the low systemic exposure, no specific studies have been conducted, which is considered acceptable.

Special populations

No information on linaclotide PK is available in the elderly, children, hepatic or renal impairment, gender or race factors. The lack of measurable systemic concentrations of linaclotide and MM-419447 following oral dosing of linaclotide suggests that traditional PK studies on special populations are unlikely to yield interpretable results. The risk of altered clearance in special populations, such as renally or hepatically impaired patients, appears to be minimal given the low systemic availability of linaclotide. The lack of data together with the recommendation that the product should not be used in children is included in in the SmPC.

Since patients with chronic inflammatory bowel disease were excluded from the phase 3 protocols and no trials were conducted with patients with bowel inflammation, no information is available regarding bioavailability in more severe intestinal inflammation. According to the characteristics of linaclotide, a study in a diseased gut model would be of limited value and bibliographic data shows that inflammatory conditions appear to have little effect on drug absorption. In addition, during Phase 3 trials, a difference in exposure between IBS-C patients and healthy volunteers was not detected.

Therefore the lack of information regarding the effects of inflammation on absorption and the recommendation not to use linaclotide in these patients is adequately reflected in the SmPC.

Pharmacokinetic interaction studies

Linaclotide is, according to in-vitro investigations, neither a substrate, nor an inducer or inhibitor of relevant cytochrome drug metabolising enzymes, nor for a variety of relevant transporters, such as p-glycoprotein, MRP2-4, BCRP, OATP1B1 and B3, PEPT1, or OCTN1 at relevant concentrations.

Linaclotide is unlikely to affect non-metabolic drug clearance processes, such as renal and biliary excretion. Additionally, linaclotide is not expected to affect highly protein-bound drugs, as it does not circulate in the bloodstream to an appreciable extent.

Based on the a.m. properties, the possibility of an altered absorption of other compounds due to an influence on the gut motility is assessed to be remote. In addition, and contrary to other medications altering gut motility, linaclotide influences colonic motility only, and has negligible influence on gastric and small bowel motility. Also, altered absorption is anticipated to be associated to the occurrence of prolonged or severe diarrhoea only. The applicant has, however, included appropriate warning

statements into the SmPC for these cases. A relevant interaction potential is therefore not expected with the compound.

A clinically relevant interaction with the concomitant intake of a high-fat meal has been found in the food interaction study MCP-103-103, with the meal exerting exaggerated pharmacodynamic effects. The mechanism of this interaction is unclear. Importantly, the treatment recommendation as given in the SmPC has also been applied throughout the later development stages in patients, and found to be sufficiently safe.

Pharmacokinetics using human biomaterials

The company has conducted several in-vitro studies, using human biomaterials, for which the following table gives an overview:

Table 5: In-vitro studies using human biomaterial – overview:

Study Description and Report Study Number	Test System	Test Article Concentration (µg/ml)	Summary of Results
ABSORPTION			
Assessment of the ability of linaclotide to permeate intestinal epithelial cells [**PRD-RPT-EXP-00031**]	Caco-2 cells	Linaclotide: 0.24, 2.4, 24	Linaclotide has a low permeability profile in Caco-2 cells.
METABOLISM			
Linaclotide metabolism and degradation in the luminal contents of the human intestine [**MDP-103-041-IAR-01**]	Reconstituted intestinal fluid from human cadavers	Linaclotide: 100	The linaclotide metabolic/degradation pathway in humans is qualitatively the same as that in the rat, including formation of MM-419447 and proteolytic digestion of both active peptides.
Linaclotide stability in human intestinal microsomes[b] [**MDP-103-056-IAR-02**]	Pooled mixed-gender human intestinal microsomes	Linaclotide: 12	Linaclotide is not metabolized by human intestinal microsomes.
DRUG-DRUG INTERACTION			
Determination of the potential P-glycoprotein (P-gp) substrate or inhibitory activity of linaclotide[b] [**MDP-103-057-IAR-01**]	Caco-2 cells	Linaclotide: 0.12, 1.2, 12	Linaclotide is not a substrate for the efflux transporter P-glycoprotein.
	Caco-2 cells	Linaclotide: 0.24, 2.4, 24	Linaclotide is not an inhibitor of the efflux transporter P-glycoprotein.

Study Description and Report Study Number	Test System	Test Article Concentration (µg/ml)	Summary of Results
Assessment of the potential for linaclotide and MM-419447 to inhibit efflux and uptake transporters[b] [**SOLVO-Almirall-03-30Sep2010**]	Membrane vesicles from insect or mammalian cells over-expressing specific human efflux transporters	Linaclotide: 0.153, 1.53, 15.3	Linaclotide does not inhibit MRP2, MRP3, MRP4, or BCRP efflux transporters.
		MM-419447: 0.136, 1.36, 13.6	MM-419447 does not inhibit MRP2, MRP3, or MRP4, and weakly inhibits (18%) BCRP at the highest tested concentration (13.6 µg/ml).
	Membrane vesicles from insect or mammalian cells over-expressing specific human uptake transporters	Linaclotide: 0.153, 1.53, 15.3	Linaclotide does not inhibit OATP1B1, OATP1B3, PEPT1, or OCTN1 uptake transporters, and inhibits (55%) OATP2B1 at the highest tested concentration (15.3 µg/ml).
		MM-419447: 0.136, 1.36, 13.6	MM-419447 does not inhibit OATP1B1, OATP1B3, OATP2B1, or OCTN1, and weakly inhibits (18%) PEPT1 at the highest tested concentration (13.6 µg/ml).
Assessment of the human intestinal CYP450 inhibition potential of linaclotide[b] [**MDP-103-066-IAR-01**]	Pooled mixed-gender human intestinal microsomes	Linaclotide: 0.1625, 0.325, 0.65, 1.3, 2.6, 5.2	Linaclotide does not inhibit the common intestinal enzymes CYP2C9 and CYP3A4.
Assessment of the human liver CYP450 inhibition potential of linaclotide and MM-419447[b] [**AML/21**]	Pooled mixed-gender human liver microsomes	Linaclotide & MM-419447: 0.00005, 0.0005, 0.005, 0.015, 0.05	Linaclotide and MM-419447 do not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4 liver enzymes.
Assessment of the human liver CYP450 induction potential of linaclotide and MM-419447 [b] [**MDP-103-088-IAR-01**]	Fresh human hepatocytes from three donors	Linaclotide & MM-419447: 0.25, 2.5, 50 (CYP1A2 and 2B6) 0.25, 2.5, 50, 625, 1250, 5000 (CYP3A4/5)	Neither linaclotide nor MM-419447 induces CYP1A2, 2B6, or 3A4/5 liver enzymes.

Based on the in vitro studies it has been determined that – besides the degradation in the intestines – obviously also the low permeability in intestinal cells is responsible for the missing systemic availability.

In order to elucidate the fate of the compound within the human body further, the company has conducted studies to measure the degradation of the compound in intestinal fluid, which resulted in the same pattern of degradation as in animals, starting with the reduction of disulfide bonds, and further proteolysis by unspecific peptidases. A single active metabolite, MM-419447 has been detected, with similar pharmacodynamic properties, being a 13-amino-acid peptide. All other cleavage products

investigated are pharmacologically inactive, and finally are undergoing proteolytic degradation to individual amino acids in intestinal fluids.

The in-vitro Study PRD-RPT-EXP-00031 using Caco-2 cells indicate that linaclotide has a low permeability coefficient and is minimally absorbed across the intestinal epithelial layer.

2.4.3. Pharmacodynamics

The PD of orally administered linaclotide were evaluated in healthy subjects and patients through bowel habit assessments of stool consistency (BSFS), straining (using the seven-point Ease of Passage Scale or a five-point straining scale), stool frequency, and stool weight. The BSFS score used to determine stool consistency enabled patients to classify the form or consistency of their stool into one of seven categories, ranging from hard (Type 1) to entirely liquid (Type 7), with Types 3-4 representing the normal form [Heaton et al, 1991]. Because the form of the faeces largely depends on the time spent in the colon, measuring stool consistency using the BSFS is a surrogate for GI transit [Heaton et al, 1994]. Two different straining scales enabled patients to report the level of difficulty associated with defecation. During the Phase 1 and 2a clinical PD studies (MCP-103-001, MCP 103-002, and MCP-103-005), a seven-point Ease of Passage Scale was used (1 = manual disimpaction; 2 = enema needed; 3 = straining needed; 4 = normal; 5 = urgent without pain; 6 = urgent with pain; 7 = incontinent). For the PD food-effect study, MCP-103-103, a five-point ordinal straining scale (1 = not at all; 2 = a little bit; 3 = a moderate amount; 4 = a great deal; 5 = an extreme amount) that more closely captured symptoms of straining experienced by patients was used. The PD effects of linaclotide on GI function were determined in IBS-C patients by measuring the ascending colon emptying t½ value and the colonic geometric center at 24 hours relative to baseline (Study MCP-103-005). A summary of the Clinical Pharmacology studies is given in Table 6.

Table 6: Summary of Clinical Pharmacology studies

Study Description (Study Number)	Linaclotide Dose (Subjects)	PD Parameter Assessed	Summary of Results
PD Effect of Single, Ascending Linaclotide Doses on Bowel Habits (MCP-103-001)	Single Doses Placebo (6); 29 µg (4) 97 µg (8); 290 µg (4); 966 µg (4); 2897 µg (4)	BSFS Score (stool consistency) Stool Frequency Straining Score (Ease of Passage Scale) Stool Weight	BSFS score increased from baseline (indicating softer, looser stools) for each of the linaclotide doses, with greatest increases seen at doses ≥ 290 µg.
PD Effect of Multiple, Ascending Linaclotide Doses on Bowel Habits (MCP-103-002)	QD x 7 Days Placebo (16); 29 µg (8); 97 µg (8); 290 µg (8); 966 µg (8)	BSFS Score (stool consistency) Stool Frequency Straining (Ease of Passage Scale) Stool Weight	Statistically significant increases were seen in BSFS score from baseline (indicating softer, looser stools) in the 29 µg. ($p < 0.05$), 290 µg. ($p < 0.001$), and 966 µg. ($p < 0.001$) linaclotide groups compared to placebo. Increases were also seen for stool weight and Ease of Passage Scale scores (indicating less straining) for all linaclotide doses versus placebo ($p < 0.01$ for the 966 µg. dose).
Effect of Food on PD of Linaclotide on Bowel Habits (MCP-103-103)	QD x 7 days 290 µg (9 Fed, 10 Fasted)	BSFS Score (stool consistency) Stool Frequency Straining (ordinal straining scale; 1-5)	Increases in BSFS score (indicating softer, looser stools) were seen in fed subjects compared to fasted subjects ($p = 0.0092$) and SBM ($p < 0.005$) and CSBM ($p < 0.05$) frequency increased in fed subjects compared to fasted subjects. Results indicate an increased PD effect when linaclotide is administered with food.

PD Effect of Multiple Linaclotide Doses on GI Transit and Bowel Habits in IBS-C Patients (MCP-103-005)	QD x 7 Days Placebo (12); 97 µg (12); 966 µg (12)	Ascending Colon Emptying Time (primary PD endpoint)	A statistically significant overall treatment effect was seen for ascending colon emptying time ($p = 0.013$) and overall colonic transit at 48 hours ($p = 0081$). Statistically significant overall treatment effects ($p < 0.05$) were also seen for stool frequency (increased), BSFS score (increased, indicating softer, looser stools), straining (decreased), and time to first BM (reduced).
		Colonic Geometric Center at 24 h (primary PD endpoint)	
		Colonic Geometric Center at 48 h	
		Gastric Emptying Time	
		Percent Colonic Filling	
		Sense of Complete Evacuation (yes or no)	
		Time to First BM	
		BSFS Score (stool consistency)	
		Stool Frequency	
		Straining (Ease of Passage Scale)	

AC $t_{\frac{1}{2}}$ = Ascending Colon Emptying Time; BM = Bowel Movement; BSFS = Bristol Stool Forms Scale; CF 6 = Colonic Filling at 6 hours; CSBM = Complete Spontaneous Bowel Movement, an SBM accompanied by the patient self-reporting a feeling of complete evacuation; GC 24 = Colonic Geometric Center at 24 hours (or geometric center at a specific time); GE $t_{\frac{1}{2}}$ = Gastric Emptying half-time; h = hours; PD = Pharmacodynamic; QD = Once Daily; SBM = Spontaneous Bowel Movement, a bowel movement occurring in the absence of laxative/enema/suppository use during the preceding 24 hours

Mechanism of action

Linaclotide is a potent and selective agonist of the guanylate cyclase-C receptor, which is lining the luminal surface of the gastrointestinal tract. The compound is structurally related to the guanylin peptide family, which is involved in the regulation of intestinal fluid homeostasis and bowel function. GC-C responds to guanylin, uroguanylin, and ST, resulting in the elevation of intracellular cyclic guanosine monophosphate (cGMP), and an increase in chloride and bicarbonate secretion into the intestinal lumen through activation of the cystic fibrosis transmembrane conductance regulator (CFTR). This anion secretion results in an increase in intestinal fluid secretion and a reflex acceleration of gastrointestinal (GI) transit. Fluid absorption in the colon is also inhibited. The linaclotide's chemical structure and effect is homologous to that of bacterial heat-stable enterotoxins (STs) contributing to global endemic diarrhoea [Bharucha & Waldman, 2010].

Furthermore activation of GC-C results in an extracellular increase in concentrations of cyclic guanosine monophosphate (cGMP). The increased extracellular cGMP is proposed to act on afferent nerves to decrease sensitivity to nociceptive stimuli thereby reducing abdominal pain, abdominal discomfort, and visceral hypersensitivity.

Primary and Secondary pharmacology

Linaclotide's PD studies in healthy subjects showed evidence of dose-response on stool softening. The effects of linaclotide on stool consistency (BSFS score) were observed following once-daily oral administration of linaclotide at dose levels of 29, 97, 290, and 966 µg, with the most profound effects noted following the administration of the 290 and 966 µg doses. The once-daily oral administration of 97 µg or 966 µg of linaclotide softened stools (BSFS score), increased stool frequency, improved ease of passage, increased colonic transit, and decreased time to first bowel movement and colonic emptying time, with a dose response for stool consistency. In the phase IIa study MCP-103-005, linaclotide accelerated the emptying of the ascending colon and increased overall colonic transit, but had no effect on gastric emptying or small bowel transit. Significant linaclotide treatment effects were seen for multiple bowel habit parameters, including stool consistency, straining, stool frequency, and time to first bowel movement.

The company has shown an effect of the compound on bowel movements and colonic transit time, properties appearing to be important in the treatment of constipation, and also in constipation predominant IBS. However, the company has not investigated the modulating effects on pain and/or pain perception in humans. This has been done in animals only, and there is a postulate derived from these animal studies, how pain modulation can be achieved by the compound (see above). Therefore, as such, the biological plausibility of these effects is not questioned, and by analysing the clinical data as regards the influence on pain and pain related parameters, and investigating the pain effects on

different grades of constipation, the applicant has proven the independence of the effect on pain and pain related symptoms to a satisfactory extent. It could also be shown with data from the scientific literature, that compounds with a sole "laxative action" do usually not achieve pain relief in IBS-C patients. The missing of an explicit pharmacodynamic study in humans as regards pain effects is considered overall acceptable.

No clinical data on secondary pharmacology are available, apart from the evaluations of ECGs during phase 3. There are no effects on ECGs (see chapter on clinical safety).

2.4.4. Discussion on clinical pharmacology

The extent of the clinical programme to investigate the pharmacology was limited in view of the low systemic availability of linaclotide. Due to the degradation of the product in the intestinal tract, and its low permeability across membranes, as proven from in-vitro and animal studies, it had been anticipated that the systemic availability of the product would be very low. This has been confirmed in the clinical part of the evaluations. Apart from the detection of minor amounts of the compound and its primary metabolite in a minority of healthy volunteers when treated with a 10-times higher than clinical dose, and apart from 2 of over 400 patients (with sparse PK sampling), no measurable plasma concentrations of the compound could be found. This made the further conduct of clinical pharmacology studies inadequate, and many of the properties of the compound could be elucidated from pre-clinical investigations only. The available data is considered sufficient to characterise the PK and PD to a satisfactory extent.

A pharmacodynamically proven food interaction has been found with exaggerated PD action after intake of a high fat meal which might lead to an increased risk for adverse events in the clinical setting. The proposed mode of intake (for commercial use and in phase 3) takes account of this with the recommendation to take the (study) medication half an hour before the meals. No specific studies of the relation between linaclotide timing of administration in relationship with food intake and efficacy and safety have been performed. Importantly, the treatment recommendation as given in the SmPC has also been applied throughout the later development stages in patients, and found to be sufficiently safe.

The compound – due to its influence on gastrointestinal motility – has a theoretical potential to influence (decrease) the absorption of other drugs, especially in the event of diarrhoea. Based on the PD property to influence colonic motility only, this potential might, however be small and thus adequate warning statements included into the product information was regarded to be satisfactory.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology programme, despite being limited in extent, is deemed appropriate to investigate the PD characteristics of linaclotide for the proposed indication taking into consideration the almost complete missing of systemic availability, the specificity of the receptor interaction, and the nature of the compound as a protein. Relevant information in terms of the food effect as well as the potential impact on the absorption of other drugs have been adequately addressed in the SmPC. The overall PD development is therefore considered satisfactory.

2.5. Clinical efficacy

2.5.1. Dose response study

Study MCP-103-202, named "A randomized, multicenter, double-blind, placebo-controlled, dose-range-finding, parallel-design, phase 2 trial of oral linaclotide acetate administered to patients with Irritable Bowel Syndrome with Constipation" was conducted between March 2007 and February 2008 in 92 study centres in the United States. The study duration was three months, with a 2-week post-treatment observation phase.

The patients were randomised into one of 5 groups with doses of 72, 145, 290, and 579 µg linaclotide and placebo. The primary efficacy endpoint was defined as the change in the weekly normalised CSBM rate during weeks 1 through 12 of the treatment period from the overall weekly normalised CSBM rate during the pre-treatment period. The secondary endpoints comprised further bowel movement (BM) related measurements, but also the evaluation of abdominal pain, and the overall Degree of Relief of IBS symptoms on a 7-point scale. 996 patients were included into the trial, of which 420 were finally randomised. For the safety population the treatment groups were generally balanced with respect to baseline demographics. The mean patients age was 44.4 years (range 18-72). Only 12 patients were older than 65 (ranging from 0 in the placebo group to 4 in the 290 µg-group). There were around 17% African American patients, and 7% Hispanic/Latino patients without relevant differences between the dose groups.

The following table shows the primary analysis for efficacy:

Table 3: Mean change from pre-treatment to treatment period in weekly normalised CSBM frequency (ITT population):

			Linaclotide				
		Placebo	75 ug	150 ug	300 ug	600 ug	All
Pretreatment Period	N	85	79	82	84	89	334
	Mean	0.32	0.40	0.23	0.24	0.29	0.29
	(SD)	(0.544)	(0.652)	(0.495)	(0.488)	(0.564)	(0.554)
	Median	0.00	0.00	0.00	0.00	0.00	0.00
	min,max	0.0, 2.5	0.0, 2.4	0.0, 2.4	0.0, 2.4	0.0, 2.5	0.0, 2.5
Treatment Period	N	85	79	82	84	89	334
	Mean	1.47	3.55	2.79	3.93	3.10	3.34
	(SD)	(1.727)	(3.755)	(3.871)	(3.748)	(3.579)	(3.744)
	Median	0.95	2.61	1.42	3.04	1.95	2.33
	min,max	0.0, 7.8	0.0, 19.1	0.0, 27.5	0.0, 19.5	0.0, 19.1	0.0, 27.5
LS Mean Change	N	85	79	82	84	89	
	Mean	1.01	2.90	2.49	3.61	2.68	
	(SE)	(0.372)	(0.385)	(0.380)	(0.372)	(0.369)	
	p-value[a]						<.0001
LS Mean Difference from Placebo	Mean		1.89	1.48	2.60	1.66	
	(SE)		(0.510)	(0.505)	(0.502)	(0.494)	
	p-value[b]		0.0002	0.0036	<.0001	0.0008	

Similar results (albeit with some weaker p-values) were seen in the secondary evaluations as regards stool form, and BM-related evaluation of responders. Highly statistically significant differences to placebo were seen for the evaluation of straining, and the IBS Degree of Relief response criterion.

2.5.2. Main study(ies)

Study LIN-MD-31

Study LIN-MD-31 was a phase III, randomised, double-blind, placebo-controlled, parallel-group trial of linaclotide, administered orally for 12 weeks followed by a 4-week randomised withdrawal period in patients with irritable bowel syndrome with constipation. The study was conducted at 111 study centres located in the United States, and 7 centres located in Canada. The study took place between 14th July, 2009, and 12th July, 2010.

Methods

Study Participants

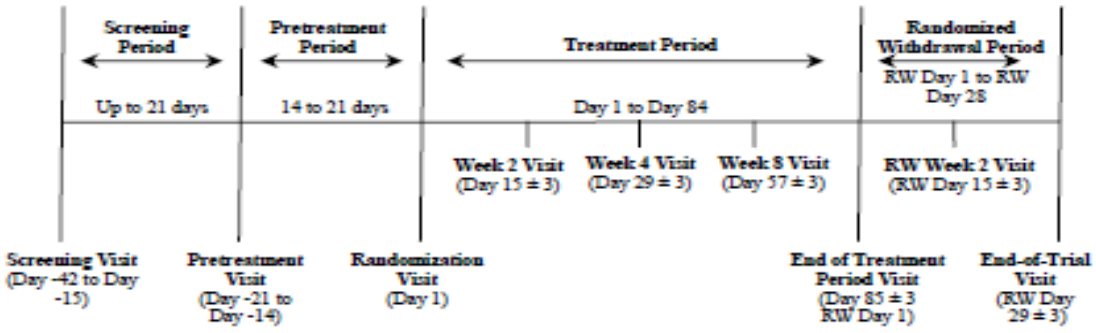
The study was conducted in the USA and in Canada. The inclusion of the patient population was based on (slightly modified) Rome II criteria for IBS-C, which were partly already resembling the newly established Rome III criteria (as of 2006), resulting in an almost complete concordance of fulfilment of the Rome II and Rome III criteria in the included patient population. The included patient population is regarded to fully reflect a patient population suffering from IBS-C.

Treatments

Patients were receiving identically appearing capsules containing 290 µg linaclotide or placebo. By exclusion criteria, patients were requested not to change their exercise and dietary habits. Patients were instructed to take 1 capsule of the study drug in the morning at least 30 minutes before breakfast. The only "official" rescue medication was bisacodyl during the treatment. All other medicines taken by the patients for the treatment of IBS or constipation related symptoms had to be discontinued, however, the use of fibre, bulk laxatives, stool softeners, and probiotics was acceptable, provided the patient had been on a stable dose during the 30 days before screening.

The following graph shows the overall course of the study including the randomised withdrawal period after the three months active treatment.

Figure 7: Overview of trial design:



Objectives

The objective of the trial is given as to determine the efficacy and safety of linaclotide administered to patients with IBS-C (superiority vs. placebo).

Outcomes/endpoints

In the original version of the protocol, three primary efficacy parameters were defined: 1. The 12-week abdominal pain and CSBM ("APC") responder (defined as a 75% of the time responder), 2. the 12-week CSBM responder (also a 75% responder), and 3. the 12-week abdominal pain responder (also defined as a 75% responder); all assessed on a weekly basis.

In September 2009, the primary parameter was changed in the protocol amendment No. 2, now requesting 4 co-primary evaluations of efficacy, and referring to the following:

1.)9/12 weeks APC 3+1 responder rate, 2) 9/12 weeks CSBM 3+1 response rate, 3) 9/12 weeks abdominal pain response rate, and 4) 6/12 week APC+1 responder rate, defined as follows:

- A weekly APC 3+1 responder is defined as a patient who is both a weekly abdominal pain responder and a weekly CSBM 3+1 responder.
- A weekly CSBM 3+1 responder is defined as a patient who has a CSBM weekly rate of at least 3 and an increase of at least 1 from baseline for that week. If a patient did not complete at least 4 daily IVRS calls the patient will not be considered a responder in that week.
- A weekly abdominal pain responder is a patient who has a decrease of at least 30% in the mean abdominal pain score from baseline. Requirements for the completeness of the IVRS data similar to the above
- A weekly APC+1 responder is a patient who is both a weekly abdominal pain responder and a weekly CSBM + 1 responder. A weekly CSBM + 1 responder is a patient who has an increase of at least 1 in the CSBM weekly rate.

Protocol amendment No. 2 also defined a hierarchical structure for the statistical evaluation, defining the four co-primary endpoints as the first step, four of the secondary endpoints as the second step (CSBM frequency, SBM frequency, stool consistency, and severity of straining). The third step of evaluation was to test three secondary parameters, namely the change in abdominal pain, the change in abdominal discomfort, and the change in bloating. Fourth and fifth steps were also introduced. The parameters tested in an individual step were all to be tested using an overall type I error rate of 0.05 by means of a Hochberg procedure to control for multiple parameters within this step (see statistical evaluation).

It also re-defined the complete list of secondary and tertiary endpoints.

Protocol amendment No. 1 introduced differential primary endpoints to meet European requirements, and the evaluation of a per-protocol population, instead of an "evaluable" population. The co-primary efficacy parameters for the European submission were defined as follows:

1. A 12 week abdominal pain/abdominal discomfort responder is a patient who for at least 6 out of 12 weeks of the treatment period has an improvement from baseline of 30% or more in either the mean abdominal pain score or mean abdominal discomfort score for that week with neither of these scores worsening from baseline for that week. If a patient does not have an abdominal pain score or an abdominal discomfort score for a particular treatment period week, the patient will not be considered a responder for that treatment period week.

2. A 12 week IBS Degree of relief responder is a patient whose response to the Degree of relief of IBS symptoms question is "considerably relieved " or "completely relieved" (i.e. a score of ≤2) for at least 6 of the 12 weeks in the treatment period. If a patient does not have an IBS degree of relief score for that treatment period week, the patient will not be considered a responder for that treatment period week.

The null-hypothesis for this "European analysis" was therefore set to "no difference in the proportion of 12-week abdominal pain/discomfort responder or no difference in the proportion of the 12-week IBS degree of relief responder.

The secondary endpoints as of the "European analysis amendment" in its first version (amendment No. 1) referred back to the original study protocol. The following secondary endpoints were included in the original study protocol:

- The change from baseline in the 12-week CSBM frequency
- The change from baseline in the 12-week SBM frequency
- The change from baseline in the 12 week stool consistency (using BSFS)
- The change from baseline in the 12 week severity of straining (using a 5-point ordinal scale)
- The change from baseline in the 12-week percent of abdominal pain-free days.
- The change from baseline in the 12-week abdominal pain and discomfort scales (evaluated separately using an 11-point NRS).
- The change from baseline in the 12-week bloating (assessed using also an 11-point NRS).

From these, protocol amendment No.2 (the "European" part of this amendment) defined "main secondary parameters" and "supportive secondary parameters" as follows:

The main parameters:

- The change from baseline in the 12-week CSBM frequency
- The change from baseline in the 12 week stool consistency (using BSFS)
- The change from baseline in the 12 week severity of straining
- The change from baseline in the 12-week bloating

The "supportive" parameters:

The change in SBM frequency, the change in the abdominal pain score, the change in percent of abdominal pain-free days, the change in the abdominal discomfort scale, the change in the EQ-5D VAS, the change in the EQ-5D utility index score, and the change in the IBS-QOL (evaluations of Quality of Life, see below).

Tertiary endpoints were defined as follows (as of the original protocol):

A 12-week longitudinal analysis of primary efficacy 75% weekly responder parameters, a 12-week 75% responder analysis for the following parameters: improvement of ≥30% for abdominal discomfort (on 11-point NRS), the same for bloating, ≥1 improvement in CSBM frequency, ≥2 improvement in SBM frequency, ≥1 improvement in severity of straining (on a 5-point scale), ≥2 improvement in stool consistency (on a 7-point scale), a CSBM responder based on having a weekly of 3 or more CSBMs.

The following mean changes of parameters were also included in the tertiary endpoints: The change from baseline in abdominal cramping, the change from baseline in abdominal fullness. Further analysis were to include CSBM and SBM within 24 hours of receiving study drug responders, 12-week ABC (abdominal pain, bloating, and constipation responder, weekly abdominal pain/bloating responder, weekly constipation responder; evaluation of no. of unsuccessful BMS, change from baseline in IBS symptoms severity, constipation severity, degree of relief of IBS symptoms, evaluation of "monthly" responders, "adequate relief", evaluation of rescue medication, evaluation of IBS-SSS, treatment satisfaction, Quality of Life (IBS-QOL, SF-12, EQ-5D, and pharmacoeconomic evaluations (WPAI:IBS-C, HRUQ).

Further analyses are mentioned for the randomised withdrawal period, which are however, defined as descriptive only. For this period, three treatment sequences, are of course defined: 290µg/290µg, 290 µg/placebo, and placebo/290 µg. Most primary, and a couple of secondary, but not all secondary and tertiary parameters were to be evaluated.

Additional Efficacy Parameters have been included with protocol amendment No. 2 as follows:

- 12-week abdominal pain/abdominal discomfort sustained responder, and
- 12-week degree of relief sustained responder

defining sustained responders on the basis of the primary endpoints with the additional requirement of being a responder in at least 2 of the 4 weeks before ending the trial (or before discontinuing the trial, whatever is applicable).

Further analyses were done on a subgroup of 65 linaclotide and 72 placebo patients with the conduct of the triplicate ECG programme, and blood draws for PK analysis, conducted at visit 3 (randomisation visit), approximately 2 hours after first dose of study medication was taken, and at the week 4 visit.

Justification and validation of endpoints:

For the IBS Global Relief of Responder, it is directly referred to the European guidance document on IBS. The threshold of "Considerably" or "Completely Relieved" (i.e. a score of ≤ 2) was selected based on the recommendations of the IMMPACT Consensus Statement, in which the CID of the Patient Global Impression of Change (PGIC) scale (7-point scale with the options "very much improved", "much improved", "minimally improved", "no change", "minimally worse", "much worse", "very much worse") was established as "much" and "very much" improved. The same PGIC responder definition has been used as an anchor in determining the clinical importance of improvement in the pain NRS, and in the validation of the Global Improvement Scale (GIS) for IBS, symptoms according to a study by Gordon et al (published in 2003). Furthermore, this scale was used in the Phase 2b MCP-103-202 and showed construct validity, discriminating ability, and responsiveness in the IBS-C population.

For the use of the abdominal pain/discomfort endpoint, it is argued that the threshold of 30% improvement from baseline as a minimal clinically important difference (CID) for pain was chosen based on several publications. Specifically, a meta-analysis of 10 clinical trials in various chronic pain conditions using an 11-point NRS demonstrated that 30% reduction of the NRS represented a CID. The IMMPACT Consensus Statement concluded that a 10-20% represents a minimally important improvement, and a 30% a moderately important improvement. Finally, a recent publication on the validation of the pain NRS in IBS, the minimal CID was found to be 29, 5% [3].

[3] Spiegel B et al: Measuring IBS patient reported outcomes with an abdominal pain numeric rating scale: results from the proof cohort. Aliment Pharmacol Ther 2009; 20: 1159-1170.

Furthermore, the analysis of the Phase 2b study data showed that a responder definition based on a 30% reduction from baseline in abdominal pain and abdominal discomfort for 50% of the weeks yields the highest degree of diagnostic accuracy based on IBS degree of relief used as an anchor.

Information was provided on the validation of 12 PRO instruments used in the phase 2b trial. The items assessed were straining, UBM frequency, SBM frequency, CSBM frequency, abdominal pain, abdominal discomfort (however, with the 5-point scale used in the phase 2b study), bloating, adequate relief, global relief, IBS symptom severity, constipation severity, and BSFS. The items were assessed as regards test-retest reliability, validity (construct validity and discriminating ability), responsiveness and for the definition of a minimally important difference (MID). All tests revealed satisfactory results for the items included. The MID was determined with three different methods: an "anchor based method" in which the global relief was used as the "anchor", the SEM "method", and the 0.5 SD unit change. This analysis, however, was considered to be "explorative" only. However, the results of this evaluation is given in the following table, to enable a comparison with the results achieved in the phase 3 trials:

Table 14: IBS-C item MID estimates at week 1:

	Anchor-Based: Global Relief = "Somewhat Relieved" Mean Change (SD)	SEM	Half SD
CSBM Frequency	1.80 (2.66)	1.52	1.90
SBM Frequency	4.59 (4.10)	2.96	2.50
UBM Frequency	2.00 (2.70)	1.76	1.66
Straining	1.13 (0.84)	0.57	0.47
BSFS	1.74 (1.54)	1.15	0.78
Abdominal Pain	0.53 (0.54)	0.34	0.40
Abdominal Discomfort	0.49 (0.54)	0.33	0.37
Bloating	0.49 (0.54)	0.34	0.43
IBS Symptom Severity	0.74 (0.65)	0.58	0.41
Constipation Severity	1.00 (0.93)	0.76	0.54
Adequate Relief	0.40 (0.53)	0.43	0.25
Global Relief	1.22 (0.67)	0.66	0.48

The CHMP notes that as regards the IBS Degree of Relief response criterion, obviously no specific validation data appear to be available, however, some have obviously been generated based on the phase 2 data. Also, the outcome measure is indeed in agreement with the requirements as given in the European guidance, and therefore considered to be overall acceptable.

The use of the NRS-scales is relatively new in the IBS setting, and the use of a 30% threshold is obviously not only partially validated (as in the Spiegel publication given above), but has also been advocated by the (preliminary) IBS guideline of the FDA. It is clear that for somatic and visceral pain, a MCID has previously been accepted to be at 30% (or even less), however, the data presented in the study by Spiegel are the only data that do indeed present the evaluation of a MCID in abdominal pain in IBS patients. The argumentation of the company is therefore overall considered to be acceptable.

The above shown MCID definitions were used to assess the clinical relevance of the results.

Sample size

The sample size was calculated to be 800 patients (400 in each treatment arm), which were to provide an overall power of at least 95% to detect a difference of 15% in the percentage of patients being abdominal pain/discomfort responders (45% vs. 60%) and in the percentage of patients being IBS degree of relief responder (21% vs 36%) with a two-sided alpha of 0.05.

Randomisation

Randomisation took place at visit 3 (after the pre-treatment period). At this time the investigational site called the Interactive Voice Response System (IVRS, provided by the CRO ICON Clinical Research, Sugar Land, Texas, USA) to register the patient for pre-randomisation transition. After that, the patient called IVRS to enter the diary responses, which were then used to verify the inclusion and exclusion criteria and confirming eligibility. After checking for consistency with the investigational site, the IVRS randomised the patients. The randomisation list was generated by the Sponsor (Forest Research Institute Inc.). Patients were randomised in a 1:1 ratio with block randomisation consisting of blocks of 4 in order to ensure balanced distribution. At the end-of-treatment (ETP) visit, patients not withdrawing were assigned in a double-blind fashion for the randomised withdrawal (RW) period. Patients on linaclotide 290 µg were randomised to continue linaclotide or switch to matching placebo, while patient on placebo were allocated to linaclotide 290 µg.

Blinding (masking)

The randomization codes were generated by the Randomization Code Administrator, an individual within Statistical Programming at Forest Research Institute, Inc., who generated the randomization codes and was not assigned the role of Statistical Programmer for this study. The randomization codes were provided on a compact disc to the IVRS contract research organization (ICON Clinical Research) by the Forest Research Institute, Inc., Randomization Code Administrator; the codes were password protected. The kit randomization schedule was created by the IVRS contract research organization.

For the double-blind treatment period, patients were supplied with identically appearing capsules containing 266 µg linaclotide, or placebo.

Statistical methods

In order to fulfil different requirements of EMA and FDA, different statistical analysis plans (SAP) with different primary/secondary endpoints were applied for the EU and the US application. The following description of statistical methods is based on the European SAPs only.

The double-blind, placebo-controlled study LN-MD-31 had the co-primary endpoints "12-week abdominal pain/discomfort response" and "12 week IBS degree of relief response". The responders were determined according to pre-specified criteria. Statistically significant changes versus placebo were required in both primary efficacy parameters for the trial to have met the primary efficacy objective.

All efficacy analyses were based on the ITT Population. The PP Population was used as a sensitivity analysis. The ITT population was defined as all patients in the Safety Population who had at least 1 post randomization entry of the US primary efficacy assessment (ie, an assessment of Abdominal Pain

at Its Worst or the daily IVRS information that determines whether a spontaneous bowel movement (SBM) is a complete spontaneous bowel movement (CSBM).

The PP population was defined as a subset of ITT population constituted by those patients who: (a) met all inclusion/exclusion criteria liable to affect the efficacy assessment and (b) did not present serious deviations of the protocol that may affect efficacy.

For both co-primary efficacy parameters, the proportion of responders in the linaclotide and placebo groups was compared using the Cochran-Mantel-Haenszel (CMH) test controlling for geographical region. The number and percentage of responders for each treatment group, the difference in responder rates between the treatment groups, the odds ratio based on the CMH-method with corresponding confidence intervals, and the two-sided p-value associated with the CMH test are presented.

Continuous secondary endpoints were analysed using analysis of covariance (ANCOVA) models with fixed effect terms for treatment group and geographical region and the patient's corresponding baseline value of the parameter as a covariate.

The analyses of the primary and secondary efficacy parameters were based on the ITT population. It was distinguished between main, supportive and additional secondary efficacy endpoints. The overall type I family-wise error rate for the co-primary and main secondary efficacy endpoints was controlled at the 0.05 significance level using a 2-step serial gatekeeping procedure. In each step, a set of hypotheses was tested; progression to the next step occurred only if all hypotheses in the previous step were rejected. Within each step, the type I error was controlled at the 0.05 level: In the first step, statistical significance was needed for both co-primary endpoints; the type I error rates in the subsequent step(s) were controlled using the Hochberg procedure. The supportive and additional secondary endpoints were explored without control of the type I error rate, statistical tests being meant to be considered descriptively.

An observed-cases approach to missing data was applied. Missing values were not imputed. If the value for a primary endpoint was missing for a treatment period week, the patient was considered a non-responder for that week; for weekly responder parameters based on IVRS daily assessments, a patient with less than 4 complete IVRS calls during a treatment week was not considered a responder for that week. As sensitivity analyses, for parameters that were defined on a weekly basis, a last observation carried forward (LOCF) approach was also applied, imputing the last non-missing weekly value. The protocol allowed for rescue medication but data were included in the analysis irrespective of rescue medication usage.

Further analyses that can be considered as sensitivity analyses were provided for the abdominal pain/discomfort response and IBS degree of relief response for the 12 week treatment period. The primary endpoint "abdominal pain/discomfort response" was analyzed using alternate responder definitions for weekly response (≥40% and ≥50% improvement from baseline instead of ≥30%). A longitudinal analysis was provided for abdominal pain/abdominal discomfort weekly response and the IBS degree of relief weekly response utilizing a generalized linear model using the logit as link function and the exchangeable log odds ratio structure, based on the observed cases during the treatment period. The models used treatment group, region, week, week by treatment interaction as factors. An analysis of sustained responders was also provided, which defined sustained responders as those responders who were weekly responders in 2 of the 4 last weeks before the ending of the treatment period or discontinuing the trial.

Centre effects were not explored due to the small number of patients per centre. The primary analysis was stratified by geographical region. The consistency of the treatment effect for the primary

endpoints was explored on the pooled ITT-population of the pivotal studies by pre-specified subgroup analyses by age and gender and in additional post-hoc subgroup analyses by race, ethnicity, and BMI.

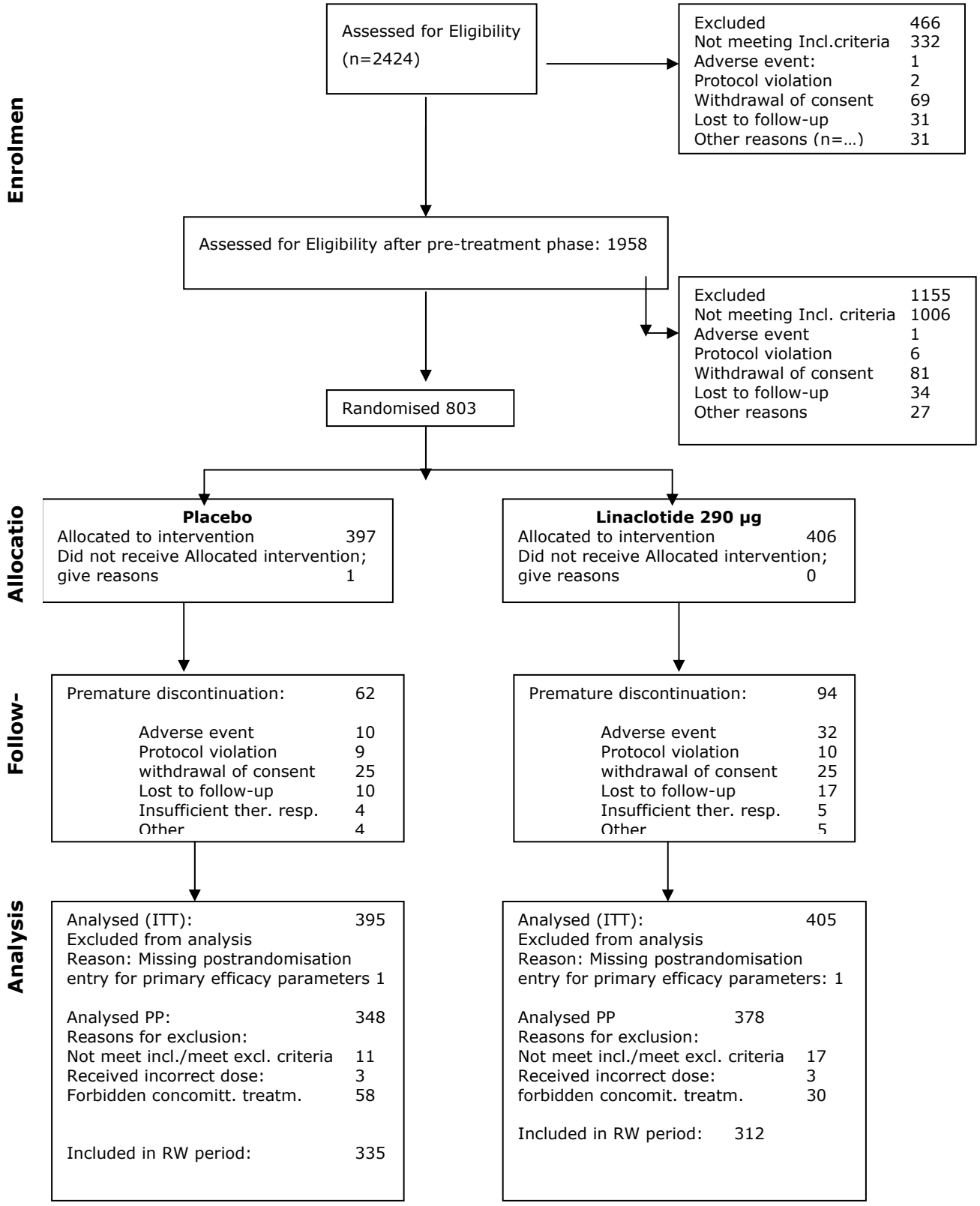
The 12 week treatment period was followed by a 4 week randomized withdrawal period. For this period, descriptive statistics only were provided; no statistical tests were performed.

Results

Participant flow

Overall, 80.6% of the patients completed the double-blind treatment period of the study. The number of discontinuations from the active treatment group was higher than for placebo (23.2% vs. 15.6%, which is reflecting the higher percentage of patients discontinuing as a results of AEs (7.9% vs. 2.5%; p=0.0007). The results are shown in the following graphical presentation:

Figure 8: Number of patients in study LIN-MD-31



Originally, 805 patient identification numbers (PID) were handed out, and the reduction by two patients is attributed to a randomisation of two patients at more than one study centre (additionally one of these two was taking part in the screening period a third time). For these 2 patients, the fact was detected prior to breaking the blind, and the procedures to handle these two patients were included in the SAP amendment. It was determined that the data from the two patients would be included under their first randomised PID and that the data of the other PIDs would not be included in the efficacy and safety analyses but included in the data listings.

After data lock point, and after finalisation of the study report, it was detected that an additional 9 patients had been already included in other linaclotide studies before inclusion into this study. This is presented as an Addendum to the Clinical Study Report.

Recruitment

The study was running between 14th July 2009 (first patient included), and 12th July, 2010, a total of about 13 months.

Conduct of the study

During the conduct of the study 2 protocol amendments were made (see above "Outcomes / Endpoints"). As these mainly referred to the (statistical) analysis of the trial, the conduct of the study as such was not affected. All endpoints included in the European evaluation (including the statistical analysis plan) were already included in the first version of the protocol. It is considered that the protocol amendments had no influence on the conduct of the study.

Baseline data

The demographic data of the included patient population is shown in the following table. Overall 90.5% of the patients were female, and about 75% of the patients were Caucasian. No meaningful differences were seen between the groups, however, mean weight was higher in the linaclotide group.

Table 16: Demographic and baseline characteristics (Safety population)

Characteristic	*Placebo (N = 396)*	*Linaclotide (N = 406)*	*Total (N = 802)*	*P-value*
Age, years				
Mean ± SD	43.7 ± 12.9	43.3 ± 12.7	43.5 ± 12.8	0.6528
≥ 65 years, n (%)	26 (6.6)	19 (4.7)	45 (5.6)	0.3832
Range	18, 84	19, 81	18, 84	
Sex, n (%)				
Male	38 (9.6)	38 (9.4)	76 (9.5)	0.9295
Female	358 (90.4)	368 (90.6)	726 (90.5)	
Race, n (%)				
Caucasian	302 (76.3)	315 (77.6)	617 (76.9)	0.6391
Non-Caucasian	94 (23.7)	91 (22.4)	185 (23.1)	
Ethnicity, n (%)				
Hispanic	57 (14.4)	56 (13.8)	113 (14.1)	0.8354
Non-Hispanic	339 (85.6)	350 (86.2)	689 (85.9)	
Weight, kg				
Mean ± SD	74.6 ± 18.3	77.2 ± 18.8	75.9 ± 18.6	0.0375
Height, cm				
Mean ± SD	164.3 ± 8.3	165.2 ± 8.3	164.7 ± 8.3	0.1186
BMI. kg/m^2				
Mean ± SD	27.6 ± 6.2	28.3 ± 6.4	27.9 ± 6.3	0.1172

The concomitant disease conditions by the patients (in 96% of the patients) comprised most commonly haemorrhoids (27%), gastroesophageal reflux (22%), drug hypersensitivity (20%), insomnia (18%), headache 17%), seasonal allergy (17%), hypertension (17%), depression (17%), and anxiety (16%). A total of 13.8% of the female patients were postmenopausal, and 25% had undergone hysterectomy. The "efficacy baseline variables" are shown in the following table:

Table 17: Efficacy Variables at baseline – ITT population

Parameter	*Placebo (N = 395)*	*Linaclotide (N = 405)*	*P-value*
	Mean ± SD	*Mean ± SD*	
CSBM rate per week	0.24 ± 0.50	0.20 ± 0.46	0.3149
SBM rate per week	1.90 ± 1.40	1.94 ± 1.38	0.6937
BSFS	2.41 ± 1.03	2.26 ± 1.00	0.0463
Straining score	3.43 ± 0.81	3.57 ± 0.76	0.0196
Abdominal pain	5.63 ± 1.71	5.66 ± 1.65	0.8553
Abdominal pain-free days	1.69 ± 6.00	2.06 ± 6.48	0.3971
Abdominal discomfort score	6.04 ± 1.67	6.17 ± 1.60	0.2734
Bloating score	6.50 ± 1.89	6.71 ± 1.77	0.0996

The evaluation of concomitant medication at baseline did not reveal obvious differences between the groups. Altogether, 88% of the patients used concomitant medication. The highest used was seen for propionic acid derivatives (usually NSAIDs; 21%), anilides (21%), multivitamins (18%), PPIs (15%), progestogens and estrogens, fixed combinations (14%), SSRIs (10%), and other antidepressants (10%).

Numbers analysed

The numbers analysed are given above (participant flow). The ITT population comprised 395 and 405, and the PP population 378 and 348 patients in the placebo and linaclotide groups, respectively.

Outcomes and estimation

As reported above, the study report includes an evaluation based on the EU SAP, and an evaluation based on the US SAP. For the purpose of this AR, the "European results" are mainly reported.

The evaluation of the primary and main secondary parameters for EU as defined in the protocol and European SAP- are shown in the following table. All comparisons turned out to be statistically significant:

Table 18: Overview of primary and main secondary efficacy parameters for the 12 week treatment period (ITT population):

Parameter	*Placebo (N=395)*	*Linaclotide (N=405)*		
	Primary Efficacy Parameter			
	n (%)	**n (%)**	**Odds Ratio (95% CI)**	**p-Value[a] (Significant by MCP)**
12-Week Abdominal pain/abdominal discomfort Responder	165 (41.8)	222 (54.8)	1.70 (1.28, 2.25)	0.0002 (yes)
12-Week IBS Relief Responder	73 (18.5)	150 (37.0)	2.61 (1.89, 3.62)	<0.0001 (yes)
	Main Secondary Efficacy Parameters			
	LS Mean (SE)	**LS Mean (SE)**	**LSMD (95% CI)**	**p-Value[a] (Significant by MCP)**
Change from baseline in 12-week CSBM frequency rate	0.705 (0.128)	2.272 (0.127)	1.568 (1.24, 1.89)	<0.0001 (yes)
Change from baseline in 12-week stool consistency	0.662 (0.061)	2.071 (0.060)	1.409 (1.25, 1.57)	<0.0001 (yes)
Change from baseline in 12-week severity of straining	–0.651 (0.042)	–1.306 (0.042)	–0.655 (–0.76, –0.55)	<0.0001 (yes)
Change from baseline in 12-week bloating	–1.100 (0.100)	–1.944 (0.099)	–0.844 (–1.10, –0.59)	<0.0001 (yes)

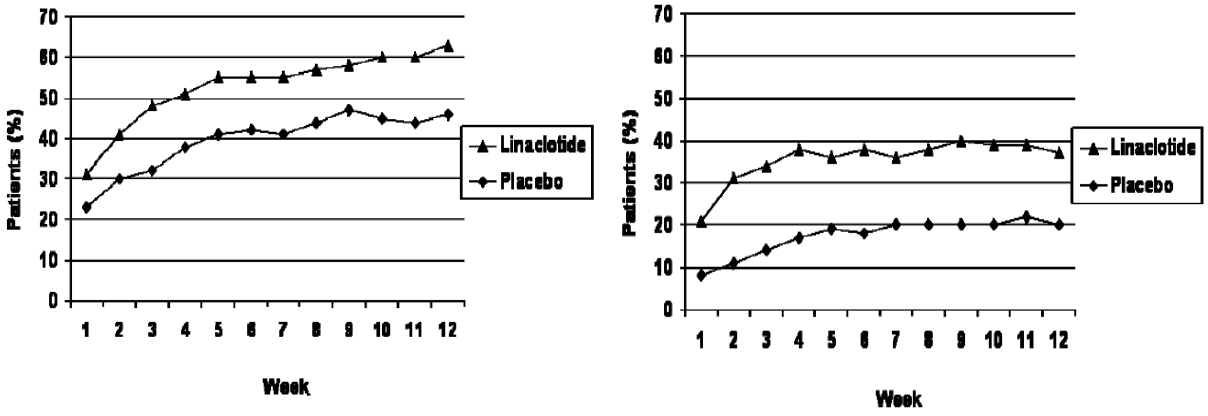
A supportive evaluation (sensitivity analysis) of the primary endpoints is presented with additional analyses applying the LOCF approach to the ITT population, and with the PP-population (applying the OC approach):

Table 19: EU additional analyses: Primary efficacy parameters LOCF (ITT) and PP populations (OC)

Analysis	*Responder n (%)*		*Odds ratio (95% CI); p-Value*
	Placebo (N =395 ITT, 348 PP)	*Linaclotide (N=405 ITT, 378 PP)*	
12-week abdominal pain/abdominal discomfort responders – LOCF approach (ITT population)	178 (45.1)	244 (60.3)	1.86 (1.40, 2.47); p<0.0001
12-week abdominal pain/abdominal discomfort responders - PP population (OC approach)	150 (43.1)	209 (55.3)	1.64 (1.22, 2.20); p=0.0010
12-week IBS degree of relief responders - LOCF (ITT population)	80 (20.3)	168 (41.5)	2.83 (2.06, 3.89); p<0.0001
12-week IBS degree of relief responders - PP population (OC approach)	66 (19.0)	139 (36.8)	2.50 (1.78, 3.52); p<0.0001

The following two graphs show the display of the longitudinal analysis of the two co-primary endpoints. This shows that the effect of linaclotide was already significant in the first week of treatment, and stayed significant throughout the treatment period.

Figures 9 and 10: Longitudinal analysis of European co-primary endpoints up to 12 weeks – OC approach/ITT population (left panel: abdominal pain/discomfort responder; right panel: IBS degree of relief responder).



Results of a variety of supportive secondary endpoints are shown in the following table. All results showed highly statistically significant differences.

Table 20: Supportive secondary endpoints (EU evaluation; ITT population).

Variable		placebo	linaclotide	LSMD (95% CI) p-value
12-week SBM frequency	Baseline	1.897	1.935	2.769
	End of treatment	3.174	5.977	(2.32 – 3.22)
	Difference	1.130	3.898	<0.0001
12-week abdominal pain	Baseline	5.63	5.66	-0.74
	End of treatment	4.38	3.65	(-0.98 - -0.50)
	Difference	-1.13	-1.87	<0.0001
12-week abd. pain free days	Baseline	1.69	2.06	- 0.74
	End of treatment	6.99	11.88	(-0.099 - -0.494)
	Difference	5.31	9.81	0.00014
12 week abd. discomfort	Baseline	6.04	6.17	-0.74
	End of treatment	4.72	4.07	(-0.99 - -0.49)
	Difference	-1.21	-1.95	<0.0001

Especially for the EU analysis, the analysis of sustained response was conducted, defining a sustained response as an overall 50% response with an additional 50% response during the last 4 weeks thus excluding a deterioration towards the end of treatment. These analyses are shown the following table:

Table 21: Analyses of sustained response for abdominal pain/discomfort response and for IBS degree of relief response (ITT population):

Analysis	*Responder n (%)*		*Odds ratio (95% CI); p-Value*
	Placebo (N =395)	*Linaclotide (N=405)*	
12-week abdominal pain/abdominal discomfort sustained responders – OC approach	164 (41.5)	215 (53.1)	1.60 (1.21, 2.12); p = 0.0010
12-week abdominal pain/abdominal discomfort sustained responders – LOCF approach	176 (44.6)	236 (58.3)	1.75 (1.32, 2.32); p<0.0001
Analysis	*Responder n (%)*		*Odds ratio (95% CI); p-Value*
	Placebo (N =395)	*Linaclotide (N=405)*	
12-week IBS degree of relief sustained responders – OC approach	72 (18.2)	137 (33.8)	2.30 (1.66, 3.20); p<0.0001
12-week IBS degree of relief sustained responders – LOCF approach	79 (20.0)	157 (38.8)	2.56 (1.86, 3.53); p<0.0001

A "sensitivity analysis" was conducted with the evaluation of the abdominal pain/discomfort primary endpoint defined at different levels of response. The responder for the co-primary was defined as a patient with an at least 30% improvement in the NRS ratings. The additional evaluations set this increase to 40% and 50%. Almost similar rates were achieved with these evaluations, and all differences were statistically significant.

Table 22: 12-week abdominal pain/abdominal discomfort 40% and 50% responders – ITT population

Analysis	*Responder n (%)*		*Odds ratio (95% CI); p-Value*
	Placebo (N =395)	*Linaclotide (N=405)*	
12-week abdominal pain/abdominal discomfort 40% responders	133 (33.7)	195 (48.2)	1.84 (1.38, 2.45); p<0.0001
12-week abdominal pain/abdominal discomfort 50% responders	101 (25.6)	157 (38.8)	1.86 (1.37, 2.52); p<0.0001

Similar results were achieved, if these evaluations were restricted to abdominal pain only (without integrating the discomfort evaluations).

Evaluation of Quality of Life

The evaluation of the 12-week VAS of EQ-5D questionnaire (using the LOCF approach; ITT population) revealed a mean increase from baseline (using a 100 point NRS) of 5.56 points for linaclotide, and 3.75 for placebo. This difference was not statistically significant (p=0.0637). However, when using the EQ-5D Utility Index Score, the change from baseline in the linaclotide group was significantly greater (p-value 0.001) than in the placebo group. The partly discrepant results of this part of the QoL-evaluations are seen in the following table, which shows the change from baseline for each dimension of the EQ-5D Questionnaire:

Table 24: Change from baseline in 12-week responses for each dimension of the EQ-5D Questionnaire – ITT population

Dimension	*Most positive of the Possible Responses*	*Percentage of Patients Giving Response*			
		Placebo (n = 395)		*Linaclotide (n = 405)*	
		Baseline	*Week 12*	*Baseline*	*Week 12*
Mobility	I have no problems in walking about	86.1	88.1	85.2	91.0
Self Care	No problems with self care	98.7	97.7	98.5	98.8
Usual Activities	No problems performing	75.7	79.9	74.8	84.5
	usual activities				
Pain/ Discomfort	I have no pain or discomfort	5.1	21.4	8.6	34.5
Anxiety/ Depression	I am not anxious or depressed	59.2	65.7	59.0	65.3

The IBS-QOL evaluation, which is based on a 0- to 100 VAS, with higher scores indicating better Quality of Life is also presented. Almost all results for this QoL instrument (including the overall evaluation) revealed statistically significant advantages for the active treatment. The results are shown in the following table:

Table 25: Change from baseline in IBS-QOL parameters at end of treatment period.

IBS-QOL Parameter Score	*Placebo (N = 395)*		*Linaclotide (N = 405)*		
	Mean ± SD		*Mean ± SD*		*P-value*
	Baseline	*Change*	*Baseline*	*Change*	
Overall	60.3 ± 21.7	15.0 ± 18.2	59.9 ± 20.0	18.5 ± 18.7	0.0044
Dysphoria subscale	62.2 ± 25.3	17.0 ± 21.2	60.8 ± 23.5	20.7 ± 21.5	0.0202
Interference with activity subscale	67.0 ± 24.7	12.8 ± 20.6	65.9 ± 23.2	14.0 ± 20.3	0.6095
Body image subscale	47.7 ± 23.2	18.2 ± 21.0	47.3 ± 22.5	23.5 ±23.4	0.0003
Health worry subscale	45.5 ± 26.3	19.6 ± 24.9	43.6 ± 24.5	26.0 ± 25.2	0.0007
Food avoidance subscale	48.1 ± 28.9	16.0 ± 24.5	49.5 ± 28.7	21.2 ± 26.7	0.0003
Social reaction subscale	65.8 ± 25.9	12.3 ± 22.8	66.6 ± 24.9	15.0 ± 22.9	0.0188
Sexual subscale	67.0 ± 33.7	13.0 ± 25.5	66.5 ± 30.1	16.6 ± 26.2	0.0179
Relationships subscale	71.3 ± 25.6	10.8 ± 21.3	73.5 ± 22.9	12.1 ± 19.9	0.0374

The assessment of Quality of Life via the generic SF-12 health survey scores revealed that the health status of the trial population was similar to averages reported for IBS-C patients in the literature. There was a small increase in health status in both placebo and linaclotide treatment groups at the end of the treatment period which was statistically significant.

Small changes with missing statistical significance were seen for the evaluation of work productivity, and health resource use evaluations.

The CHMP raised questions around the inclusion of a population without relevant reductions of Quality of Life. In their response the applicant could clearly display that the included patient population did indeed suffer from a clearly reduced Quality of Life. The overall results were not only consistent with an overall reduction of Quality of Life compared to the normal population, but also were compliant with the results of investigations in similar populations reported in the literature, in two out of three QoL parameters for which a comparison was possible. The issue was therefore considered resolved.

The missing effect in the HCRU questionnaire is – from a regulatory point of view – not considered to be a concern, and may indeed be attributable to the need for a different design in such kind of studies. It could also, however, be attributable to the missing sensitivity of the instrument used, as the baseline data indicated minimal health care resource utilisation (looking at the categories in the scales, these appear indeed to measure more "severe" forms of health care utilisation such as emergency visits, hospitalisation etc.).

Ancillary analyses

The evaluation of the primary endpoints according to the US SAP is shown in the following table.

Table 23: Overview of primary efficacy parameters for the 12-week treatment period – ITT population

Primary Efficacy Parameters				
	Placebo (N = 395)	*Linaclotide (N = 405)*	*Statistics*	
Parameter	*n (%)*	*n (%)*	*Odds Ratio (95% CI)*	*P-value[a] (Significant by MCP)*
9/12 Week APC 3+1 responder	20 (5.1)	49 (12.1)	2.60 (1.51, 4.47)	0.0004 (yes)
9/12 Week CSBM 3+1 responder	25 (6.3)	79 (19.5)	3.65 (2.26, 5.88)	< 0.0001 (yes)
9/12 Week abdominal pain responder	107 (27.1)	139 (34.3)	1.41 (1.04, 1.91)	0.0262 (yes)
6/12 Week APC +1 responder	83 (21.0)	136 (33.6)	1.93 (1.40, 2.66)	< 0.0001 (yes)

The secondary efficacy parameters for the "US evaluation" have all already been reported in the above, partly also being secondary, partly being additional/tertiary endpoints only.

An evaluation was provided looking for the incremental levels of CSBM rate and abdominal pain. The two parameters "Level of improvement of CSBM rate" and "Level of decrease of abdominal pain" are presented in graphical form:

Figure 11: Percentage of patients with improvement in 12-week CSBM rate by level of improvement – ITT population

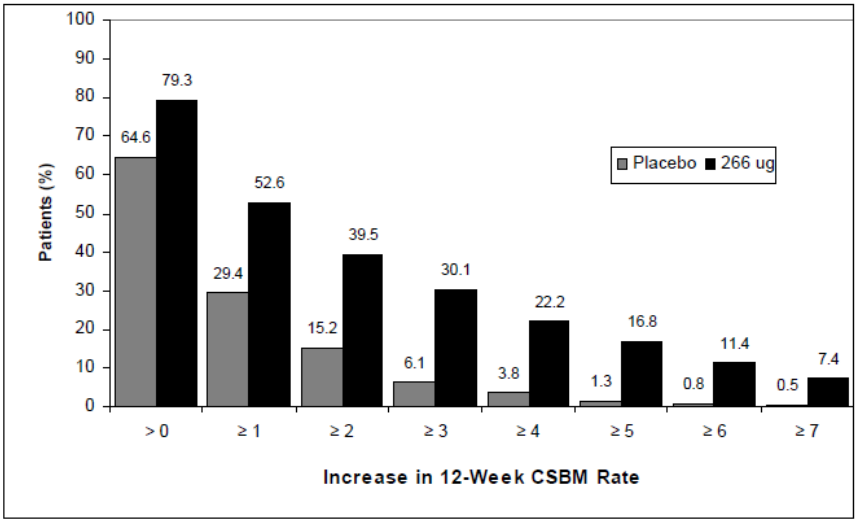
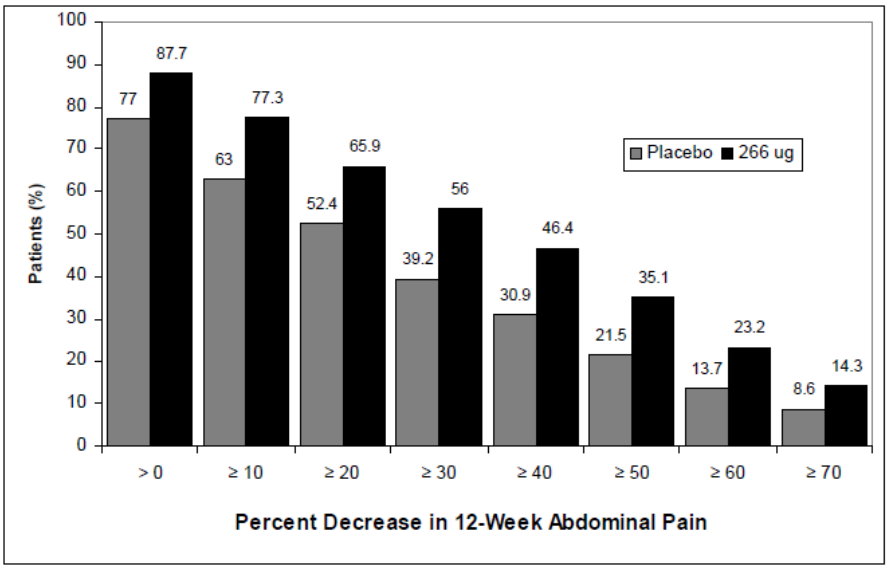


Figure 12: Percentage of patients with decreases in 12-week abdominal pain by level of decrease – ITT population.



Further endpoints not included in the special European section of evaluation comprise the following: the severity of straining, the 6/12 week CSBM+1 responders, the 6/12 weeks abdominal pain (without discomfort) responder, and a list of 20 "additional efficacy responder" analysis. The results are shown in the following tables:

Table 26: Efficacy results for endpoints not presented in the EU evaluation:

Variable		placebo	linaclotide	LSMD (95% CI) or odds ratio(95%CI) p-value
Severity of straining	Baseline	3.449	3.579	-0.655
	End of treatment	2.779	2.164	(-0.763 - -0.546)
	Difference	-0.651	-1.306	<0.0001
6/12 week CSBM+1 responder	Responder	117 (29.6%)	197 (48.6%)	2.28 (1.70; 3.06)
	Non-responder	278 (70.4%)	208 (51.4%)	<0.0001
6/12 weeks abdominal pain responder	Baseline	148 (37.5%)	203 (50.1%)	1.69 (1.27; 2.24)
	End of treatment	247 (62.5%)	202 (49.9%)	0.0003

Table 27: Efficacy results of the "additional efficacy responders" according to FDA evaluation:

Efficacy Parameter	*Placebo (N = 395)*		*Linaclotide (N = 405)*		
	N_1	*n (%)*	N_1	*n (%)*	*P-value*
9/12 week abdominal discomfort responder	395	95 (24.1)	405	130 (32.1)	0.0107
9/12 week APC + 1 responder	395	42 (10.6)	405	72 (17.8)	0.0037
9/12 week bloating responder	395	71 (18.0)	405	111 (27.4)	0.0013
9/12 week constipation severity responder	395	100 (25.3)	405	189 (46.7)	< 0.0001
9/12 week CSBM + 1 responder	395	68 (17.2)	405	131 (32.3)	< 0.0001
9/12 week CSBM 3 responder	395	26 (6.6)	405	80 (19.8)	< 0.0001
9/12 week IBS symptom severity responder	395	96 (24.3)	405	166 (41.0)	< 0.0001
9/12 week SBM + 2 responder	395	58 (14.7)	405	165 (40.7)	< 0.0001
9/12 week severity of straining responder	348	54 (15.5)	360	143 (39.7)	< 0.0001
9/12 week stool consistency responder	348	12 (3.4)	360	96 (26.7)	< 0.0001
6/12 week abdominal discomfort responder	395	146 (37.0)	405	195 (48.1)	0.0013
6/12 week APC 3 + 1 responder	395	39 (9.9)	405	93 (23.0)	< 0.0001
6/12 week bloating responder	395	118 (29.9)	405	176 (43.5)	0.0001
6/12 week constipation severity responder	395	168 (42.5)	405	241 (59.5)	< 0.0001
6/12 week CSBM 3 + 1 responder	395	50 (12.7)	405	129 (31.9)	< 0.0001
6/12 week CSBM 3 responder	395	51 (12.9)	405	130 (32.1)	< 0.0001
6/12 week IBS symptom severity responder	395	148 (37.5)	405	228 (56.3)	< 0.0001
6/12 week SBM + 2 responder	395	116 (29.4)	405	233 (57.5)	< 0.0001
6/12 week severity of straining responder	348	94 (27.0)	360	205 (56.9)	< 0.0001

Also evaluated was the response regarding BMs (SBM and CSBM) within the first 24 hours after treatment, which was statistically significantly different between the two treatment groups

(p<0.0001). The percent changes from baseline in abdominal pain, abdominal discomfort, and bloating are shown in the following table, which also includes a separate evaluation of the subgroups with relatively high discomfort and bloating scores (≥3) at baseline. This indeed shows that the net effect is slightly greater with the higher baseline score population:

Table28: Percent changes from baseline in 12-week abdominal pain, abdominal discomfort, and bloating – ITT population.

Parameter	*Placebo (N = 395)*	*Linaclotide (N = 405)*	*P-value[a]*
Abdominal Pain			
LSMC from baseline (SE)	–20.40 (1.68)	–33.47 (1.66)	< 0.0001
LSMD (95% CI)	—	–13.07 (–17.37, –8.77)	
n	395	405	
Abdominal Discomfort			
LSMC from baseline (SE)	–19.81 (1.58)	–31.74 (1.56)	< 0.0001
LSMD (95% CI)	—	–11.93 (–15.97, –7.89)	
n	395	405	
Abdominal Discomfort in Patients with Score ≥ 3 at Baseline			
LSMC from baseline (SE)	–19.79 (1.58)	–31.94 (1.57)	< 0.0001
LSMD (95% CI)	—	–12.15 (–16.21, –8.09)	
n	393	402	
Bloating			
LSMC from baseline (SE)	–16.48 (1.94)	–28.01 (1.92)	< 0.0001
LSMD (95% CI)	—	–11.53 (–16.50, –6.57)	
n	394	405	
Bloating in Patients with Bloating Score ≥ 3 at Baseline			
LSMC from baseline (SE)	–16.29 (1.53)	–29.66 (1.52)	< 0.0001
LSMD (95% CI)	—	–13.37 (–17.29, –9.44)	
n	389	399	

Also of interest appears to be the evaluation of changes in other abdominal symptoms that are not considered to be specific for IBS-C. These are shown in the following table:

Table 29: Changes from baseline in 12-week assessments of other abdominal and bowel symptoms – ITT population.

Parameter	*Placebo (N = 395)*	*Linaclotide (N = 405)*	*P-value[a]*
Abdominal Fullness			
Baseline, Mean (SD)	6.504 (1.771)	6.821 (1.721)	
LSMC from baseline (SE)	–1.133 (0.101)	–2.009 (0.100)	< 0.0001
LSMD (95% CI)	—	–0.876 (–1.134, –0.618)	
n	395	405	
% of Days with Abdominal Pain Score < 3			
Baseline, Mean (SD)	8.44 (14.17)	8.00 (13.68)	
LSMC from baseline (SE)	–0.27 (0.05)	0.14 (0.05)	< 0.0001
LSMD (95% CI)	—	0.41 (0.28, 0.55)	
n	395	405	
Abdominal Cramping			
Baseline, Mean (SD)	5.362 (1.942)	5.399 (1.876)	
LSMC from baseline (SE)	–1.137 (0.090)	–1.742 (0.090)	< 0.0001
LSMD (95% CI)	—	–0.605 (–0.837, –0.373)	
n	395	405	
Unsuccessful BMs			
Baseline, Mean (SD)	7.795 (7.606)	9.029 (8.150)	
LSMC from baseline (SE)	–3.910 (0.232)	–4.705 (0.230)	0.0090
LSMD (95% CI)	—	–0.795 (–1.391, –0.199)	
n	395	405	
IBS Symptom Severity			
Baseline, Mean (SD)	3.659 (0.618)	3.735 (0.629)	
LSMC from baseline (SE)	–0.545 (0.038)	–0.999 (0.038)	< 0.0001
LSMD (95% CI)	—	–0.454 (–0.552, –0.355)	
n	389	395	
Constipation Severity			
Baseline, Mean (SD)	3.727 (0.643)	3.818 (0.644)	
LSMC from baseline (SE)	–0.571 (0.042)	–1.177 (0.042)	< 0.0001
LSMD (95% CI)	—	–0.606 (–0.714, –0.498)	
n	389	395	

The relief of IBS symptoms was not only assessed by the way described for the European primary endpoint, but also using defining a responder as a patient with "somewhat relief, "considerable relief", or complete relief" for 100% of the weekly scores, or with considerable or complete relief for at least 50% of the weekly scores. A 12-week monthly IBS-C responder was defined as a patient who was somewhat, considerably or completely relieved for all 4 weeks, or considerably or completely relieved for at least 2 weeks of a month and had not response indicating any worsening (score of 5, 6, or 7), no increase in rescue medicine use, and did not discontinue from the study due to lack of efficacy. "Adequate relief" was assessed on the basis of the yes/no answer to the question "Overall, have you had adequate relief from your IBS symptoms during the past 7 days". The results of these evaluations are shown in the following table

Table 30: Relief of IBS symptoms responders – ITT population

	Placebo (N = 395)	*Linaclotide (N = 405)*
	n (%)	*n (%)*
12-Week Degree of Relief of IBS Symptoms Responders		
Responder	96 (24.3)	167 (41.2)
Nonresponder	299 (75.7)	238 (58.8)
Difference (linaclotide – placebo)	—	16.9
P-value	—	< 0.0001
12-Week Monthly IBS-C Responders		
Responder	110 (27.8)	190 (46.9)
Nonresponder	285 (72.2)	215 (53.1)
Difference (linaclotide – placebo)	—	19.1
P-value	—	< 0.0001
9/12 Week Adequate Relief of IBS Symptoms Responders		
Responder	84 (21.3)	149 (36.8)
Nonresponder	311 (78.7)	256 (63.2)
Difference (linaclotide – placebo)	—	15.5
P-value	—	< 0.0001
6/12 Week Adequate Relief of IBS Symptoms Responders		
Responder	135 (34.2)	198 (48.9)
Nonresponder	260 (65.8)	207 (51.1)
Difference (linaclotide – placebo)	—	14.7
P-value	—	< 0.0001

The intake of rescue medication was also evaluated. At baseline, the median percentage of days of medication used was 7.69 in both treatment groups. The least squares mean change from baseline in the percentage of days during the treatment period during which rescue medication was reported to be used was 2.6% for placebo, and – 7.2'% for linaclotide. The percentage of patients who reported an increase from baseline in the number of days with recue medication use was 29.4% for placebo, and 17.3% for linaclotide. Both associated p-values were <0.00001.

The IBS-SSS (Irritable Bowel Severity Scoring System), a partially validated outcome measure developed for use in IBS was also evaluated. The IBS-SSS comprises 5 symptoms which are all rated on a 0-100 VAS. The results are shown in the following table:

Table 31: Changes from baseline to end of treatment period in IBS-SSS – ITT population:

Parameter	*Placebo (N = 395)*	*Linaclotide (N = 405)*	*P-value[a]*
Severity of Abdominal Pain			
Baseline, Mean (SD)	67.22 (20.98)	69.63 (18.62)	
LSMC from baseline (SE)	–21.54 (1.53)	–30.20 (1.52)	< 0.0001
LSMD (95% CI)	—	–8.66 (–12.59, –4.74)	
n	367	374	
Frequency of Abdominal Pain			
Baseline, Mean (SD)	68.15 (24.64)	67.33 (22.31)	
LSMC from baseline (SE)	–18.46 (1.60)	–26.80 (1.58)	< 0.0001
LSMD (95% CI)	—	–8.34 (–12.43, –4.26)	
n	368	374	
Severity of Abdominal Distension			
Baseline, Mean (SD)	69.97 (24.26)	73.34 (22.65)	
LSMC from baseline (SE)	–17.96 (1.56)	–27.03 (1.55)	< 0.0001
LSMD (95% CI)	—	–9.07 (–13.07, –5.06)	
n	368	374	
Dissatisfaction with Bowel Habits			
Baseline, Mean (SD)	89.48 (16.50)	90.78 (16.18)	
LSMC from baseline (SE)	–19.02 (1.72)	–33.64 (1.71)	< 0.0001
LSMD (95% CI)	—	–14.62 (–19.05, –10.20)	
n	367	372	
Interference of IBS with Life in General			
Baseline, Mean (SD)	64.21 (25.49)	66.09 (23.80)	
LSMC from baseline (SE)	–20.24 (1.50)	–29.38 (1.49)	< 0.0001
LSMD (95% CI)	—	–9.14 (–13.00, –5.28)	
n	368	373	
Total Score			
Baseline, Mean (SD)	359.15 (78.04)	367.50 (70.51)	
LSMC from baseline (SE)	–96.79 (6.40)	–147.06 (6.35)	< 0.0001
LSMD (95% CI)	—	–50.26 (–66.70, –33.82)	
n	366	372	

The Summary of patient satisfaction with treatment and question on likelihood on treatment continuation assessment are also reported (both evaluated based on a 5-point scale) both resulted in highly statistically significant advantages for the active treatment.

The CHMP notes that the additional analyses presented above do support the overall robustness of the results. This not only can be concluded for the type of endpoints, but – when considering the PP-evaluations and comparison of LOCF and OC analyses– also for the type of evaluation.

Randomised withdrawal period:

At the end of treatment, the patients in the RW population who were treated with placebo had a less robust response to treatment compared with the patients treated with linaclotide. This was true for both bowel habits and abdominal symptoms. However, after the placebo patients were treated with linaclotide during this period, there was a clear improvement in all of these parameters approaching the improvement attained by the linaclotide patients at the end of the 12-week period. In contrast patients who were treated with linaclotide during the 12-week period, and then re-randomised to placebo in the RW period had a decrease in the improvements attained over the course of linaclotide treatment. There was clearly no evidence of a rebound effect after linaclotide withdrawal. The response to linaclotide was overall maintained when linaclotide treatment was prolonged during the RW period.

The next table shows these results for a variety of "numerical" endpoints:

Table 32: Overview of efficacy parameters during the combined treatment and randomised withdrawal period (comparison to baseline values) – RW population:

Parameter	*Placebo - Lin (N =333)*	*Lin- Placebo (N = 154)*	*Lin-Lin (N = 158)*
	Mean ± SD (n)	*Mean ± SD (n)*	*Mean ± SD (n)*
Change From Baseline in CSBM Frequency Rate			
At End of Treatment Period	0.940 ± 1.766 (333)	2.405 ± 3.265 (154)	2.446 ± 3.412 (158)
At End of Study	1.990 ± 2.767 (333)	0.988 ± 1.751 (154)	2.296 ± 2.917 (158)
Change From Baseline in SBM Frequency Rate			
At End of Treatment Period	1.308 ± 2.617 (333)	4.000 ± 4.251 (154)	4.012 ± 4.286 (158)
At End of Study	3.107 ± 3.905 (333)	1.624 ± 2.597 (154)	3.788 ± 3.760 (158)
Change From Baseline in Stool Consistency			
At End of Treatment Period	0.717 ± 1.367 (255)	2.061 ± 1.643 (123)	2.231 ± 1.582 (126)
At End of Study	1.869 ± 1.451 (284)	0.956 ± 1.342 (128)	2.195 ± 1.518 (132)
Change From Baseline in Severity of Straining			
At End of Treatment Period	–0.793 ± 1.005 (255)	–1.453 ± 0.917 (123)	–1.497 ± 1.075 (126)
At End of Study	–1.228 ± 1.017 (284)	–1.019 ± 0.934 (128)	–1.471 ± 1.037 (132)
Change From Baseline in Abdominal Pain			
At End of Treatment Period	–1.646 ± 2.117 (330)	–2.610 ± 2.110 (150)	–2.621 ± 2.322 (157)
At End of Study	–2.059 ± 2.102 (332)	–2.143 ± 2.092 (152)	–2.787 ± 2.286 (158)
Change From Baseline in Abdominal Discomfort			
At End of Treatment Period	–1.720 ± 2.182 (330)	–2.611 ± 2.237 (150)	–2.803 ± 2.467 (157)
At End of Study	–2.113 ± 2.120 (332)	–2.148 ± 2.157 (152)	–2.919 ± 2.458 (158)
Change From Baseline in Bloating			
At End of Treatment Period	–1.595 ± 2.213 (330)	–2.490 ± 2.408 (150)	–2.917 ± 2.681 (157)
At End of Study	–2.068 ± 2.282 (332)	–2.078 ± 2.198 (152)	–3.071 ± 2.669 (158)
Change From Baseline in Percent of Abdominal Pain-Free Days			
At End of Treatment Period	7.748 ± 23.299 (330)	12.157 ± 27.200 (150)	15.558 ± 34.007 (157)
At End of Study	9.715 ± 24.716 (332)	9.153 ± 22.558 (152)	16.644 ± 33.785 (158)

The evaluation of rescue medication confirmed these results: When patients were switched from placebo to active there was a decrease in the use of recue medications. In contrast, patients who were switched from linaclotide to placebo had an increase of rescue medication use, while the patients remaining on linaclotide had no meaningful change.

The evaluation of the IBS-SSS and the evaluation of treatment satisfaction and continuation results confirmed these findings.

The "EU primary efficacy parameters" were also evaluated during the RW period, and the results of this evaluation are presented in the following table. The results as above are confirmed for the abdominal

pain/discomfort responder evaluation, but not for the IBS Degree of Relief evaluation, which saw a decrease in response rates in all groups. According to the study report, this is attributable to missing data. Allegedly many patients attended the end of study visit before last IVRS call.

Table 33: Abdominal pain/discomfort and IBS Degree of Relief responders at end of 12-week treatment and end of RW period

Parameter	*Placebo – Lin (N =333)*	*Lin- Placebo (N = 154)*	*Lin-Lin (N = 158)*
	n (%)	**n (%)**	**n (%)**
Abdominal Pain/Abdominal Discomfort Responders			
End of Treatment Period	169 (50.8)	107 (69.5)	106 (67.1)
End of Study	205 (61.6)	85 (55.2)	100 (63.3)
IBS Degree of Relief Responders			
End of Treatment Period	76 (22.8)	62 (40.3)	62 (39.2)
End of Study	49 (14.7)	12 (7.8)	23 (14.6)

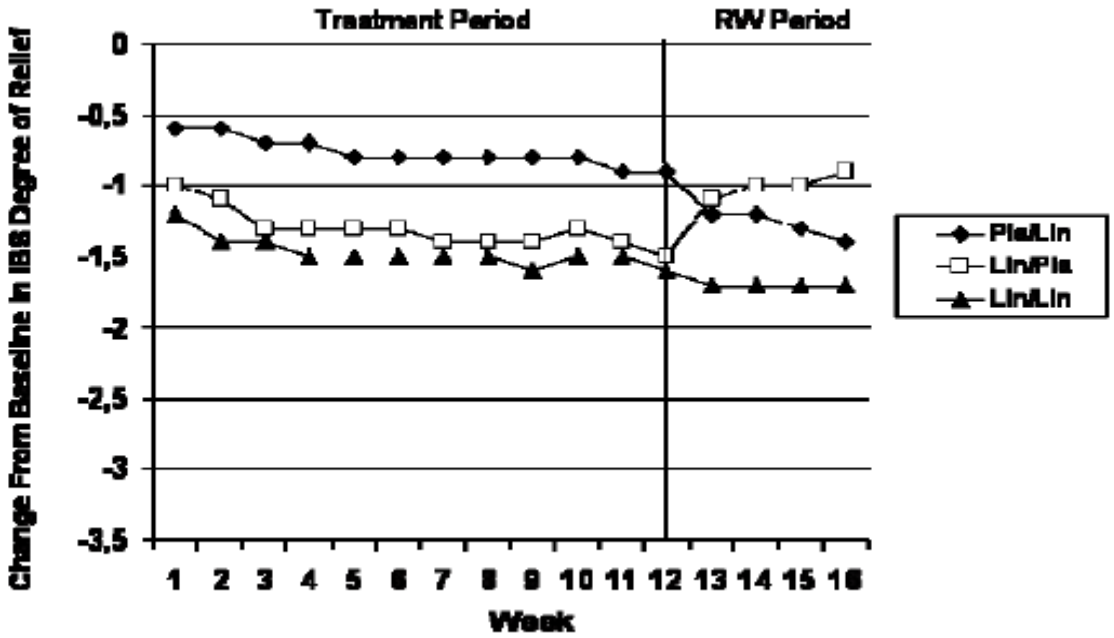
The separate evaluation of abdominal pain, abdominal discomfort and IBS Degree of Relief scores is shown in the following table:

Table 34: Abdominal pain and abdominal discomfort and IBS Degree of Relief at end of 12-week treatment and end of study – ITT population

Parameter	*Placebo – Lin (N =333)*	*Lin- Placebo (N = 154)*	*Lin-Lin (N = 158)*
	Mean ± SD (n)	**Mean ± SD (n)**	**Mean ± SD (n)**
Abdominal Pain Average Weekly Score (Change from Baseline)			
At End of Treatment Period	-1.65 ± 2.12 (330)	-2.61 ± 2.11 (150)	-2.62 ± 2.32 (157)
At End of Study	-2.20 ± 2.24 (316)	-2.04 ± 2.31 (147)	-2.68 ± 2.33 (147)
Abdominal Discomfort Average Weekly Score (Change from Baseline)			
At End of Treatment Period	-1.72 ± 2.18 (330)	-2.61 ± 2.24 (150)	-2.80 ± 2.47 (157)
At End of Study	-2.26 ± 2.28 (316)	-2.01 ± 2.36 (147)	-2.84 ± 2.53 (147)
IBS Degree of Relief Average Weekly Score (Change from Baseline)			
At End of Treatment Period	-0.90 ± 1.12 (296)	-1.51 ± 1.07 (131)	-1.61 ± 1.31 (132)
At End of Study	-1.40 ± 1.25 (99)	-0.86 ± 1.09 (43)	-1.72 ± 1.40 (38)

As an example for the graphical evaluations of the RW period, the evaluation of the IBS Degree of Relief average score is shown, based on the RW population only. Similar results (graphical displays) are shown for the other parameters.

Figure 13: Change from baseline in the IBS Degree of relief weekly average score up to 16 weeks (OC) – RW population



Study MCP-103-302

Study MCP-103-302 was a phase 3, randomised, double-blind, placebo-controlled, parallel group trial of linaclotide administered orally for 26 weeks in patients with Irritable Bowel Syndrome with Constipation. The study was conducted between 02nd July, 2009, and 03rd September, 2010 at 111 trial centres (of which 102 indeed randomised patients) in the United States.

Methods

Study Participants

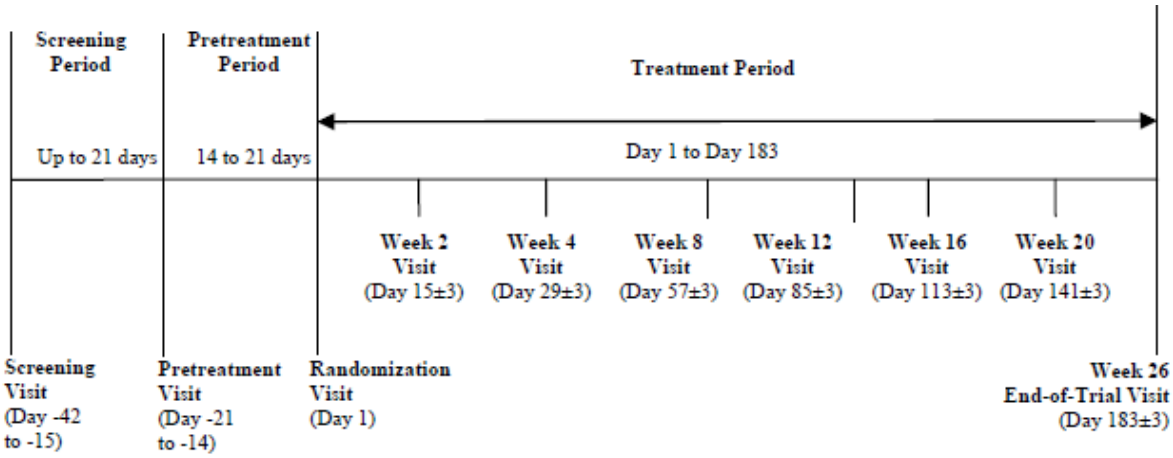
The study was conducted in the USA and in Canada. The inclusion of the patient population was based on (slightly modified) Rome II criteria for IBS-C, which were partly already resembling the newly established Rome III criteria (as of 2006), resulting in an almost complete concordance of fulfilment of the Rome II and Rome III criteria in the included patient population. The included patient population is regarded to fully reflect a patient population suffering from IBS-C.

Treatments

The treatments were similar as in study LIN-MD-31

The overall design is similar to study LIN-MD-31 except for the randomised withdrawal period, and with the treatment duration being 6 months, instead of 3. The design is shown in the following graph:

Figure 14: Illustration of trial design for study MCP-103-302:



Objectives

The objective(s) of the trial is defined similarly as in study LIN-MD-31.

Outcomes/endpoints

The endpoints were also similarly defined as in study LIN-MD-31, however, with the additions following the longer treatment duration. The following endpoints, almost similar to LIN-MD-31 were relevant for this study:

- EU primary endpoints:
    - 12-week 6/12 abdominal pain/abdominal discomfort responder
    - 12-week 6/12 IBS Degree of Relief Responder.
- US primary endpoints:
    - 9/12 week abdominal pain and CSBM (APC) 3+1 responder,
    - 9/12 week CSBM 3+1 responder
    - 9/12 week abdominal pain responder
    - 6/112 week APC+1 responder
- US secondary endpoints:
    - Change from baseline in the 12-week CSBM frequency
    - Change from baseline in the 12-week SBM frequency
    - Change from baseline in the 12 week stool consistency
    - Change from baseline in the 12-week severity of straining
    - Change from baseline in the 12-week abdominal pain
    - Change from baseline in the 12-week abdominal discomfort
    - Change from baseline in the 12-week bloating
    - 6/12 week CSBM+1 responder

- 6/12 week abdominal pain responder
- Change from baseline in 12-week percent of abdominal pain-free days.

For the EU, the secondary endpoints were defined almost similar, with the exception of the two 6/12 week responder analyses, which were not included as secondary endpoints. In addition to the US-defined secondary endpoints, the following were added:

- 26-week (13/26) abdominal pain/abdominal discomfort responder
- 26-week (13/26) IBS Degree of Relief of Responder
- Change from baseline in EQ-5D VAS at week 12
- Change from baseline in EQ-5D Utility Index Score at week 12
- Change from baseline in patients assessment of IBS-QOL at week 12

The secondary endpoints were then – as in study LIN-MD-31 grouped as "main" and "supportive" secondary endpoints.

The main secondary endpoints were the following: The two 26 weeks evaluations, and the 12-weeks evaluations of CSBM, stool consistency, straining, and bloating. All other secondary endpoints were to be handled as being supportive. For the European analysis, a 3-stop serial gate-keeping multiple comparisons procedure was planned, with the first step comprising the two co-primary efficacy parameters, the second step testing the two 26-weeks endpoints, and the third step comprising the 12-week CSBM, stool consistency, straining, and bloating endpoints.

For the US, the serial 5-step gate-keeping approach was used, in which progression to the next stop only had to go forward if all individual null hypotheses within a step were rejected at the stop-specific overall significance level. All subsequent steps had to stop if any null hypothesis within a stop was not rejected. The steps consisted of the following: 1.) the four co-primary efficacy parameters; 2.) the first four secondary endpoints; 3.) the next three secondary endpoints (pain, discomfort, bloating); 4.) the fourth step was to test the two 6/12 week related secondary parameters; 5.) the final step was to test the single remaining secondary parameter.

A range of additional efficacy parameters (more than 40 positions) were then defined, taking into account the 26-weeks evaluations (evaluating not only 13/26 weeks responder parameters, but also 20/26 responders) at this step only.

Sample size

Sample size planning was similar to study LIN-MD-31. 800 patients were planned to be included.

Randomisation

Randomisation was conducted in similar way as in study LIN-MD-31.

Blinding (masking)

The blinding procedures were similar to study LIN-MD-31.

Statistical methods

In order to fulfil different requirements of EMA and FDA, different statistical analysis plans (SAP) with different primary/secondary endpoints were applied for the EU and the US application. The following description of statistical methods is based on the European SAPs only.

The double-blind, placebo-controlled pivotal study MCP-103-302 had the co-primary endpoints "12-week abdominal pain/discomfort response" and "12 week IBS degree of relief response". The responders were determined according to pre-specified criteria. Statistically significant changes versus placebo were required in both primary efficacy parameters for the trial to have met the primary efficacy objective. In study MCP-103-302, the "26-week abdominal pain/discomfort response" and "26 week IBS degree of relief response", which are the relevant endpoints to support the indication of long-term continuous treatment according to the "Points to consider on the evaluation of medicinal products for the treatment of irritable bowel syndrome" (CPMP/EWP/785/97), were among the main secondary endpoints.

For both co-primary efficacy parameters, the proportion of responders in the linaclotide and placebo groups was compared using the Cochran-Mantel-Haenszel (CMH) test controlling for geographical region. The number and percentage of responders for each treatment group, the difference in responder rates between the treatment groups, the odds ratio based on the CMH-method with corresponding confidence intervals, and the two-sided p-value associated with the CMH test are presented.

Continuous secondary endpoints were analysed using analysis of covariance (ANCOVA) models with fixed effect terms for treatment group and geographical region and the patient's corresponding baseline value of the parameter as a covariate.

The analyses of the primary and secondary efficacy parameters were based on the ITT population. In order to confirm the robustness of the results, the primary efficacy endpoints and the response rates for the 26 week treatment period were also analyzed using the PP Population.

It was distinguished between main, supportive and additional secondary efficacy endpoints. The overall type I family-wise error rate for the co-primary and main secondary efficacy endpoints was controlled at the 0.05 significance level using a 3-step serial gatekeeping procedure. In each step, a set of hypotheses was tested; progression to the next step occurred only if all hypotheses in the previous step were rejected. Within each step, the type I error was controlled at the 0.05 level: In the first step, statistical significance was needed for both co-primary endpoints; the type I error rates in the subsequent step(s) were controlled using the Hochberg procedure. The supportive and additional secondary endpoints were explored without control of the type I error rate, statistical tests being meant to be considered descriptively.

An observed-cases approach to missing data was applied. Missing values were not imputed. If the value for a primary endpoint was missing for a treatment period week, the patient was considered a non-responder for that week; for weekly responder parameters based on IVRS daily assessments, a patient with less than 4 complete IVRS calls during a treatment week was not considered a responder for that week. As sensitivity analyses, for parameters that were defined on a weekly basis, a last observation carried forward (LOCF) approach was also applied, imputing the last non-missing weekly value. The protocol allowed for rescue medication but data were included in the analysis irrespective of rescue medication usage.

Further analyses that can be considered as sensitivity analyses were provided for the abdominal pain/discomfort response and IBS degree of relief response for the 12 week treatment period and for

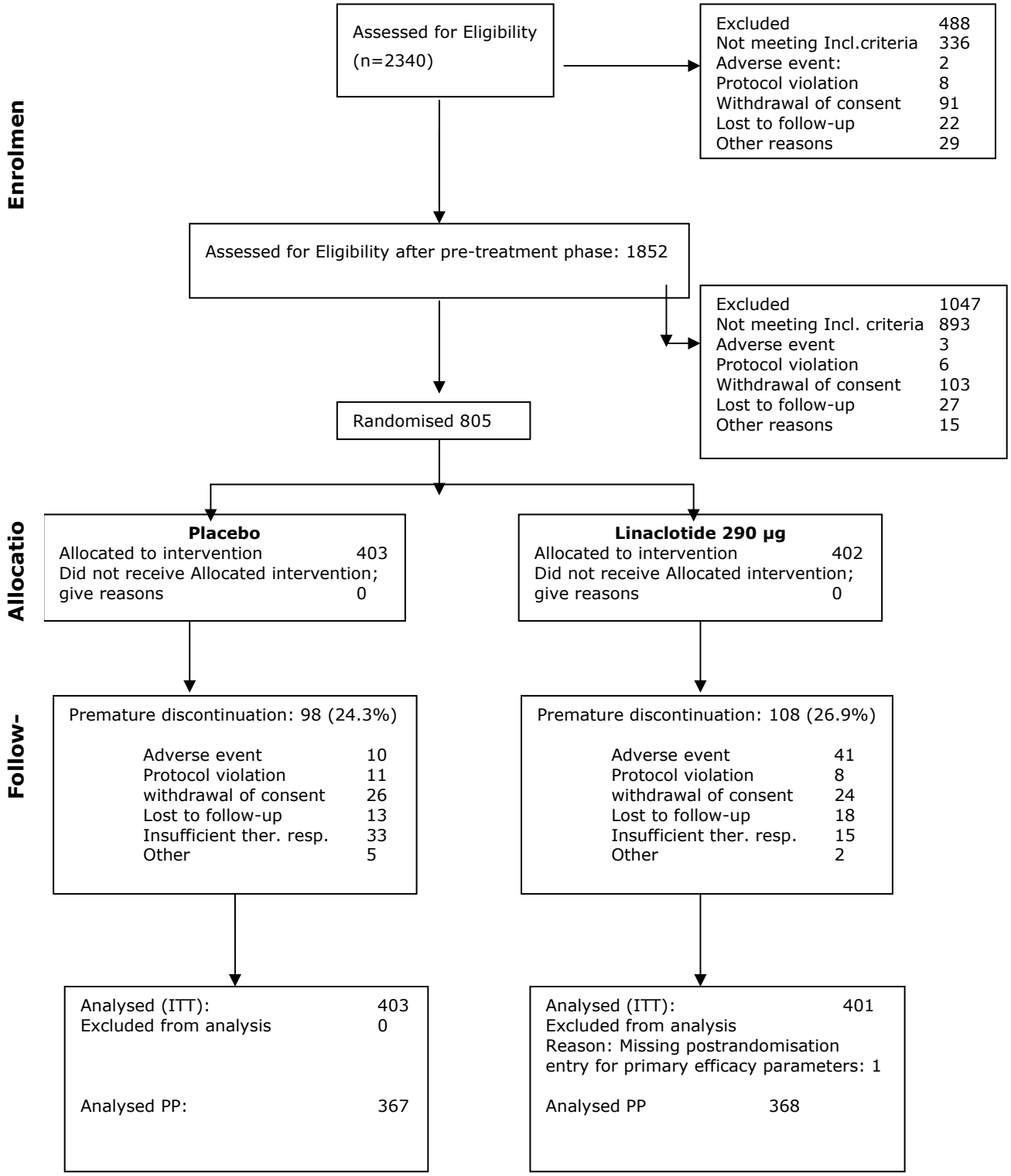
the 26 week treatment period. The primary endpoint "abdominal pain/discomfort response" was analyzed using alternate responder definitions for weekly response (≥40% and ≥50% improvement from baseline instead of ≥30%). A longitudinal analysis was provided for abdominal pain/abdominal discomfort weekly response and the IBS degree of relief weekly response utilizing a generalized linear model using the logit as link function and the exchangeable log odds ratio structure, based on the observed cases during the treatment period. The models used treatment group, region, week, week by treatment interaction as factors. An analysis of sustained responders was also provided, which defined sustained responders as those responders who were weekly responders in 2 of the 4 last weeks before the ending of the treatment period or discontinuing the trial.

Centre effects were not explored due to the small number of patients per centre. The primary analysis was stratified by geographical region. The consistency of the treatment effect for the primary endpoints was explored on the pooled ITT-population of the pivotal studies by pre-specified subgroup analyses by age and gender and in additional post-hoc subgroup analyses by race, ethnicity, and BMI.

Results

Participant flow

Figure 15: Number of patients for study MCP-103-302



Double-entry patients were noted before finalising of the final report as 6 patients had previously participated in or were actively participating in another study of linaclotide at the time they enrolled in the study. An Addendum to the study report lists these patients. Of the six, two had previously taken part in a phase 2b study, one had taken part in a phase 3 and in a long-term safety trial, one was taking part in a long-term safety trial, and one had been enrolled into the pre-treatment period of another phase 3 trial. These patients do increase the number of patients with protocol deviation defined as class 1 (patients that entered the trial though they did not satisfy the entry criteria) from 38 to 44.

Recruitment

The pivotal study MCP-103-302 was conducted between July-2009 (first patient recruited) and September 2010 (last patient completed) in 111 centers in US. Again, randomisation was relatively fast, apparently. The time that elapsed between first patient in and last patient out was a little longer than in the other study, obviously attributable to the longer duration of the trial.

Conduct of the study

Protocol amendments without impact on the conduct of the trial were implemented in similar way as in study LIN-MD-31

Baseline data

The demographic baseline data are shown in the following table. As can be seen there were statistically significant differences in the gender distribution, and regarding height, with no other parameters showing relevant or significant differences. The majority of patients were Caucasian, and female (78.0% and 89.6%).

Table 35: Demographic and Baseline Characteristics (ITT population):

Demographic Characteristic	Placebo (N=403)	Linaclotide (N=401)	Total (N=804)	p-value
Age, years				
Mean (SD)	44.0 (13.4)	44.6 (13.1)	44.3 (13.3)	0.4695
Median (Min, Max)	44.0 (18, 87)	45.0 (19, 82)	44.0 (18, 87)	
Age, n (%)				
18 to < 40 years	153 (38.0)	142 (35.4)	295 (36.7)	
40 to < 65 years	233 (57.8)	236 (58.9)	469 (58.3)	0.5174
≥ 65 years	17 (4.2)	23 (5.7)	40 (5.0)	
Gender, n (%)				
Female	352 (87.3)	368 (91.8)	720 (89.6)	0.0379
Male	51 (12.7)	33 (8.2)	84 (10.4)	
Race, n (%)				
Asian	6 (1.5)	2 (0.5)	8 (1.0)	
Black/African American	78 (19.4)	70 (17.5)	148 (18.4)	0.5619
Caucasian	311 (77.2)	316 (78.8)	627 (78.0)	
Other	8 (2.0)	13 (3.2)	21 (2.6)	
Ethnicity, n (%)				
Hispanic/Latino	38 (9.4)	43 (10.7)	81 (10.1)	0.5390
Not Hispanic/Latino	365 (90.6)	358 (89.3)	723 (89.9)	
Height, cm				
Mean (SD)	165.8 (7.8)	164.7 (7.9)	165.2 (7.9)	0.0343
Median (Min, Max)	165.1 (139.7, 193.0)	165.1 (134.6, 188.0)	165.1 (134.6, 193.0)	
Weight, kg				
Mean (SD)	76.4 (18.4)	75.5 (18.1)	75.9 (18.3)	0.4924
Median (Min, Max)	73.0 (43.9, 142.5)	72.1 (43.6, 173.6)	72.6 (43.6, 173.6)	
BMI, kg/m^2				
Mean (SD)	27.7 (6.2)	27.8 (5.9)	27.7 (6.1)	0.9348
Median (Min, Max)	26.5 (16.4, 54.2)	26.6 (17.7, 51.0)	26.6 (16.4, 54.2)	

The most frequent concomitant conditions reported in the patients were haemorrhoids, (33.4%), depression (27.7%), hysterectomy (27.8%), gastrointestinal reflux disease (25.1%), seasonal allergies (19.4%), hypertension (19.3%), drug hypersensitivity (17.3%), headaches (15.7%), anxiety 17.0%, and insomnia (17.3%). The baseline variables used for efficacy (and, of course for inclusion) are shown in the following table. No relevant nor significant differences between the treatment groups were seen. Baseline was quite similar to the baseline values in the other study.

Table 36: Baseline efficacy parameters (ITT population):

Efficacy Parameter	Statistic	Placebo (N=403)	Linaclotide (N=401)	Total (N=804)	p-value
Weekly CSBM Rate	n	403	401	804	0.2080
	Mean (SD)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	
	Median	0.0	0.0	0.0	
	Min, Max	0.0, 2.9	0.0, 2.4	0.0, 2.9	
Weekly SBM Rate	n	403	401	804	0.9748
	Mean (SD)	1.7 (1.4)	1.7 (1.4)	1.7 (1.4)	
	Median	1.5	1.5	1.5	
	Min, Max	0.0, 5.4	0.0, 5.8	0.0, 5.8	
Stool Consistency (BSFS)	n	344	342	686	0.2499
	Mean (SD)	2.3 (1.0)	2.4 (1.1)	2.3 (1.0)	
	Median	2.0	2.0	2.0	
	Min, Max	1.0, 6.0	1.0, 6.0	1.0, 6.0	
Straining	n	344	342	686	0.6346
	Mean (SD)	3.5 (0.8)	3.6 (0.8)	3.6 (0.8)	
	Median	3.6	3.6	3.6	
	Min, Max	1.0, 5.0	1.0, 5.0	1.0, 5.0	
Abdominal Pain	n	403	401	804	0.4525
	Mean (SD)	5.5 (1.7)	5.6 (1.7)	5.6 (1.7)	
	Median	5.3	5.4	5.4	
	Min, Max	2.9, 10.0	2.9, 10.0	2.9, 10.0	
Percent of Abdominal Pain Free Days	n	403	401	804	0.9702
	Mean (SD)	2.1 (6.3)	2.1 (7.0)	2.1 (6.7)	
	Median	0.0	0.0	0.0	
	Min, Max	0.0, 57.1	0.0, 53.8	0.0, 57.1	
Abdominal Discomfort	n	403	401	804	0.2282
	Mean (SD)	6.0 (1.7)	6.1 (1.7)	6.1 (1.7)	
	Median	5.8	6.1	5.9	
	Min, Max	2.1, 10.0	2.5, 10.0	2.1, 10.0	
Bloating	n	403	401	804	0.2304
	Mean (SD)	6.5 (1.8)	6.6 (1.9)	6.6 (1.8)	
	Median	6.5	6.6	6.6	
	Min, Max	1.6, 10.0	0.0, 10.0	0.0, 10.0	

The evaluation of concomitant medication at baseline did also not reveal obvious differences between the groups. Altogether, 90% of the patients used concomitant medication. The highest used was seen for propionic acid derivatives (usually NSAIDs; 19%), anilides (17%), multivitamins (17%), PPIs (17%), progestogens and estrogens, fixed combinations (15%), SSRIs (15'%), other antidepressants (14%), HMG CoA reductase inhibitors (12%), and benzodiazepines (11%).

Numbers analysed

See above: Participant flow.

Outcomes and estimation

The following table shows the evaluation of the primary and main secondary "European endpoints".

Table 37: Overview of primary and main secondary efficacy parameters for the EU evaluation:

Parameter	Placebo (N =403)	Linaclotide (N =401)		
	Step 1 - Primary Efficacy Parameters			
	n (%)	**n (%)**	**Odds Ratio (95% CI)**	**p-Value[a] (Significant by MCP)**
12-Week Abdominal Pain/Abdominal Discomfort Responder	155 (38.5)	217 (54.1)	1.90 (1.43, 2.52)	<0.0001 (yes)
12-Week IBS Degree of Relief Responder	67 (16.6)	158 (39.4)	3.26 (2.34, 4.53)	<0.0001 (yes)
	Step 2 - Main Secondary Efficacy Parameters			
26-Week Abdominal Pain/Abdominal Discomfort Responder	145 (36.0)	215 (53.6)	2.06 (1.55, 2.73)	<0.0001 (yes)
26-Week IBS Degree of Relief Responder	68 (16.9)	149 (37.2)	2.90 (2.09, 4.04)	<0.0001 (yes)
	Step 3 - Main Secondary Efficacy Parameters			
	LS Mean (SE)	**LS Mean (SE)**	**LSMD (95% CI)**	**p-Value[a] (Significant by MCP)**
Change from baseline in 12-week CSBM frequency rate	0.70 (0.12)	2.24 (0.12)	1.54 (1.23, 1.85)	<0.0001 (yes)
Change from baseline in 12-week stool consistency	0.61 (0.06)	1.91 (0.06)	1.31 (1.15, 1.47)	<0.0001 (yes)
Change from baseline in 12-week severity of straining	−0.66 (0.05)	−1.24 (0.04)	−0.57 (−0.69, −0.46)	<0.0001 (yes)
Change from baseline in 12-week bloating	−1.03 (0.10)	−1.91 (0.09)	−0.88 (−1.12, −0.64)	<0.0001 (yes)

The same supportive evaluation as in study LIN-MD-31 (sensitivity analysis) of the primary endpoints is presented with additional analyses applying the LOCF approach to the ITT population, and with the PP-population (applying the OC approach), however, only for the 12-week results.

Table 38: EU additional analyses: Primary efficacy parameters LOCF (ITT) and PP populations (OC)

Analysis	Responder (%)		
	Placebo N=395 ITT N=367 PP	Linaclotide N=405 ITT N=368 PP	Odds ratio (95% CI); p-Value
12-Week Abdominal Pain/Abdominal Discomfort Responders – LOCF approach (ITT population)	172 (42.7)	246 (61.4)	2.15 (1.62, 2.85); p<0.0001
12-Week Abdominal Pain/Abdominal Discomfort Responders - PP population (OC approach)	145 (39.5)	202 (54.9)	1.86 (1.39, 2.50); p<0.0001
12-week IBS Degree of Relief Responders - LOCF (ITT population)	74 (18.4)	174 (43.4)	3.39 (2.46, 4.67); p<0.0001
12-Week IBS Degree of Relief Responders - PP population (OC approach)	62 (16.9)	146 (39.7)	3.21 (2.28, 4.53); p<0.0001

The "sensitivity analyses" are presented in the following table for the 26-weeks results:

Table 39: 26-week abdominal pain/discomfort responder – OC approach (ITT population), LOCF (ITT population) and PP population (OC approach):

Analysis	Responder (%)		
	Placebo (N =403 ITT, 367 PP)	Linaclotide (N=401 ITT, 368 PP)	Odds ratio (95% CI); p-Value
26-Week Abdominal Pain/Abdominal Discomfort Responders – OC approach (ITT population)	145 (36.0)	215 (53.6)	2.06 (1.55, 2.73); p<0.0001
26-Week Abdominal Pain/Abdominal Discomfort Responders – LOCF approach (ITT population)	185 (45.9)	263 (65.6)	2.26 (1.70, 3.00); p<0.0001
26-Week Abdominal Pain/Abdominal Discomfort Responders - PP population (OC approach)	135 (36.8)	198 (53.8)	2.00 (1.49, 2.69); p<0.0001

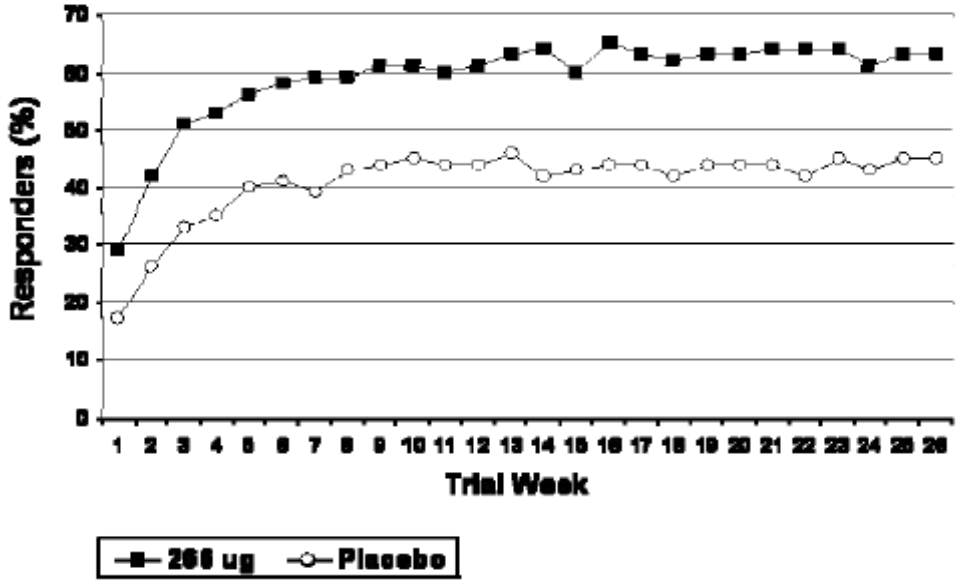
Table 40: 26 week IBS Degree of Relief responders – OC approach (ITT population), OC approach (ITT population) sensitivity analysis, LOCF approach (ITT population) and PP population (OC approach).

Analysis	Responder (%)		
	Placebo (N =403 ITT, 367 PP)	Linaclotide (N=401 ITT, 368 PP)	Odds ratio (95% CI); p-Value
26-Week IBS Degree of Relief Responders – OC approach (ITT population)	68 (16.9)	149 (37.2)	2.90 (2.09, 4.04); p<0.0001
26-Week IBS Degree of Relief Responders – OC approach – Sensitivity Analysis (ITT population)	70 (17.4)	153 (38.2)	2.92 (2.10, 4.05); p<0.0001
26-Week IBS Degree of Relief Responders - LOCF (ITT population)	83 (20.6)	188 (46.9)	3.39 (2.48, 4.62); p<0.0001
26-Week IBS Degree of Relief Responders - PP population (OC approach)	63 (17.2)	137 (37.2)	2.84 (2.01, 4.01); p<0.0001

The CHMP notes that the study results appear to be robust and overall insensitive to this analysis. All results are highly statistically significant. The magnitude of effect appears to be a net gain in responder rates of just under 20% for abdominal pain/discomfort, and just above 20% for the IBS Degree of Relief responder.

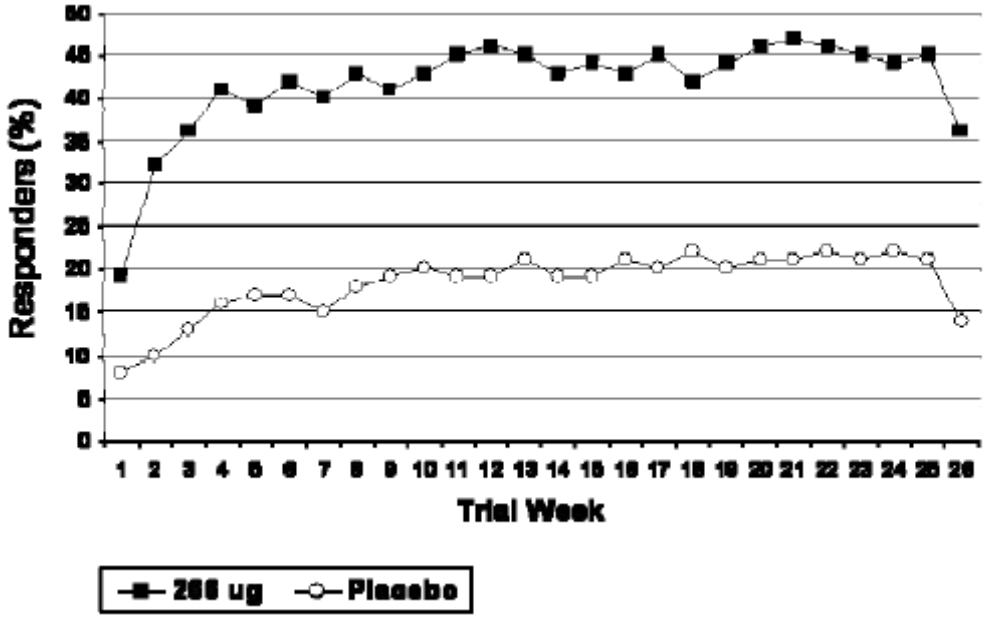
An overall longitudinal analysis of abdominal pain/discomfort weekly responders is given for 12 and 26 weeks, with estimated responder rates being 0.54 and 0.59 for linaclotide, and 0.37 and 0.41 for placebo at the two points of analysis (both p-values <0.00001). The longitudinal analysis also shows that already at week 1 of the analyses there was a significant difference between linaclotide and placebo. The longitudinal analysis is shown in the following graph.

Figure 16: Longitudinal analyses of abdominal pain/discomfort weekly responders up to 26 weeks – OC approach – ITT population.



Similar results were seen for the IBS Degree of Relief responder analyses, of which the graphical display is shown in the following.

Figure 17: Longitudinal analysis of IBS Degree of Relief responders up o 26 weeks – OC approach – ITT population:



There is an apparent decrease in responder rates for the week 26 time-point (decrease from 0.45 to 0.36 in the linaclotide, and from 0.21 to 0.14 in the placebo group) which occurred again because of missing values, in patients that had the end of study visit before the last IVRS call.

The further secondary endpoints included in the gate-keeping procedure for the European SAP are presented in the following table:

Table 41: European main secondary endpoints: 12-week data, ITT population.

Variable		placebo	linaclotide	LSMD (95% CI) p-value
12-week CSBM frequency	Baseline	0.213	0.176	1.54 (1.23, 1.85
	End of treatment	0.884	2.374	
	Difference	0.699	2.239	<0.0001)
12-week stool consistency	Baseline	2.293	2.381	1.31 (1.14, 1.47)
	End of treatment	2.976	4.314	
	Difference	0.607	1.914	<0.0001
12-week severity of straining	Baseline	3.545	3.570	- 0.572
	End of treatment	2.854	2.295	(-0.686, -0.459)
	Difference	ß-663	1.235	<0.0001
12 week bloating	Baseline	6.494	6.650	-0.882
	End of treatment	5.445	4.681	(-1.123, -0.641)
	Difference	-1.032	-1-914	<0.0001

The evaluation of these European secondary endpoints for the 26-weeks time-point are presented here:

Table 42: European secondary endpoints: 26 weeks data, ITT population:

Variable		placebo	linaclotide	LSMD (95% CI) p-value
26-week CSBM frequency	Baseline	0.213	0.176	1.5324
	End of treatment	0.894	2.375	(1.206, 1.842)
	Difference	0.681	2.199	<0.001
26-week stool consistency	Baseline	2.293	2.381	1.240
	End of treatment	3.017	4.289	(1.081, 1.398)
	Difference	0.725	1.900	<0.0001
26-week severity of straining	Baseline	3.547	3.562	-0.580
	End of treatment	2.823	2.251	(-0.694, -0.466)
	Difference	-0.724	-1.311	<0.0001

Variable		placebo	linaclotide	LSMD (95% CI) p-value
26 week bloating	Baseline	6.494	6.650	-0.959
	End of treatment	5.284	4.434	(-1.219, -0.699)
	Difference	-1.210	-2.215	<0.0001

The CHMP notes that it can be shown that the results after 26 weeks are similar to the ones achieved after 12 weeks. Obviously efficacy can be maintained over the longer treatment period. All p-values still indicated consistent high significance.

The further supportive EU secondary endpoints are presented in the following tables. Similar to the results for the main secondary endpoints as above, the 12- and 26 weeks data are presented in this AR, contrary to the study report, where the 26-weeks data are only included in the appendices:

Table 43: European additional secondary endpoints: 12- and 26 weeks data, ITT population:

Variable		placebo	linaclotide	LSMD (95% CI) p-value
12-week SBM frequency	Baseline	1.739	1.745	2.704
	End of treatment	2.987	4.225	(2.255, 3.153)
	Difference	1.313	4.017	<0.0001
26-week SBM frequency	Baseline	1.739	1.745	2.671
	End of treatment	2.814	5.495	(2.227, 3.115)
	Difference	1.075	3.749	<0.0001
12-week abdominal pain severity	Baseline	5.535	5.628	- 0.782
	End of treatment	4.397	3.683	(-1.019, -0.545)
	Difference	-1.070	-1.852	<0.0001
26 abdominal pain severity	Baseline	5.535	5.628	-0.855
	End of treatment	4.247	3.455	(-1.109, -0.601)
	Difference	-1.288	-2.173	<0.0001
12-week percent of abdominal pain free days	Baseline	2.069	2.083	0.227
	End of treatment	6.893	12.570	(0.105, 0.348)
	Difference	4.825	10.487	0.0003
26-week percent of abdominal pain free days	Baseline	2.069	2.083	0.246 *
	End of treatment	8.214	14.629	(0.123, 0.369)
	Difference	6.145	12.545	<0.0001

Variable		placebo	linaclotide	LSMD (95% CI) p-value
12 week abd. discomfort severity	Baseline	5.980	6.124	-0.837 (-1.071, -0.603)
	End of treatment	4.851	4.116	
	Difference	-1.103	-1.940	<0.0001
26 week abd. discomfort severity	Baseline	5.980	6.124	-0.916 (-1.166, -0.663)
	End of treatment	4.695	3.875	
	Difference	-1.261	-2.176	<0.0001

*evaluation of LS mean differences done by ANCOVA (rank-transformed normal scores)

The further analysis presents the evaluation of the so-called "sustained response", for both endpoints, including the "sensitivity analyses" for the different imputation methods (OC and LOCF). The results are as follows:

Table 44: 12-week and 26 abdominal pain/discomfort sustained responders ITT-population:

Analysis	Responder n (%)		Odds ratio (95% CI); p-Value
	Placebo (N =403)	Linaclotide (N=401)	
12-Week Abdominal Pain/Abdominal Discomfort Sustained Responders – OC approach	153 (38.0)	215 (53.6)	1.90 (1.43, 2.52); p < 0.0001
12-Week Abdominal Pain/Abdominal Discomfort Sustained Responders – LOCF approach	167 (41.4)	235 (58.6)	2.01 (1.52, 2.67); p<0.0001
26-Week Abdominal Pain/Abdominal Discomfort Sustained Responders – OC approach	134 (33.3)	208 (51.9)	2.17 (1.63, 2.88); p < 0.0001
26-Week Abdominal Pain/Abdominal Discomfort Sustained Responders – LOCF approach	173 (42.9)	247 (61.6)	2.15 (1.62, 2.85); p<0.0001

Table 45: 12-week and 26-week IBS Degree of relief sustained responders – ITT approach:

Analysis	Responder n (%)		Odds ratio (95% CI); p-Value
	Placebo (N =403)	Linaclotide (N=401)	
12-Week IBS Degree of Relief Sustained Responders – OC approach	63 (15.6)	147 (36.7)	3.12 (2.23, 4.38); p<0.0001
12-Week IBS Degree of Relief Sustained Responders – LOCF approach	72 (17.9)	165 (41.2)	3.21 (2.32, 4.43); p<0.0001
26-week IBS Degree of Relief Sustained Responders – OC approach	57 (14.1)	133 (33.2)	3.00 (2.12, 4.25); p<0.0001
26-week IBS Degree of Relief Sustained Responders – OC approach- sensitivity analysis	65 (16.1)	143 (35.7)	2.87 (2.05, 4.01); p<0.0001
26-Week IBS Degree of Relief Sustained Responders – LOCF approach	80 (19.9)	179 (44.6)	3.25 (2.37, 4.44); p<0.0001

The analysis of the different grades of response (40% and 50% response) is presented in the following table:

Table 46: 12-week abdominal pain/discomfort 40% and 50% responders – ITT population:

Analysis	Responder (%)		Odds ratio (95% CI); p-Value
	Placebo (N 403)	Linaclotide (N=401)	
12-Week Abdominal Pain/Abdominal Discomfort 40% responders	114 (28.3)	195 (48.6)	2.42 (1.80, 3.24); p<0.0001
12-Week Abdominal Pain/Abdominal Discomfort 50% Responders	72 (17.9)	166 (41.4)	3.25 (2.35, 4.50); p<0.0001

Similar results are also reported fro the abdominal pain (only) responders.

The CHMP notes that the 40% and 50% responder results for abdominal pain remain consistent with the overall results, and the magnitude of gain of effect even appears to be greater the "harder" the requirements are.

The CHMP requested a 26-weeks analysis together with subgroup analysis as regards gender, race, and age. It could be shown that an overall positive effect is preserved across these categories in the primary and main secondary parameters, although some variability and even reduction of the magnitude of the effect is observed. However, the notion that this can be attributed to the lower numbers included in these subgroups can be accepted overall.

Regarding the category "age" the company again shows acceptable consistency across the results for the 12-week evaluation. However, there is a gross deviation in the responder analysis for the 26-week evaluation, indicating that there might be almost no effect on abdominal pain/discomfort, but a more than double effect (compared to the overall population) in the IBS Degree of Relief response.

Table 1.4: Subgroup analyses by age at 26 weeks for the primary efficacy endpoints and main secondary efficacy endpoints (ITT population, study MCP-103-302):

26 weeks	*< 65 years*			*≥65 years*		
Parameter	*Linaclotide N=378*	*Placebo N=386*		*Linaclotide N=23*	*Placebo N=17*	
Primary Efficacy Parameter						
	%	%	**OR (95% CI)**	%	%	**OR (95% CI)**
Abdominal pain/ discomfort Responder	53.97	35.49	**2.13***** (1.60, 3.85)	47.83	47.06	**0.91** (0.26, 3.18)
IBS Relief Responder	37.57	17.36	**2.85***** (2.04, 3.99)	30.43	5.88	**6.11** (p=0.08) (0.69, 54.38)
Main Secondary Efficacy Parameters						
	LS Mean (SE) Change from baseline		**LSMD (95% CI)**	LS Mean (SE) Change from baseline		**LSMD (95% CI)**
Bloating (11-point NRS)	-2.21 (0.10)	-1.25 (0.10)	**- 0.97***** (-1.24, -0.70)	-1.69 (1.21)	-1.13 (1.15)	**-0.60** (-1.36, 0.16)
Stool consistency (BSFS Score)	1.92 (0.06)	0.69 (0.06)	**1.23***** (1.06, 1.39)	2.06 (0.26)	0.89 (0.30)	**1.18**** (0.34, 2.01)
Straining (5-point ordinal scale)	-1.30 (0.04)	-0.73 (0.04)	**-0.58***** (-0.69, -0.46)	-1.37 (0.19)	-0.83 (0.22)	**-0.54** (-1.15, 0.07)
CSBM/week	2.09 (0.11)	0.67 (0.11)	**1.43***** (1.12, 1.74)	3.94 (0.76)	0.99 (0.89)	**2.95**** (0.59, 5.32)

Additional analysis of the company showing higher degrees of response of 40% and 50% (for the pain response) do also not indicate a clinically relevant difference between active and placebo. It is acknowledged that this analysis is based on a small dataset only; however, together with the differential effects in the elderly on Quality of Life, it contributes to the impression that – for long-term treatment – the overall effect in the elderly especially on pain related symptoms is diminished.

To address the CHMP's concerns regarding the efficacy in the elderly, the applicant has provided an additional sensitivity analysis of both phase 3 studies, comparing a "completer" population, with the pivotal ITT analysis set, trying to account for the effect of drop-outs. Differential drop-out has also been analysed, and it could be shown that adverse events were the only factor causing the differential drop-out seen in elderly patients, thus potentially substantiating the suspicion of an altered benefit-risk ratio in this population.

The completer analysis was indeed able to show that – especially in study MCP-103-302, and especially in the 6 months results – the results in the completers were consistently better than those in the ITT population; for the 3 months evaluation even reaching levels of "success" that were not substantially different from the overall results (of the other age groups).

In order to look for the inconsistency of the 6 months results with the rest of the results, the company used the required analysis of the secondary endpoints abdominal pain, abdominal discomfort, and bloating, to present the longitudinal display of the results.

Figure 4.1: Longitudinal Analysis of Percent change from baseline in Abdominal Pain at its Worst over 26 weeks (OC, ITT Population, MCP-103-302)

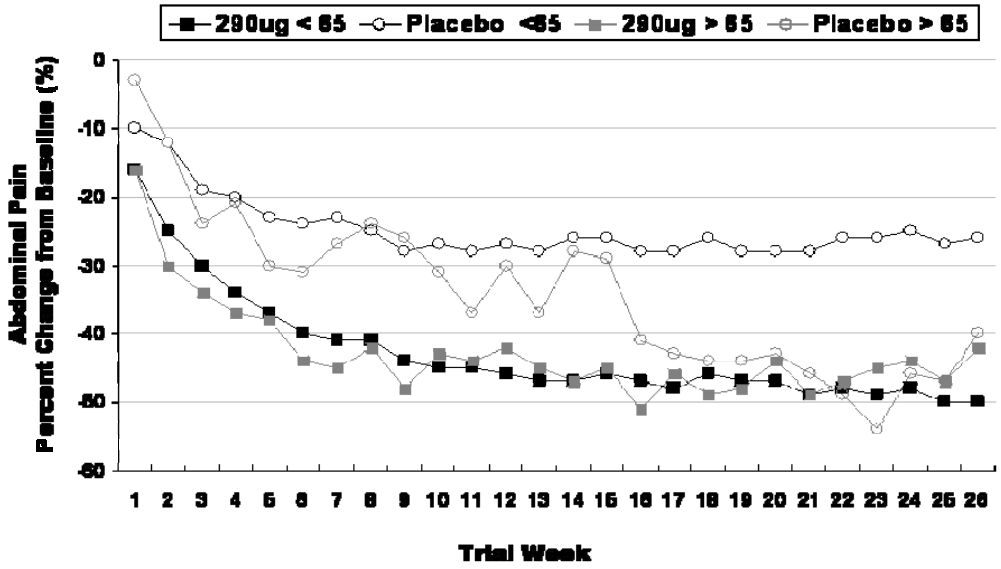


Figure 4.2: Longitudinal Analysis of Percent change from baseline in Abdominal Discomfort at its Worst over 26 weeks (OC, ITT Population, MCP-103-302)

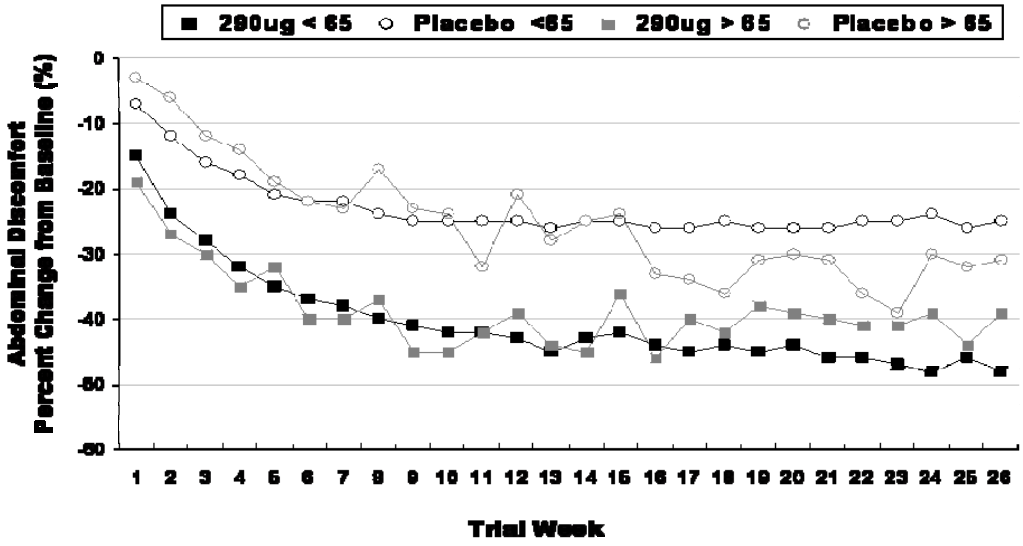
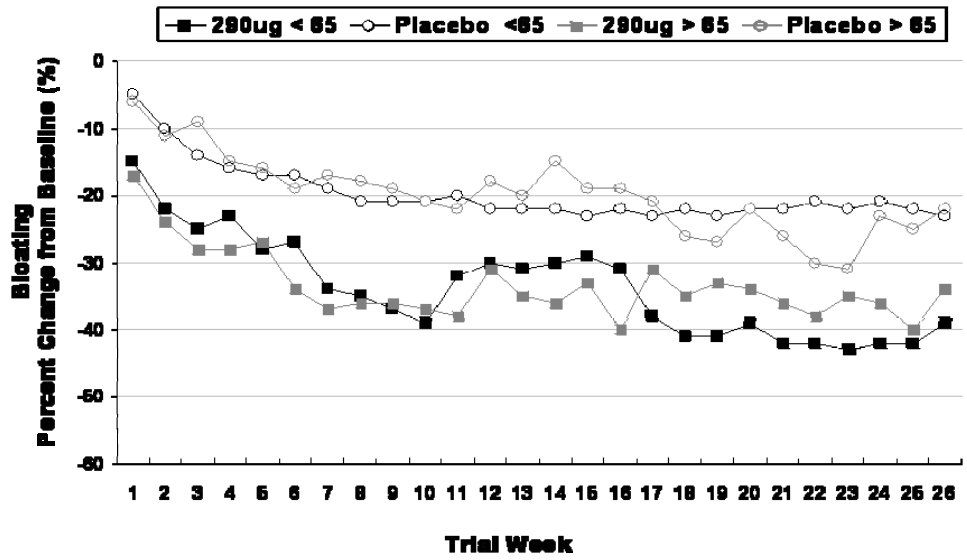


Figure 4.3: Longitudinal Analysis of Percent change from baseline in Bloating over 26 weeks (OC, ITT Population, MCP-103-302)



These data support that the variability in the results from week to week was increased, especially after 12 weeks treatment, not only in the active, but also in the placebo treatment group, with an apparent trend to higher placebo responses in the elderly population than in the total population. Therefore, the CHMP concluded that the apparently reduced efficacy seen in the elderly after long-term treatment in the abdominal pain/discomfort responder endpoint, is most likely caused by a combination of differential drop-out, highly increased variability (mainly to small numbers), and an increased placebo response. In the opinion of the CHMP, the overall response in the elderly population is not significantly reduced.

Evaluation of Quality of Life:

The evaluations of Quality of Life included the EQ-5D VAS score, the EQ-5D Utility Index Score, and the IBS-QOL disease specific QoL-instrument. The results of the EQ-5D VAS is presented in the following table, showing a statistically significant superiority for linaclotide both for the 12- as well as the 26 weeks evaluation:

Table 48: Change from baseline in the 12- and 26-weeks VAS of EQ-5D questionnaire (LOCF) ITT population.

Visit	Statistic	Placebo (N=403)	Linaclotide (N=401)
Baseline	Mean	72.80	73.55
	SD	17.20	17.81
	SEM	0.87	0.90
	Median	77.00	79.00
	Min, max	15.0, 100.0	8.0, 100.0
	n	395	393
12-Week	Mean	77.56	80.57
	SD	17.20	16.18
	SEM	0.86	0.81
	Median	80.00	85.00
	Min, max	10.0, 100.0	15.0, 100.0
	n	397	394
26-Week	Mean	79.20	82.01
	SD	16.53	14.94
	SEM	0.83	0.75
	Median	80.00	85.00
	Min, max	20.0, 100.0	15.0, 100.0
	n	397	394
ANCOVA results of 12-week analysis	LSMD (SE; 95% CI)	2.637 (0.947; 0.777, 4.496)	
	p-Value[a]	0.0055	
ANCOVA results of 26-week analysis	LSMD (SE; 95% CI)	2.414 (0.912; 0.624, 4.204)	
	p-Value[a]	0.0083	

In the evaluation of the utility index score of the EQ-5D, the responses to the 5 questions (relating to mobility, self-care, usual activities, anxiety/depression and pain/discomfort) the mean change from baseline in the utility index score was significantly greater in the linaclotide treatment group (0.079) than in the placebo group (0.045) (p-value 0.0005) after week 12. After 26 weeks the changes were 0.085 in the linaclotide group, and 0.059 in the placebo group (p-value: 0.0056). The changes in the different dimensions of the utility index score are shown in the following table. It is shown that the

differences are mostly, or almost exclusively attributable to the advantages for the linaclotide group in the pain/discomfort part of the evaluations. However, slightly better results are also achieved for mobility, self case, and anxiety depression, and the advantage in the "usual activities" dimension being moderate.

Table 49: Change form baseline in the 12week and 26-week responses for each dimension of the EQ-5D questionnaire – ITT population.

Dimension	Most Positive of the Possible Responses	Percentage of Patients Giving Response					
		Placebo (N=403)			Linaclotide (N=401)		
		Baseline n = 401	Week 12 n = 397	Week 26 n = 397	Baseline n = 399	Week 12 n =395	Week 26 n = 395
Mobility	I have no problems in walking about	86.3	89.2	88.7	86.0	90.9	91.9
Self Care	No problems with self care	99.0	97.7	97.5	97.7	98.5	98.5
Usual Activities	No problems performing usual activities	74.8	76.8	76.3	76.9	86.6	83.5
Pain/ Discomfort	I have no pain or discomfort	8.5	23.9	30.5	8.8	35.7	38.7
Anxiety/ Depression	I am not anxious or depressed	59.6	61.0	62.7	56.6	62.8	63.8

The results of the evaluation of the disease specific IBS-QOL instrument resulted in the figures shown in the following table. All results show statistically significant differences. All of the results were indeed highly statistically significant apart from the interference with activity subscale at week 12, which was significant at p=0.036 only.

Table 50: Change from baseline in IBS-QOL parameters at weeks 12 and 26 (ITT population)

IBS-QOL Parameter	Placebo (N=403) Mean (SD)	Linaclotide (N=401) Mean (SD)	p-value
Overall score			
Baseline score	63.42 (20.288)	61.20 (20.495)	
Change from baseline to Week 12	11.02 (15.710)	17.27 (16.837)	< 0.0001
Change from baseline to Week 26	10.90 (16.019)	17.91 (18.010)	< 0.0001
Dysphoria subscale			
Baseline score	64.93 (24.094)	62.09 (25.375)	
Change from baseline to Week 12	12.99 (18.927)	19.42 (20.765)	< 0.0001
Change from baseline to Week 26	12.68 (19.795)	19.80 (21.414)	< 0.0001
Interference with activity subscale			
Baseline score	70.57 (22.040)	68.30 (22.304)	
Change from baseline to Week 12	9.20 (17.217)	12.46 (19.090))	0.0358
Change from baseline to Week 26	8.44 (17.028)	12.58 (20.188)	0.0072
Body image subscale			
Baseline score	50.83 (23.084)	47.85 (22.304)	
Change from baseline to Week 12	13.08 (19.695)	22.01 (20.711)	< 0.0001
Change from baseline to Week 26	13.10 (20.483)	22.98 (22.065)	< 0.0001
Health worry subscale			
Baseline score	46.93 (25.095)	44.36 (23.790)	
Change from baseline to Week 12	15.61 (24.234)	25.86 (23.785)	< 0.0001
Change from baseline to Week 26	15.19 (23.801)	26.19 (24.664)	< 0.0001
Food avoidance subscale			
Baseline score	52.39 (29.963)	51.81 (30.561)	
Change from baseline to Week 12	10.52 (24.147)	19.68 (26.108)	< 0.0001
Change from baseline to Week 26	11.14 (23.780)	20.44 (27.211)	< 0.0001
Social reaction subscale			
Baseline score	68.63 (25.229)	67.21 (25.108)	
Change from baseline to Week 12	9.42 (20.181)	14.16 (20.201)	0.0009
Change from baseline to Week 26	9.67 (20.210)	15.83 (20.858)	< 0.0001
Sexual subscale			
Baseline score	71.19 (29.848)	68.14 (31.192)	
Change from baseline to Week 12	8.06 (23.103)	14.76 (26.186)	0.0003
Change from baseline to Week 26	7.73 (24.925)	15.19 (27.392)	0.0001
Relationships subscale			
Baseline score	74.96 (22.559)	73.85 (24.022)	
Change from baseline to Week 12	7.20 (17.889)	11.91 (19.752)	0.0002
Change from baseline to Week 26	7.96 (18.955)	12.17 (20.547)	0.0020

The evaluation of the WPAI: IBS-C absenteeism, presenteeism, overall productivity loss, and daily activity impairment is not included in the study report. The tables included in the appendices indicate higher effects for linaclotide both at 12 and 26 weeks. A statistical evaluation is not included. The evaluation of the Health Resource Use Questionnaire (HRUQ) did not reveal marked differences

between the groups. It was however noted that overall the baseline numbers for Health Resource Use were too low to yield any meaningful changes.

For the evaluation of the SF-12 generic QoL instrument, the study report stated that the overall summary score was similar to the general US population. However when looking into the results, it is shown that both the physical component summary scores, and, the mental component summary scores were around 45 to 46 at baseline, whereas the general population is defined by scores of 50. The changes achieved with the two treatments were consistently higher with linaclotide than with placebo in both the two main dimensions. The physical component Summary Scores increased by 3.52 and3.56 points for placebo, and for 4.64 and 4.57 points for linaclotide after 12 and 26 weeks of treatment. The respective figures for the Mental component Summary Scores were 1.19 and 1.24 for placebo, and 4.07, and 3.92 for linaclotide. A statistical evaluation of these results is not presented.

The CHMP notes that, most of the Quality of Life instruments used in the evaluation of the trial indicated advantages for the use of linaclotide in comparison to placebo, both at the 12 as well as at the 26 weeks evaluation. These results are taken as very much supportive of the evaluations presented before.

Ancillary analyses

The evaluation of the primary endpoints according to the US SAP is shown in the following table:

Table 47: Primary Efficacy Analysis US SAP – ITT population:

Variable	placebo (n=403) n(%)	linaclotide	Difference, OR for Response (+95% CI)	p-value
9/12 week APC 3+1 responder	12 (3.0)	51 (12.7)	9.7 4.65 (2.44, 8.84)	<0.0001
9/12 week CSBM 3+1 responder	20 (5.0)	72 (18.0)	13.0 4.19 (2.50; 7.03)	<0.0001
9/12 week abd. pain responder	79 (19.6)	156 (38.9)	19.3 2.62 (1.91; 3.60)	<0.0001
6/12 weeks APC+1 responder	56 (13.9)	135 (33.7)	19.8 3.16 (2.22; 4.49)	<0.0001

Regarding the incremental levels of SCBM rate and abdominal pain the following was observed:

Figure 18: Percentage of patients with improvement in 12-week CSBM rate by level of improvement – ITT population

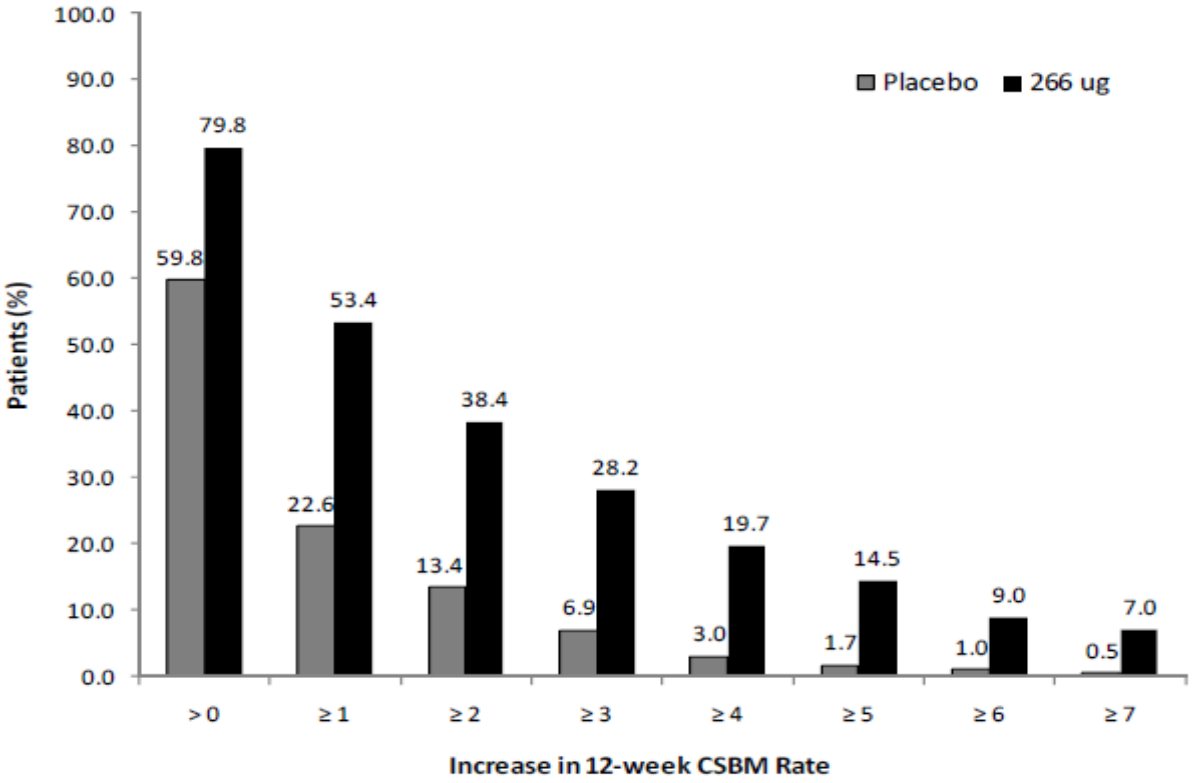
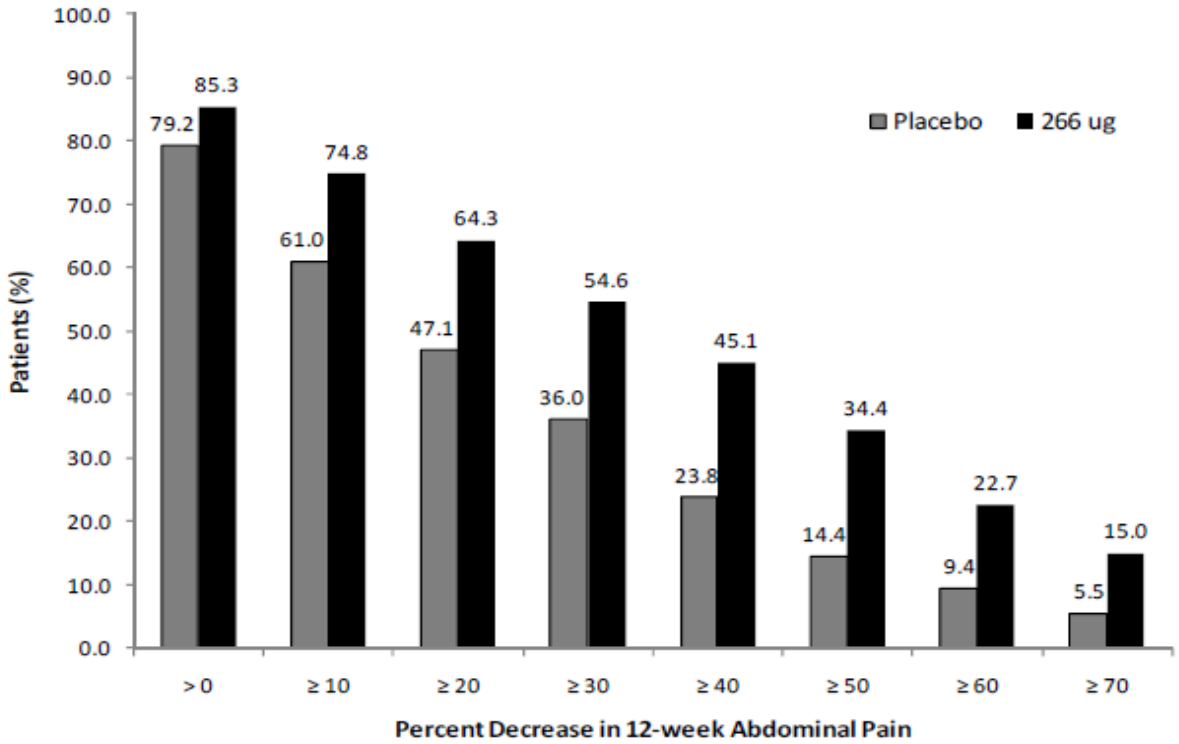


Figure 19: Percentage of patients with decreases in 12-week abdominal pain by level of decrease – ITT population.



Further endpoints not included in the special European section of evaluation comprise the 6/12 week CSBM+1 responders, the 6/12 weeks abdominal pain (without discomfort) responder, and a list of 20 "additional efficacy responder" analysis. The results are shown in the following tables:

Table 51: Efficacy results for endpoints not presented in the EU evaluation:

Variable		placebo	linaclotide	Diff. in responder rate; odds ratio(95%CI) p-value
6/12 week CSBM+1 responder	Responder	91 (22.6%)	191 (47.6%)	25.1 3.11 (2.29, 4.21) <0.0001
	Non-responder	312 (77.4%)	210 (52.4%)	
13/26 week CSBM+1 responder	Responder	75 (18.6%)	175 (43.6%)	25.0 3.36 (2.44, 4.62) <0.0001
	Non-responder	328 (81.4%)	226 (66.4%)	
6/12 weeks abdominal pain responder	Baseline	139 (34.5%)	196 (48.9%)	14.4 1.82 (1.37, 2.42) <0.0001
	End of treatment	264 (65.5%)	205 (51.1%)	
13/26 weeks abdominal pain responder	Responder	126 (31.3%)	197 (49.1%)	17.9 2.12 (1.59, 2.82) <0.0001
	Non-responder	277 (68.7%)	204 (60.9%)	

Table 52: Efficacy results of the "additional efficacy responders" according to FDA evaluation

	Placebo (N=403) n (%)		Linaclotide 266 ug (N=401) n (%)		
Additional Efficacy Responder Parameter	N_1	n (%)	N_1	n (%)	p-value
9/12 Week APC +1 Responder	403	22 (5.5)	401	91 (22.7)	< 0.0001
9/12 Week CSBM +1 Responder	403	46 (11.4)	401	136 (33.9)	< 0.0001
9/12 Week CSBM 3 Responder	403	20 (5.0)	401	72 (18.0)	< 0.0001
9/12 Week SBM +2 Responder	403	63 (15.6)	401	180 (44.9)	< 0.0001
9/12 Week Stool Consistency Responder	344	7 (2.0)	342	93 (27.2)	< 0.0001
9/12 Week Severity of Straining Responder	344	49 (14.2)	342	129 (37.7)	< 0.0001
9/12 Week Abdominal Discomfort Responder	403	63 (15.6)	401	144 (35.9)	< 0.0001
9/12 Week Bloating Responder	403	51 (12.7)	401	117 (29.2)	< 0.0001
9/12 Week IBS Symptom Severity Responder	403	96 (23.8)	401	176 (43.9)	< 0.0001
9/12 Week Constipation Severity Responder	403	96 (23.8)	401	199 (49.6)	< 0.0001
6/12 Week APC 3+1 Responder	403	25 (6.2)	401	90 (22.4)	< 0.0001
6/12 Week CSBM 3+1 Responder	403	38 (9.4)	401	118 (29.4)	< 0.0001
6/12 Week CSBM 3 Responder	403	38 (9.4)	401	119 (29.7)	< 0.0001
6/12 Week SBM +2 Responder	403	112 (27.8)	401	222 (55.4)	< 0.0001
6/12 Week Stool Consistency Responder	344	23 (6.7)	342	140 (40.9)	< 0.0001
6/12 Week Severity of Straining Responder	344	90 (26.2)	342	175 (51.2)	< 0.0001
6/12 Week Abdominal Discomfort Responder	403	124 (30.8)	401	191 (47.6)	< 0.0001
6/12 Week Bloating Responder	403	96 (23.8)	401	172 (42.9)	< 0.0001
6/12 Week IBS Symptom Severity Responder	403	144 (35.7)	401	222 (55.4)	< 0.0001
6/12 Week Constipation Severity Responder	403	159 (39.5)	401	244 (60.8)	< 0.0001
13/26 Week APC +1 Responder	403	53 (13.2)	401	130 (32.4)	< 0.0001
13/26 Week APC 3+1 Responder	403	27 (6.7)	401	84 (20.9)	< 0.0001
13/26 Week CSBM 3+1 Responder	403	34 (8.4)	401	100 (24.9)	< 0.0001

Table 53: Efficacy results of the "additional efficacy responders" according to FDA evaluation (continued)

	Placebo (N=403) n (%)		Linaclotide 266 ug (N=401) n (%)		
Additional Efficacy Responder Parameter	N_1	n (%)	N_1	n (%)	p-value
13/26 Week CSBM 3 Responder	403	35 (8.7)	401	101 (25.2)	< 0.0001
13/26 Week SBM +2 Responder	403	87 (21.6)	401	199 (49.6)	< 0.0001
13/26 Week Stool Consistency Responder	344	20 (5.8)	342	120 (35.1)	< 0.0001
13/26 Week Severity of Straining Responder	344	80 (23.3)	342	163 (47.7)	< 0.0001
13/26 Week Abdominal Discomfort Responder	403	116 (28.8)	401	193 (48.1)	< 0.0001
13/26 Week Bloating Responder	403	101 (25.1)	401	170 (42.4)	< 0.0001
13/26 Week IBS Symptom Severity Responder	403	128 (31.8)	401	213 (53.1)	< 0.0001
13/26 Week Constipation Severity Responder	403	139 (34.5)	401	221 (55.1)	< 0.0001
20/26 Week APC 3+1 Responder	403	10 (2.5)	401	48 (12.0)	< 0.0001
20/26 Week CSBM 3+1 Responder	403	14 (3.5)	401	63 (15.7)	< 0.0001
20/26 Week Abdominal Pain Responder	403	70 (17.4)	401	148 (36.9)	< 0.0001
20/26 Week APC +1 Responder	403	24 (6.0)	401	80 (20.0)	< 0.0001
20/26 Week CSBM +1 Responder	403	38 (9.4)	401	116 (28.9)	< 0.0001
20/26 Week CSBM 3 Responder	403	14 (3.5)	401	63 (15.7)	< 0.0001
20/26 Week SBM +2 Responder	403	43 (10.7)	401	138 (34.4)	< 0.0001
20/26 Week Stool Consistency Responder	344	2 (0.6)	342	74 (21.6)	< 0.0001
20/26 Week Severity of Straining Responder	344	31 (9.0)	342	113 (33.0)	< 0.0001
20/26 Week Abdominal Discomfort Responder	403	62 (15.4)	401	135 (33.7)	< 0.0001
20/26 Week Bloating Responder	403	49 (12.2)	401	111 (27.7)	< 0.0001
20/26 Week IBS Symptom Severity Responder	403	73 (18.1)	401	152 (37.9)	< 0.0001
20/26 Week Constipation Severity Responder	403	84 (20.8)	401	176 (43.9)	< 0.0001

Similar results are also presented in the following endpoints: Percent changes from baseline in abdominal pain, discomfort, and bloating, as well as for fullness, cramping, unsuccessful bowel movements, constipation severity etc.. Of remark is the fact that the only parameter that is not producing a highly significant difference (but a p-value of "only" 0.0038) is the unsuccessful BMs endpoint. Similar to LIN-MD-31, also the proportion of patients with an SBM or CSBM within 24 hours after first dose of study drug show a highly significant difference to the advantage of linaclotide. The following evaluation included in the "US part" of the evaluations gives an interesting impression of the evaluation of overall relief of IBS symptoms:

Table 54: Relief of IBS symptoms responders (ITT population):

Description	Placebo (N=403) n (%)	Linaclotide (N=401) n (%)
12-Week Degree of Relief of IBS Symptoms Responders		
Responder	85 (21.1)	182 (45.4)
Non-Responder	318 (78.9)	219 (54.6)
Difference in Responder Rate (Linaclotide - Placebo)	24.3	
p-value	< 0.0001	
12-Week Monthly IBS-C Responders		
Responder	99 (24.6)	203 (50.6)
Non-Responder	304 (75.4)	198 (49.4)
Difference in Responder Rate (Linaclotide - Placebo)	26.1	
p-value	< 0.0001	
9/12 Week Adequate Relief of IBS Symptoms Responders		
Responder	71 (17.6)	168 (41.9)
Non-Responder	332 (82.4)	233 (58.1)
Difference in Responder Rate (Linaclotide - Placebo)	24.3	
p-value	< 0.0001	
6/12 Week Adequate Relief of IBS Symptoms Responders		
Responder	103 (25.6)	219 (54.6)
Non-Responder	300 (74.4)	182 (45.4)
Difference in Responder Rate (Linaclotide - Placebo)	29.1	
p-value	< 0.0001	
20/26 Week Adequate Relief of IBS Symptoms Responders		
Responder	59 (14.6)	143 (35.7)
Non-Responder	344 (85.4)	258 (64.3)
Difference in Responder Rate (Linaclotide - Placebo)	21.0	
p-value	< 0.0001	
13/26 Week Adequate Relief of IBS Symptoms Responders		
Responder	101 (25.1)	197 (49.1)
Non-Responder	302 (74.9)	204 (50.9)
Difference in Responder Rate (Linaclotide - Placebo)	24.1	
p-value	< 0.0001	

The evaluation of the use of rescue medication also gives highly statistically significant differences to the advantage of the linaclotide group, independent from the evaluation of the overall rescue medication use, or the "per-protocol rescue medication" use. A further evaluation presented in the efficacy section of the single studies, is again the tabulation of the changes from baseline in the IBS-SSS score. Highly statistically significant results are achieved, however, only the 12-week data are presented.

Table 55: Change from baseline in the IBS-SSS during the first 12 weeks of the treatment period (ITT population)

Parameter	Placebo (N=403)	Linaclotide (N=401)
Severity of Abdominal Pain		
n	376	375
Baseline, Mean (SD)	66.941 (20.369)	69.253 (20.423)
LS Mean Change from Baseline (SE)	−17.946 (1.501)	−30.661 (1.497)
LS Mean Difference (95% CI)	−12.715 (−16.549, −8.881)	
p-value[a]	< 0.0001	
Frequency of Abdominal Pain		
n	376	375
Baseline, Mean (SD)	66.383 (24.204)	67.600 (24.057)
LS Mean Change from Baseline (SE)	−18.995 (1.606)	−27.196 (1.602)
LS Mean Difference (95% CI)	−8.201 (−12.301, −4.101)	
p-value[a]	< 0.0001	
Severity of Abdominal Distension		
n	376	375
Baseline, Mean (SD)	71.356 (21.342)	74.080 (22.460)
LS Mean Change from Baseline (SE)	−18.251 (1.570)	−28.637 (1.565)
LS Mean Difference (95% CI)	−10.386 (−14.396, −6.377)	
p-value[a]	< 0.0001	
Dissatisfaction with Bowel Habits		
n	375	375
Baseline, Mean (SD)	89.680 (16.511)	90.667 (16.638)
LS Mean Change from Baseline (SE)	−19.166 (1.748)	−34.313 (1.740)
LS Mean Difference (95% CI)	−15.147 (−19.605, −10.689)	
p-value[a]	< 0.0001	
Interference of IBS with Life in General		
n	375	375
Baseline, Mean (SD)	64.587 (24.869)	66.507 (25.105)
LS Mean Change from Baseline (SE)	−21.881 (1.452)	−29.854 (1.446)
LS Mean Difference (95% CI)	−7.974 (−11.677, −4.270)	
p-value[a]	< 0.0001	
IBS-SSS Total Score		
n	375	375
Baseline, Mean (SD)	358.880 (72.132)	368.107 (75.224)
LS Mean Change from Baseline (SE)	−95.563 (6.334)	−150.92 (6.309)
LS Mean Difference (95% CI)	−55.358 (−71.528, −39.188)	
p-value[a]	< 0.0001	

The evaluation of treatment satisfaction and willingness for treatment continuation at week 26/end of treatment also revealed consistency with the previous results (p<0.0001). Rated on a scale of 5 (with 5 presenting the most positive response), the treatment satisfaction was 2.3 in the placebo and 3.6 in the linaclotide group, and the willingness for treatment continuation was 3.1 in the placebo, and 3.8 in the linaclotide group.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. According to the EU guidelines requesting the documentation of 6 months treatment duration, study MCP-103-302 is the sole "pivotal" study for this application. These summaries should be read in conjunction on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 2. Summary of Efficacy for trial LIN-MD-31

Title: "A phase III, randomised, double-blind, placebo-controlled, parallel-group trial of linaclotide, administered orally for 12 weeks followed by a 4-week randomised withdrawal period in patients with irritable bowel syndrome with constipation"			
Study identifier	LIN-MD-31		
Design	double-blind, placebo-controlled parallel group, 4-week randomized withdrawal period.		
	Duration of main phase:		3 months
	Duration of Run-in phase:		7 days
	Duration of Extension phase:		4 weeks
Hypothesis	Superiority of linaclotide vs. placebo in the treatment of IBS-C		
Treatments groups	linaclotide 290 µg		n=406
	placebo		n=397
Endpoints and definitions	Co-Primary endpoints	abdominal pain/discomfort responder and IBS Degree of Relief of Responder	Abd. pain/discomfort response was defined as 30% improvement in NRS abdominal pain/discomfort score for 6 out of 12 treatment weeks Degree of Relief of Response was analysed from a 7-point Likert scale with a responder defined as a patients that had considerable of complete relief for 6 out of 12 treatment weeks
	Main secondary endpoints	Change in 12-week CSBM frequency	CSBM defined as a BM in the absence of use of laxatives with a sense of complete evacuation
		Change in 12 week stool consistency	Stool consistency was defined according to the 7-point Bristol-Stool-Form Scale (ranging from 1 (hard lumps, nuts) to 7 (entirely liquid, watery)
		Change in the severity of straining	Straining at BM was defined according to a 5-point Likert scale from 1 (not at all) to 5 (an extreme amount)
		Change in severity of bloating	Bloating was defined on an 11-point numerical rating scale where 0 represents no bloating and 10 represents very severe bloating

Title: "A phase III, randomised, double-blind, placebo-controlled, parallel-group trial of linaclotide, administered orally for 12 weeks followed by a 4-week randomised withdrawal period in patients with irritable bowel syndrome with constipation"			
	Secondary and other endpoints:	Change in SBM frequency	SMB frequency is defined as any BM without the use of laxatives
		Change in abdominal pain score	Abdominal pain is scored on a 11-point NRS asking for their abdominal pain at its worst over the last 24 hours
		Change in percent of abdominal pain free days	Abdominal pain free days were defined as days with a rating of 0 for the severity of abdominal pain
		Change in abdominal discomfort scale	Abdominal discomfort is scored on a 11-point NRS asking for their abdominal discomfort at its worst over the last 24 hours
		QoL measurements	Euro-QoL-5D, IBS-QoL
Database lock	03 September 2010		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT population : n=803 (395 placebo, 305 linaclotide)		
Effect estimate per comparison		**Placebo**	**linaclotide**
	Co-Primary endpoint abd. pain/discomfort responders	41.8%	54.8%
		OR: 1.7 (1.28 – 2.25), p=0.0002	
	Co-primary endpoint IBS Degree of Relief responder	18.5%	37.0%
		OR: 2.61 (1.89 – 3.62), p<0.0001	
	12 week CSBM frequency (LSM change from BL)	0.71	1.27
		Diff.: 1.57 (1.24 – 1.90), p<0.0001	
	12-week stool consistency (LSM change from BL)	0.66	2.07
		Diff.: 1.41 (1.24 – 1.57), p<0.0001	
	12-week severity of straining (LSM change from BL)	-0.65	- 1.31
		Diff.: -0.66 (-0.76 - -0.55), p<0.0001	
	12 week severity of bloating (LSM change from BL)	-1.1	-1.94
		Diff.: -0.84 (-1.10 - -0.59), p<0.0001	

Title: "A phase III, randomised, double-blind, placebo-controlled, parallel-group trial of linaclotide, administered orally for 12 weeks followed by a 4-week randomised withdrawal period in patients with irritable bowel syndrome with constipation"	
Notes	All additional secondary parameters were p<0.05 including Quality of Life (with the exception of EQ-5-D VAS, which was p=0.06); most parameters were <0.0001.

Table 3. Summary of Efficacy for trial MCP-103-302

Title: A phase 3, randomised, double-blind, placebo-controlled, parallel group trial of linaclotide administered orally for 26 weeks in patients with Irritable Bowel Syndrome with Constipation.			
Study identifier	MCP-103-302		
Design	Randomised, double-blind, placebo-controlled, parallel group trial of linaclotide with 26 weeks duration		
	Duration of main phase:		26 weeks
	Duration of Run-in phase:		1 week
	Duration of Extension phase:		N/a
Hypothesis	Superiority of linaclotide over placebo in the treatment of IBS-C		
Treatments groups	Linaclotide 290 µg		N=401, 6 months
	Placebo		N=403, 6 months
Endpoints and definitions	Co-Primary endpoints	12 week abdominal pain/discomfort responder and	Abd. pain/discomfort response was defined as 30% improvement in NRS abdominal pain/discomfort score for 6 out of 12 treatment weeks
		12 week IBS Degree of Relief of Responder	Degree of Relief of Response was analysed from a 7-point Likert scale with a responder defined as a patients that had considerable of complete relief for 6 out of 12 treatment weeks
	Main secondary endpoints	26 week abdominal pain/discomfort responder	Definition similar to primary endpoint, with the exception of need to be a responder for 13/26 weeks
		26 week IBS Degree of Relief responder	See above
		Change in 12-week CSBM frequency	CSBM defined as a BM in the absence of use of laxatives with a sense of complete evacuation
		Change in 12 week stool consistency	Stool consistency was defined according to the 7-point Bristol-Stool-Form Scale (ranging from 1 (hard lumps, nuts) to 7 (entirely liquid, watery)
		Change in 12-week severity of straining	Straining at BM was defined according to a 5-point Likert scale from 1 (not at all) to 5 (an extreme amount)
		Change in 12-week severity of bloating	Bloating was defined on an 11-point numerical rating scale where 0 represents no bloating and 10 represents very severe bloating

Title: A phase 3, randomised, double-blind, placebo-controlled, parallel group trial of linaclotide administered orally for 26 weeks in patients with Irritable Bowel Syndrome with Constipation.			
	Secondary endpoints:	12 wk. Change in SBM frequency	SMB frequency is defined as any BM without the use of laxatives
		12 wk. Change in abdominal pain score	Abdominal pain is scored on a 11-point NRS asking for their abdominal pain at its worst over the last 24 hours
		12 wk. Change in percent of abdominal pain free days	Abdominal pain free days were defined as days with a rating of 0 for the severity of abdominal pain
		12 wk Change in abdominal discomfort scale	Abdominal discomfort is scored on a 11-point NRS asking for their abdominal discomfort at its worst over the last 24 hours
		QoL measurements	Euro-QoL-5D, IBS-QoL
		26 wk abdominal pain/discomfort responder and IBS degree of relief of responder	See above
		26 wk abdominal pain/discomfort responders with different cut-off points	See above
Database lock	03.09.2010		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT population : n=805 (403 placebo, 402 linaclotide)		
Effect estimate per comparison		**Placebo**	**linaclotide**
	Co-Primary endpoint abd. pain/discomfort responders	38.5%	54.1%
		OR: 1.9 (2.4-2.5), p<0.0001	
	Co-primary endpoint IBS Degree of Relief responder	16.6%	39.4%
		OR: 3.3 (2.3 – 4.5), p<0.0001	
	Main sec. EP abd. pain/disc. responder 26 weeks	36.0%	53.6%
		OR: 2.1 (1.6 – 2.7), p<0.00001	
	Main sec. EP IBS Degree of Relief responder at 26 weeks	16.9%	37.2%
		OR: 2.9 (2.1 – 4.0)	
	12 week CSBM frequency (LSM change from BL)	0.7	2.2
		Diff: 1.54 (1.23 – 1.85; p<0.0001	

Title: A phase 3, randomised, double-blind, placebo-controlled, parallel group trial of linaclotide administered orally for 26 weeks in patients with Irritable Bowel Syndrome with Constipation.			
	12-week stool consistency (LSM change from BL)	0.60	1.91
		Diff:1.31 (1.15 – 1.47), p<0.0001	
	12-week severity of straining (LSM change from BL)	-0.66	-1.24
		Diff: -0.57 (-0.69 – -0.50), p<0.0001	
	12 week severity of bloating (LSM change from BL)	-1.03	-1.91
		Diff: - 0.88 (-1.12 - -0.64) p<0.0001	
Notes	All additional secondary parameters were p<0.05 including Quality of Life; most parameters were <0.0001.		

Analysis performed across trials (pooled analyses and meta-analysis)

A pooled analysis of the phase 3 data has been presented for the relevant outcomes. However, due to the shorter treatment duration in LIN-MD-31, this is an evaluation of the 3 months data only.

The following two tables show the pooled evaluation of the two co-primary endpoints:

Table 6: 12-Week abdominal pain/discomfort responders (pooled ITT population)

Study	Linaclotide	Placebo	Difference (%) in response rate	p-Value[a]
MCP-103-302	217/401	155/403	15.6	<0.0001
	(54.1%)	(38.5%)		
LIN-MD-31	222/405	165/395	13.0	0.0002
	(54.8%)	(41.8%)		
Pooled	439/805	320/797	14.4	<0.0001
	(54.5%)	(40. 2%)		

Table 7: 12-Week IBS Degree of Relief responders (pooled ITT population):

Study	Linaclotide	Placebo	Difference in % response rate	p-Value[a]
MCP-103-302	158/401	67/403	22.8	<0.0001
	(39.4%)	(16.6%)		
LIN-MD-31	150/405	73/395	18.6	<0.0001
	(37.0%)	(18.5%)		
Pooled	308/805	139/797	20.8	<0.0001
	(38.3%)	(17.4%)		

Clinical studies in special populations

Clinical studies in special populations were not performed. However, the company has provided (pooled) analyses of "special" patient populations.

a) Comparison of Efficacy by Age:

Sub-group analyses has been provided to support that the treatment effects associated with the 290 mg dose are associated with similar response in patients below or above the 65 years threshold. The analysis performed is presented for the pooled ITT analysis of the 3-months results:

Table 58: Subgroup analyses by age (ITT, pooled 3-months data)

	< 65 years			> 65 years		
Parameter	*Linaclotide N =763*	*Placebo N =754*		*Linaclotide N =42*	*Placebo N =43*	
Primary Efficacy Parameter						
	%	%	OR (95% CI)	%	%	OR (95% CI)
Abd. pain/ disc. Responder	54.52	39.79	1.82* (1.48, 2.23)	54.76	46.51	1.38 (0.58, 3.28)
IBS Relief Responder	38.27	17.37	2.95* (2.32, 3.74)	38.10	18.60	3.15* (1.03, 9.64)
Main Secondary Efficacy Parameters						
	LS Mean (SE) Change from baseline		*LSMD (95% CI)*	*LS Mean (SE) Change from baseline*		*LSMD (95% CI)*
Bloating (11-point NRS)	-1.90 (0.08)	-1.04 (0.08)	-0.86* (-1.05, -0.68)	-1.71 (0.26)	-0.73 (0.28)	-0.98* (-1.67, -0.28)
Stool consistency (BSFS Score)	1.99 (0.05)	0.62 (0.05)	1.36* (1.25, 1.48)	1.82 (0.18)	0.65 (0.2)	1.18* (0.68, 1.67)
Straining (5-point ordinal scale)	-1.27 (0.03)	-0.64 (0.03)	-0.63* (-0.71,-0.55)	-1.15 (0.13)	-0.67 (0.14)	-0.48* (-0.85,-0.12)
CSBM/week	2.19 (0.09)	0.66 (0.09)	1.52* (1.30, 1.75)	2.80 (0.52)	0.42 (0.58)	2.38* (0.97, 3.79)

In the table above, all results – except the evaluation of the abdominal pain/discomfort responders for the old-age sub-group yielded p-values <0.05 (marked with *).

Similar efficacy of the two age ranges is also claimed for the Quality of Life assessments (especially the IBS-QoL).

In response to questions raised by the CHMP, as discussed above, the applicant provided further subgroup analyses by age at 26 weeks for the primary efficacy endpoints and main secondary efficacy endpoints (ITT population, study MCP-103-302). Based on these analysis, in the opinion of the CHMP, the overall response in the elderly population is considered not to be significantly reduced. For details please refer to chapter "outcomes and estimations" of study MCP-103-302.

b) Subgroup analysis by gender:

A similar subgroup evaluation has been performed according to sex:

Table 59: Subgroup Analyses by gender (ITT population, pooled data)

	Females			Males		
Parameter	***Linaclotide(N= 735)***	***Placebo (N =708)***		***Linaclotide (N =70)***	***Placebo (N=89)***	
Primary Efficacy Parameter						
	%	***%***	***OR (95% CI)***	***%***	***%***	***OR (95% CI)***
Abdominal pain/ discomfort Responder	55.51	40.68	1.83* (1.49, 2.26)	44.29	35.96	1.41 (0.72, 2.77)
IBS Relief Responder	39.05	17.66	3.00* (2.35, 3.83)	30.00	15.73	2.26* (1.03, 4.96)
Main Secondary Efficacy Parameters						
	LS Mean (SE) Change from baseline		***LSMD (95% CI)***	***LS Mean (SE) Change from baseline***		***LSMD (95% CI)***
Bloating (11-point NRS)	-1.91 (0.08)	-1.03 (0.08)	-0.88* (-1.07,-0.69)	-1.73 (0.23)	-1.03 (0.22)	-0.70* (-1.25, -0.14)
Stool consistency (BSFS Score)	2.00 (0.05)	0.60 (0.05)	1.40* (1.28, 1.51)	1.81 (0.16)	0.74 (0.15)	1.06* (0.68, 1.45)
Straining (5-point ordinal scale)	-1.28 (0.03)	-0.63 (0.03)	-0.65* (-0.73, -0.56)	-1.09 (0.12)	-0.71 (0.11)	-0.38* (-0.67,-0.09)
CSBM/week	2.22 (0.10)	0.67 (0.10)	1.55* (1.32, 1.78)	2.15 (0.37)	0.56 (0.34)	1.59* (0.70, 2.48)

In the table above, all results – except the evaluation of the abdominal pain/discomfort responders for the male sub-group yielded p-values <0.05 (marked with *). Similar to the age-range sub-group analysis, similar outcome between the sexes is also claimed for Quality of Life (IBS-QoL).

During the evaluation the company has presented the relevant subgroup results for study MCP-103-302 for the 6 months treatment that was previously missing.

Table 1.2: Subgroup analyses by gender at 26 weeks for the primary efficacy endpoints and main secondary efficacy endpoints (ITT population, MCP-103-302):

26 weeks	*Females*			*Males*		
Parameter	*Linaclotide (N=368)*	*Placebo (N=352)*		*Linaclotide (N=33)*	*Placebo (N=51)*	
Primary Efficacy Parameter						
	%	*%*	***OR*** **(95% CI)**	*%*	*%*	***OR*** **(95% CI)**
Abdominal pain/ discomfort Responder	54.89	36.65	**2.10** *** (1.56, 2.84)	39.39	31.37	**1.47** (0.57, 3.8)
IBS Relief Responder	38.04	17.33	**2.28***** (0.74, 7.28)	27.27	13.73	**2.28** (0.74, 7.07)
Main Secondary Efficacy Parameters						
	LS Mean (SE) ***Change from baseline***		***LSMD*** ***(95% CI)***	***LS Mean (SE)*** ***Change from baseline***		***LSMD*** ***(95% CI)***
Bloating (11-point NRS)	-2.25 (0.10)	-1.26 (0.10)	**-0.99***** (-1.27, -0.72)	-1.63 (0.31)	-1.04 (0.25)	**-0.59** (-1.38, 0.19)
Stool consistency (BSFS Score)	1.95 (0.06)	0.66 (0.06)	**1.29***** (1.12, 1.46)	1.69 (0.20)	0.93 (0.18)	**0.76**** (0.22, 1.30)
Straining (5-point ordinal scale)	-1.33 (0.04)	-0.71 (0.04)	**-0.62***** (-0.74,-0.50)	-1.05 (0.16)	-0.86 (0.14)	**-0.19** (-0.61, 0.24)
CSBM/week	2.16 (0.11)	0.67 (0.12)	**1.49***** (1.17, 1.81)	2.63 (0.53)	0.71 (0.43)	**1.92**** (0.54, 3.29)

A display of changes from baseline in Quality of Life parameters by gender did show a consistent effect for linaclotide in all subpopulations overall. Some subpopulations in single parameters showing a diminished magnitude of effect of missing statistical significance. In the male population, generally only a trend was observed due to lower numbers of patients. One outlier result has to be mentioned: In the SF-12 PCS scale, male patients had a greater reduction in the placebo group than in the linaclotide group. Overall, the CHMP notes that a positive effect is preserved across these categories in the primary and main secondary parameters. Some variability and even reduction of the magnitude of the effect is attributed to the lower numbers included in these subgroups.

c) Analysis by Disease Severity

The applicant presents an analyses based on the evaluation of baseline values of the assessment of abdominal pain "at its worst" on the 11-point NRS, with the three sub-groups <5, ≥5 and <8, and ≥8. The subpopulations included 649, 786, and 167 patients. The following table, according to the applicant, shows that improvements in the change from baseline secondary parameters were observed for all 3 abdominal pain subpopulations. A statistically significant effect is seen in all evaluations except for the percent of abdominal pain-free days in the most severe sub-group.

Table 60: Results for the change-from baseline secondary efficacy parameters by baseline abdominal pain (IBS-C phase 3 pooled ITT population)

12-Week Change-from-Baseline Parameter	Baseline Abdominal Pain Category					
	< 5		***≥ 5 and < 8***		***≥ 8***	
	Mean Baseline (overall)	***Linaclotide 290µg N = 317 LSMD (Lin-Placebo) (95% CI)***	***Mean Baseline (overall)***	***Linaclotide 290 µg N = 403 LSMD (Lin-Placebo) (95% CI)***	***Mean Baseline (overall)***	***Linaclotide 290 µg N = 85 LSMD (Lin-Placebo) (95% CI)***
CSBMs/Week	0.3	1.5 (1.1, 1.8)[c]	0.2	1.7 (1.3, 2.0)[c]	0.1	1.4 (0.8, 2.0)[c]
SBMs/Week	2.0	2.6 (2.1, 3.1)[c]	1.8	3.0 (2.6, 3.5)[c]	1.5	2.1 (0.9, 3.2)[b]
Stool Consistency (BSFS Score)	2.5	1.4 (1.2, 1.5)[c]	2.3	1.4 (1.2, 1.6)[c]	2.1	1.2 (0.8, 1.6)[c]
Straining (5-point Ordinal Scale)	3.3	-0.6 (-0.7, -0.5)[c]	3.7	-0.7 (-0.8, -0.6)[c]	4.0	-0.5 (-0.8, -0.2)[a]
Abdominal Pain at its Worst (11-point NRS)	3.9	-0.4 (-0.6, -0.2)[c]	6.3	-1.0 (-1.3, -0.8)[c]	8.7	-0.7 (-1.5, -0.0)[a]
Abdominal Discomfort (11-point NRS)	4.6	-0.5 (-0.7, -0.2)[c]	6.7	-1.0 (-1.3, -0.8)[c]	8.8	-0.8 (-1.5, -0.1)[a]
Bloating (11-point NRS)	5.3	-0.6 (-0.8, -0.3)[c]	7.1	-1.1 (-1.4 -0.9)[c]	8.9	-0.9 (-1.6, -0.1)[a]
Percent of Abdominal Pain-free Days	4.2	4.2 (0.8, 7.6)[a]	0.5	6.3 (3.7, 8.9)[c]	0.1	3.3 (-1.2, 7.8)

In response to questions from the CHMP the applicant could convincingly show that at first, the included patient population is most likely a population that is indeed suffering from moderate to severe disease by the more "modern" criteria according to the Rome Working Team Report of 2011 (Drossman 2011). This particularly relates to the severity as defined by the IBS-SSS, the severity of abdominal pain and by the frequency of the symptoms. The company has furthermore analysed the study data of the 26 week trial according to several criteria as displayed in the Rome Working Team Report (and not just according to abdominal pain severity as shown above). This relates to the evaluation according to abdominal pain severity, IBS-SSS severity, and severity according to different categories of various QoL measurements, including the severity of psychiatric co-morbidity. This was done for the 26 weeks trial only, and the question therefore remains open, whether similar results could also be obtained for the 12-week study LIN-31-MD. However, the CHMP accepts that previously all results shown have proven to have a high consistency with their results, and accepts that this is assessed on the basis of the 26 weeks data only.

d) Analysis according to race/ethnicity

The analysis according to race/ethnicity has been done for the 12-week pooled data of study LIN-MD-31 and MCP-103-302. The results are presented in the following tables:

Table 61: 12-week Abdominal pain/abdominal discomfort responder by ethnicity (pooled data; ITT population):

Subgroup	Abdominal pain/discomfort response at week 12 (ITT pop. pooled data)	placebo	linaclotide	Diff. in responder rate; odds ratio(95%CI) p-value
Caucasian n=629/611	Responder	38.63%	55.01%	16.38 1.94 (1.55 – 2.43) p<0.0001
	Non-responder	61.37%	44.99%	
Black/African American n=148/153	Responder	46.41%	55.41%	9.00 1.46 (0.43 – 3.79) p=0.1124
	Non-responder	53.59%	44.59%	
Other n=28/33	Responder	39.39%	39.29%	-0.10 1.27 (0.43 – 3.79) p=0.6710
	Non-responder	60.61%	60.71%	
Hispanics n=99/94	Responder	44.68%	49.49%	4.81 1.10 (0.63 – 1.94) p=0.7326
	Non-responder	55.32%	50.51%	

Table 62: 12-week IBS Degree of Relief responder by ethnicity (pooled data; ITT population):

Subgroup	IBS Degree of Relief response at week 12 (ITT pop. pooled data)	placebo	linaclotide	Diff. in responder rate; odds ratio(95%CI) p-value
Caucasian n=629/611	Responder	16-37%	40.22%	23.85 3.41 (2.62 – 4.47) p<0.0001
	Non-responder	83.63%	59.78%	
Black/African American n=148/153	Responder	20.92%	31.08%	10.16 1.73 (1.01 – 2.90) p=0.046
	Non-responder	79.08%	68.92%	

Subgroup	IBS Degree of Relief response at week 12 (ITT pop. pooled data)	placebo	linaclotide	Diff. in responder rate; odds ratio(95%CI) p-value
Other n=28/33	Responder	21.21%	32.14%	10.98 1.89 (0.57 – 6.29) p=0.301
	Non-responder	78.79%	67.86%	
Hispanics n=99/94	Responder	21.28%	37.37%	16.09 3.06 (2.39 – 3.93) p<0.0001)
	Non-responder	78.72%	62.63%	

Within the assessment of different ethnicities, the question whether an extrapolation from a general US-American (with only a few Canadian) patient population is possible is also dealt with. The company justifies again the transferability of the data by giving detailed reference to the recommendations made in the "reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU population (EMEA/CHMP/EWP/692702/2008).

The company refers to the following:

- Extrinsic factors:
    - Medical practice: For this item it is referred to the fact that the prevalence of IBS in the US and Europe has been found to be quite similar.
    - Disease definition: The pathophysiology of IBS, does not indicated that potential differences in the two populations with regard to e.g. food habits, diet, and body mass index would implicate a different population with regard to the underlying pathophysiology
    - Study population: The inclusion criteria have been based on the Rome II criteria which have been derived from observations obtained in 13 different Western countries. It is also referred to the fact that the use of NRS in pain populations did not reveal differences between different regions with regard to response
- Intrinsic factors:
    - Genetic polymorphisms present in the US populations are not expected to differ to the European population, as this mainly consists of people with European ancestry (German, Irish, English, Italian, Polish, French, Scottish, Dutch, Norwegian, and Swedish).
    - The GC-C receptor the pharmacological target of linaclotide has been highly considered through evaluation.

The applicant therefore believes that there are no extrinisic or intrinsic factors with regard to European vs. North American patients with IBS-C, or the mechanism of action of linaclotide that would affect extrapolation of North American clinical trial results to the European population.

The argumentation of transferability of the American to the European population was accepted by the CHMP.

With their response to questions from the CHMP the applicant provided also subgroup analyses by race for the 6 month data.

Table 1.6: Subgroup analyses by race at 26 weeks for primary efficacy endpoints and main secondary efficacy endpoints (ITT, MCP-103-302):

26 weeks	*Caucasians*			*Black/African American*			*Others*		
	Lin	*Pbo*		*Lin*	*Pbo*		*Lin*	*Pbo*	
	N=316	*N=311*		*N=70*	*N=78*		*N=15*	*N=14*	
Primary Efficacy Parameters									
	%	*%*	*OR* (95% CI)	*%*	*%*	*OR* (95% CI)	*%*	*%*	*OR* (95% CI)
Abdominal pain/ discomfort Responder	52.63	33.76	2.19*** (1.59, 3.03)	58.57	46.15	1.64 (0.86, 3.15)	53.33	28.57	3.11 (0.65, 14.80)
IBS Relief Responder	37.97	15.11	3.4*** (2.32, 4.99)	31.43	23.08	1.56 (0.74, 3.28)	46.67	21.43	3.14 (0.54, 18.23)
Main Secondary Efficacy Parameters									
	LS Mean (SE)		*LSMD*	*LS Mean (SE)*		*LSMD*	*LS Mean (SE)*		*LSMD*
	Change from baseline		*(95% CI)*	*Change from baseline*		*(95% CI)*	*Change from baseline*		*(95% CI)*
Bloating (11-point NRS)	-2.21 (0.10)	-1.15 (0.11)	-1.06*** (-1.35, 0.77)	-2.19 (0.24)	-1.62 (0.23)	-0.56 (-1.23, 0.10)	-1.64 (0.43)	-1.03 (0.44)	-0.61 (-1.87, 0.66)
Stool consistency (BSFS Score)	1.93 (0.06)	0.64 (0.07)	1.29*** (1.12, 0.47)	1.85 (0.14)	0.79 (0.13)	1.06*** (0.68, 1.45)	2.27 (0.27)	1.53 (0.32)	0.75 (-0.13, 1.62)
Straining (5-point ordinal scale)	-1.28 (0.05)	-0.67 (0.05)	-0.60*** (-0.73,-0.48)	-1.42 (0.10)	-0.93 (0.10)	-0.49*** (-0.77, -0.22)	-1.44 (0.20)	-0.91 (0.24)	-0.53 (-1.20, 0.15)
CSBM/week	2.29 (0.13)	0.71 (0.13)	1.58*** (1.22, 1.94)	1.69 (0.22)	0.50 (0.21)	1.19*** (0.60, 1.79)	2.78 (0.92)	0.96 (0.95)	1.81 (-0.91, 4.54)

The CHMP notes that an overall positive effect is preserved across these categories in the primary and main secondary parameters, although some variability, and even reduction of the magnitude of the effect is observed. However, the notion that this can be attributed to the lower numbers included in these subgroups can be accepted overall.

Also subgroup analysis in the category "race" regarding QoL was provided. This analysis also shows a consistent positive effect of linaclotide vs placebo in all parameters analysed at 12 and 26 weeks in

study MCP-103-302 regardless of race. In the Caucasian population consistent statistical significance of the effect can be found with trends in non-caucasian subjects with the "outlier" being the negative effect in the SF-12 MCS evaluation.

For study LIN-MD-31, there was a consistent significance of the results apart from the EQ-5D VAS, and a consistent and similar in magnitude trend in the non-caucasian population.

Table 13.6: Change form Baseline in Quality of Life parameters according to race (Phase 3 studies)

	IBS-QoL overall		*EQ-5D VAS*		*EQ-5D UI*		*SF-12 P*		*SF-12 M*	
MCP-103-302	***C***	***NC***	***C***	***NC***	***C***	***NC***	***C***	***NC***	***C***	***NC***
12-weeks										
Placebo N C/NC 311/92	11.39 (0.92)	9.80 (1.82)	3.48 (0.79)	7.86 (1.83)	0.04 (0.01)	0.06 (0.02)	3.47 (0.37)	2.17 (0.78)	0.59 (0.53)	3.45 (1.00)
Linaclotide N C/NC 316/85	16.99 (0.91)	14.91 (1.97)	6.54 (0.78)	9.21 (1.96)	0.08 (0.01)	0.09 (0.02)	4.79 (0.37)	4.14 (0.83)	3.22 (0.52)	3.94 (1.07)
P value	0.0001	0.0341	0.0027	0.569	0.0012	0.1898	0.0061	0.0509	0.0001	0.7054
26-weeks										
Placebo N C/NC 311/92	11.01 (0.97)	10.73 (1.93)	5.30 (0.76)	8.85 (1.80)	0.05 (0.01)	0.08 (0.02)	3.50 (0.39)	2.62 (0.85)	0.06 (0.53)	4.42 (1.03)
Linaclotide N C/NC 316/85	17.44 (0.94)	15.92 (2.07)	8.17 (0.75)	9.85 (1.93)	0.08 (0.01)	0.10 (0.02)	4.81 (0.38)	4.10 (0.90)	3.23 (0.52)	3.99 (1.10)
P value	0.0001	0.0412	0.0034	0.6675	0.0026	0.6074	0.0091	0.1767	0.0001	0.7443
LIN-MD-31	***C***	***NC***	***C***	***NC***	***C***	***NC***	***C***	***NC***	***C***	***NC***
12-weeks										
Placebo N C/NC 301/94	15.37 (0.99)	13.76 (2.01)	3.60 (0.84)	4.81 (1.82)	0.04 (0.01)	0.07 (0.02)	4.20 (0.39)	3.90 (0.86)	1.82 (0.53)	1.11 (1.07)
Linaclotide N C/NC 314/91	18.62 (0.99)	17.27 (1.88)	5.21 (0.83)	6.79 (1.69)	0.08 (0.01)	0.09 (0.02)	5.37 (0.39)	5.27 (0.80)	3.30 (0.53)	3.23 (1.07)
P value	0.0136	0.1514	0.1452	0.3600	0.0006	0.3449	0.0234	0.1812	0.0365	0.0943

The CHMP notes some deviations, and missing statistical significance in the smaller subgroups of non-caucasian, which are considered to be normal variation, or due to low patient numbers in the subgroup, and do therefore not question the overall conclusions.

e) Analysis according to BMI

The results in the following tables are given for the two co-primary endpoints:

Table 63:

Subgroup	Abdominal pain/abdominal discomfort responder	placebo	linaclotide	Diff. in responder rate; odds ratio(95%CI) p-value
BMI<30 kg/m^2	Responder	39.18%	54.18%	15.00 1.85 (1.46 – 2.35) p<0.0001
	Non-responder	60.82%	45.82%	
BMI>30 kg/m^2	Responder	42.44%	55.29%	12.85 1.47 (1.17 - 2.39 p<0.0001
	Non-responder	57.56%	44.71%	
Subgroup	IBS Degree of Relief response at week 12 (ITT pop. pooled data)	**placebo**	**linaclotide**	Diff. in responder rate; odds ratio(95%CI) p-value
BMI<30 kg/m^2	Responder	16.82%	36.73%	19.91 2.84 (2.15 – 3.77) p<0.0001
	Non-responder	83.18%	63.27%	
BMI>30 kg/m^2	Responder	18.91%	41.57%	22.66 3.09 (2.04 - 4.66) p<0.0001
	Non-responder	81.09%	58.43%	

The CHMP considers that overall efficacy results (co-primary endpoints) by subgroups related to race (Caucasian, Black), ethnicity (Non-Hispanic/Latino, Hispanic/Latino patients) and BMI (< 30 kg/m2 or ≥ 30 kg/m2) are consistent with those in the overall population.

d) Analysis of onset of effect and sustainability of effect

The company also presents data on onset and persistence of the effects referring to the first week of treatment superiority in both trials (31.7% and 30.0% responders for abdominal pain/discomfort and IBS Degree of Relief during first week on linaclotide, and 21.6% and 8.4% for placebo; p<0.0001) and the onset of effect regarding the BM-related parameters (SBM and CSBM were registered from the first day (e.g. CSBM on first day: 31% for linaclotide, 11% for placebo). For the persistence of effect, it is referred to the evaluations of sustained response as given in the evaluation of the two studies.

e) Withdrawal effects/Rebound

For withdrawal and rebound effects, the company is referring to the results of LIN-MD-31 which included the randomised withdrawal period. These results are reported in the respective chapters of the individual study data presentation and are not repeated here again. There appeared to be no rebound phenomenon, and persistence of effect is dependant on continued intake of linaclotide. The company also notes that withdrawal and rebound are evaluated after 3 months treatment only. It is made the case that – as the overall efficacy results are not different between 3 and 6 months – the withdrawal should also have no different effects if done after 3 or 6 months therapy.

The CHMP notes that the requirements of the European guidance on IBS request the documentation of re-treatment. It is, however, understood that, of course, the product under consideration is meant for continuous treatment only. However, it is clear from the safety evaluation that especially for the occurrence of diarrhoea, a cessation, or interruption of treatment might be necessary at times. Also, even if long-term treatment is the rule, patients might request a treatment free interval ("drug holiday"), at times when a long-term beneficial effect has been achieved. Therefore, there appears to be a need to also document to some extent the effects of re-treatment.

During assessment the applicant presented updated figures showing that obviously withdrawal of treatment does influence treatment satisfaction in a relatively fast manner, and re-treatment does indeed bring the treatment satisfaction back to the levels before treatment withdrawal. The CHMP considers this to be overall re-assuring regarding the effects of a potential re-treatment (in case of treatment free intervals due to adverse events (e.g. diarrhoea) or due to any other cause.

Supportive study(ies)

The company has filed all clinical studies that have been conducted in the indication Chronic Constipation (CC) as additional supportive material. The development in this indication comprises two phase 2, and two phase 3 double-blind, placebo controlled studies. Because no support for clinical efficacy in an IBS-C population can be derived from these studies, only the safety data was relevant for the assessment (see section "Clinical Safety").

Two long-term safety studies in IBS-C patients are being conducted by the applicant, which were still ongoing at the time of submission of the MAA. For these two studies, only a protocol is submitted, and the (interim) analysis of data is included in other documents. Both studies have a duration of 78 weeks. These safety studies consist of the following two studies.

- Study MCP-103-305: This study recruited patients who had completed MCP-103-303, MCP-103-302 or any phase 2 study. It also included patients who were ineligible to take part in the a.m. phase 3 studies, but fulfilled the criteria for the LTS study.
- Study LIN-MD-02: This study included patients that had completed the phase 3 studies LIN-MD01, and LIN-MD-31 or any of the phase 2 studies, and it included patients who fulfilled the criteria for these studies, but were not eligible for one of the two phase 3 studies.

The inclusion criteria for these two studies specified that – apart from the "roll-over" patients (RO patients) as described above, the "Randomisation ineligible" patients (RI patients) can be included.

The CHMP noted that given these criteria the inclusion for the LTS-studies is less strict, as regards the severity and stability of the IBS-C subgroup diagnosis (e.g. allowing only minor abdominal pain, allowing loose stools being present).

The only "efficacy related parameter" that can be traced is the treatment satisfaction analysis, which is based on the self administration of an overall question on treatment satisfaction using a 5-point scale, ranging from 1 (not at all satisfied) to 5 (very satisfied). The CHMP notes that these data are of limited value for the evaluation as regards efficacy since treatment satisfaction measurement does not at all indicate whether the level of e.g. abdominal pain relief or CSBM frequency can indeed be maintained across longer time-periods. The data presented here cannot really contribute to the overall assessment of efficacy, and it is noted that long-term efficacy documentation has to solely rely on the data of the 6 months efficacy study MCP-103-302. Moreover, the interpretation of these data is of course hampered by the high number of drop-outs/withdrawals (partly based on the fact of ongoing trials, but partly of course also based on real drop-outs, which are partly attributable (as seen in the efficacy evaluation) to adverse events, namely diarrhoea.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The company has conducted three appropriately designed trials (1 phase 2b and 2 phase 3. All trials have been randomised, placebo controlled, with at least 3 months duration. All three studies were conducted in the USA and in Canada. All three studies used a screening period (21-28 days depending on the study), and a 14-17 days run-in period, during which eligibility was assessed. This is considered to be fully appropriate. The transfer of these data from North America to Europe is considered adequate based on the scientific justification presented by the applicant. The recruitment and finalisation of the studies was relatively fast, despite considerable size, which is, however, not surprising considering the prevalence of the disease. The inclusion criteria appeared to be adequate as regards the diagnosis of true IBS with constipation. The inclusion of the patient population was based on (slightly modified) Rome II criteria for IBS-C, which were partly already resembling the newly established Rome III criteria (as of 2006), resulting in an almost complete concordance of fulfilment of the Rome II and Rome III criteria in the included patient population. The included patient population is regarded to fully reflect a patient population suffering from IBS-C.

It could be shown that the included patient population was suffering from frequent and severe symptoms, and recurrence of symptoms was immediately observed after withdrawal of the treatment.

The applicant has also shown that the claim of treating patients with moderate and severe disease only is substantiated by the inclusion criteria, and the finally included study population. With the analysis of the data from the included patient population, and data from the scientific literature, it can be accepted that the included patient population indeed represents a moderately to severely affected patient population which requires continuous treatment. It could also be shown that – when applying a more updated concept of severity in IBS – the response to treatment does not differ according to severity and that only a minimal proportion of "mildly" diseased patients were included into the programme.

The methods of evaluation and the choice of endpoints for the three trials, and especially the two phase 3 trials appear to be fully adequate. Overall there is sufficient robustness of the results across subgroups.

The two phase 3 trials had different treatment durations, only one of the trials complying with the European requirement of documenting efficacy, for compounds meant to be used continuously, for six months. The other trial, which was of 3 months duration, included a randomised withdrawal period of 4 weeks, thus documenting withdrawal and potential rebound effects. This however, means that the documentation of withdrawal and rebound has not been done after longer treatment periods. The company has provided argumentation in support of the transfer of the three-months withdrawal data to later time-points based on the continuing efficacy after 6 months when compared to 3 months. It is also argued that a differential withdrawal effect is lacking biological plausibility. This is overall and finally accepted, and the documentation of withdrawal after long-term treatment (of 6 or 12 months duration) is not regarded to be overall necessary. The fact, that only one trial has been conducted with the treatment duration of 6 months requires a robust demonstration of efficacy for such (single pivotal) trials, i.e. the need to provide overall outstanding robustness of results, and full validity of the data. According to the CHMP, this overall robustness of the results has clearly been shown, as indicated below.

Both of the phase 3 trials have used the endpoints recommended by the European guidance on IBS, and were fully compliant with a Scientific Advice given earlier in the development as regards the endpoints. The company has also produced some validation data on the use of the NRS-scale in this

patient population for the dimensions abdominal pain, and abdominal discomfort. Therefore, the chosen primary endpoints (Abdominal pain/discomfort responder and IBS Degree of Relief responder) are overall considered to be fully appropriate. A wealth of secondary endpoints have been investigated, including several levels of response in the different dimensions, including 4 co-primary endpoints requested by the FDA (which were different from the European primary endpoints), and including the evaluation of Quality of Life, which is compliant with the requirements of the IBS PtC stating that QoL has to be regarded a "main secondary" endpoint. Both studies are based on sound statistical planning and evaluation, including the drawing up of different Statistical Analysis Plans for the US and Europe.

Efficacy data and additional analyses

In the dose-range-finding study, a relatively clear dose-response relationship could be seen with consistently statistically significantly superior effects for the two higher doses compared to placebo, whereas the two lower doses were clearly less successful. The fact that in this exploratory study the efficacy endpoints were not completely in line with the European regulatory requirements is regarded acceptable. It is noted that the final choice of dose for phase 3 was, however, not only based on the efficacy evaluation, but on safety also, which revealed a clearly higher rate of safety related events in the highest dose group, making the choice of the 290 µg dose to be investigated in phase 3 completely reasonable. It is therefore concluded that indeed, strong phase 2 data are available for the compound, which contributes to the overall robustness of the data.

Both phase 3 studies have yielded highly significant results as regards the superiority of linaclotide over placebo, in the co-primary required by the European guidance. In addition, the primary endpoints according to the American requirements as well as a multitude of secondary endpoints were statistically significant. It is noted that 6-months data are presented that appear to confirm the efficacy already achieved after three months, without decreasing effects. This comprised responder analyses, as well as the evaluation of "continuous" endpoints, investigating the main features of IBS-C, mainly abdominal pain and discomfort, as well as a variety of parameters investigating the associated bowel movement irregularities. Taken together the available data from the two studies individually, the pooled data, as well as the various sub-group analyses, the efficacy demonstration is considered very robust.

Clinical relevance of the results has been shown, however, it is pointed out that there are regularly about 50% of the patient population that do not fully respond to the treatment. In that sense, the SmPC was revised to include advises physicians that if patients have not experienced improvement in their symptoms after 4 weeks of treatment, the patient should be re-examined and the benefits and risks of continuing treatment reconsidered.

Relevant differences in the changes of Quality of Life parameters have also been shown. The results of the three months evaluation are also highly consistent across the two studies conducted in phase 3, and the pooled analyses of these results only confirmed what has been shown for the single studies.

The analysis across relevant subgroups of patients, which were represented in the studies in lower numbers only, such as men, the elderly, and ethnic minorities, have – due to the lower numbers and the increased variability – partly resulted in more inconsistent results. However, beneficial effects could be shown in all subgroups, and the previously missing subgroup results on the 6-months evaluation have also been shown. In case of the even more inconsistent results in the elderly population a satisfactory explanation was found and appropriate statements for a more careful and repeated evaluation of the risk-benefit ratio during treatment in this patient population is included into the SmPC.The available data from study LIN-MD-31 support that a rebound effect can be excluded. In patients switched from placebo to active a relatively rapid response can be achieved which is almost

similar to the response achieved after 3 months (and 4 months) treatment. Patients being randomised to placebo from active treatment experience a deterioration, but remain on a higher level of response than at baseline.

2.5.4. Conclusions on the clinical efficacy

The company has shown overall highly statistically significant superiority in the treatment of IBS-C with linaclotide over placebo, and the database for the claimed long-term continuous treatment approach is considered to be sufficiently large. Strong consistency of results and of statistical significance has been shown across two trials, and across a huge variety of endpoints, including improvement of Quality of Life. Acceptable consistency has also been shown across patients' subgroups. Clinical relevance of the results has been shown. The overall documentation of efficacy is considered to be satisfactory.

2.6. Clinical safety

Patient exposure

The clinical safety of linaclotide has been investigated in 13 clinical studies. Of these, there were 3 studies in healthy volunteers (comprising 22 placebo, and 75 linaclotide treated subjects) and 10 studies in 4,370 patients with either CC or IBS-C (2753 IBS-C patients, and 1627 CC patients).

Table 74: Number of patients exposed to linaclotide in the overall clinical programme

Protocol number	Number of Patients					
	Placebo	***Linaclotide, µg/day***				
		< 145	**145**	**290**	**> 290**	**Any dose**
Phase 3 Placebo-Controlled Trials (Group 1)						
IBS-C Patients						
LIN-MD-31 (up to 12 weeks)	395	—	—	405	—	405
MCP-103-302 (up to 26 weeks)	403	—	—	402	—	402
IBS-C Subtotal (Treatment Period)	***798***			***807***		***807***
CC Patients						
LIN-MD-01 (up to 12 weeks)	215	—	213	205	—	418
MCP-103-303 (up to 12 weeks)	208	—	217	217	—	434
CC Subtotal (Treatment Period)	***423***		***430***	***422***		***852***
Placebo-controlled Phase 3 Total (Treatment Period)	**1218**	**—**	**430**	**1227**	**—**	**1657**
Placebo-Controlled Phase 2 Studies						
IBS-C Patients						
MCP-103-005 (5 days)	12	12	—	—	12	24
MCP-103-202 (up to 12 weeks)	85	79	82	85	89	335
IBS-C Subtotal	***97***	***91***	***82***	***85***	***101***	***359***
CC Patients (Group 2)						
MCP-103-004 (up to 2 weeks)	10	12	—	10	10	32
MCP-103-201 (up to 4 weeks)	69	59	56	62	63	240
CC Subtotal	***79***	***71***	***56***	***72***	***73***	***272***
Placebo-controlled Phase 2 total	**176**	**162**	**138**	**157**	**174**	**631**
Open-Label Phase 3 Studies (Group 3)						
IBS-C Patients						

	Number of Patients				
LIN-MD-02	—	—	1029	—	1029
MCP-103-305	—	—	1117	—	1117
IBS-C Subtotal	—	—	***2146***	—	***2146***

	Number of Patients				
CC Patients					
LIN-MD-02	—	—	523	—	523
MCP-103-305	—	—	606	—	606
CC Subtotal	—	—	***1129***	—	***1129***
LTS Study Total	**—**	**—**	**3270**	**—**	**3270**
All Linaclotide Patients (Group 4)[a]					
IBS-C Patients	**—**	***91***	***2609[b]***	***101***	***2753***
CC Patients	**—**	***71***	***1519[c]***	***73***	***1627***
Total Number of Patients	**1394**	**162**	**4128**	**174**	**4370**

In Group 3, patients were required to start treatment at 290 µg but could downtitrate to 145 µg for intolerable AEs.

a Patients could be counted in more than one dose group in Group 4.

b Includes 2493 patients from a Phase 3 study and 116 patients from a Phase 2 study

c Includes 1424 patients from a Phase 3 study and 95 patients from a Phase 2 study

Of these total number of patients, 631 were treated with linaclotide in placebo-controlled phase 2 studies, including 359 patients with IBS-C, and 272 patients with CC with a treatment duration between 5 days and 12 weeks. The placebo-controlled phase 3 studies comprised 807 patients in the IBS-C indication, and 852 patients with CC treated with linaclotide, with treatment duration between 3 months and 6 months. Two open-label safety studies have included 3,270 patients altogether, of which 1,129 were defined as suffering from CC, and 2,146 patients defined as suffering from IBS-C. These two latter studies include patients being rolled over from some of the phase 2 studies, and from the phase 3 studies, as well as patients that were not completely fulfilling the inclusion criteria in the double-blind phase 3 studies during the run-in periods (but otherwise complied with inclusion criteria as regards the history of the disease).

As regards the duration of treatment, the following table reflects the total exposure according to different categories of treatment duration, indication, and dose groups (in the CC studies only).

Table 75: Patient exposure to linaclotide in phase 3 placebo-controlled trials (both indications; safety population.

Exposure	IBS-C Patients		CC Patients			CC + IBS-C Patients	
	Placebo (N = 798)	*Linaclotide 290 µg (N =807)*	*Placebo (N = 423)*	*Linaclotide* 145 µg (N = 430)	*Linaclotide* 290 µg (N = 422)	*Placebo (N = 1218)*	*Linaclotide (N = 1657)*
Treatment duration, days							
Mean	116.0	111.8	79.0	77.5	76.7	103.3	93.9
SD	56.5	58.5	18.2	20.2	21.1	50.1	46.7
Median	87.0	86.0	85.0	85.0	85.0	85.0	85.0
Min, Max	1, 195	1, 212	5, 104	1, 102	1, 111	1, 195	1, 212
Treatment duration, n (%)							
≥ 1 day	798 (100)	807 (100)	423 (100)	430 (100)	422 (100)	1218 (100)	1657 (100)
≥ 7 days	791 (99.1)	792 (98.1)	421 (99.5)	424 (98.6)	412 (97.6)	1209 (99.3)	1626 (98.1)
≥ 14 days	774 (97.0)	778 (96.4)	418 (98.8)	415 (96.5)	405 (96.0)	1189 (97.6)	1596 (96.3)
≥ 30 days	735 (92.1)	731 (90.6)	398 (94.1)	400 (93.0)	392 (92.9)	1130 (92.8)	1521 (91.8)

	IBS-C Patients		CC Patients			CC + IBS-C Patients	
≥ 60 days	696 (87.2)	670 (83.0)	376 (88.9)	372 (86.5)	364 (86.3)	1070 (87.8)	1404 (84.7)
≥ 90 days	357 (44.7)	335 (41.5)	25 (5.9)	20 (4.7)	14 (3.3)	382 (31.4)	368 (22.2)
≥ 120 days	319 (40.0)	307 (38.0)	0	0	0	319 (26.2)	306 (18.5)
≥ 150 days	309 (38.7)	299 (37.1)	0	0	0	309 (25.4)	298 (18.0)
≥ 180 days	285 (35.7)	272 (33.7)	0	0	0	285 (23.4)	271 (16.4)
Patient-years	253.5	247.0	91.5	91.2	88.7	344.4	426.1

CC Trials: LIN-MD-01 (Treatment Period = 84 days) and MCP-103-303 (Treatment Period = 84 days); IBS-C Trials: LIN-MD-31 (Treatment Period = 84 days) and MCP-103-302 (Treatment Period = 182 days).
CC = chronic constipation; IBS-C = irritable bowel syndrome with constipation

In the placebo controlled trials, 1,404 patients have been treated longer than 60 days (670 IBS-C, and 736 in CC) 335 and 34 (in the IBS-C and CC indication) have been treated longer than 90 days, and 272 in IBS-C have been treated longer than 180 days. In the LTS-studies (with the original data cut-off October 2010), mean duration of treatment was 200.4 days in the IBS-C, and 359.4 days in the CC patients, with 269 IBS-C and 715 CC patients being treated for longer than 360 days at the time of data lock.

A similar table is presented for the LTS-studies, shown in the following table:

Table 76: Patient exposure to linaclotide in the phase 3 open-label LTS-studies (safety population):

	IBS-C (N = 2146)	*CC (N = 1129)*	*IBS-C + CC (N = 3270)*
Treatment duration, days			
Mean	200.3	359.4	255.3
SD	129.4	190.6	170.9
Median	196.0	453.0	223.0
Min, Max	1, 562	1, 570	1, 570
Treatment duration, n (%)			
≥ 1 day	2146 (100)	1129 (100)	3270 (100)
≥ 7 days	2101 (97.9)	1115 (98.8)	3211 (98.2)
≥ 30 days	1980 (92.3)	1063 (94.2)	3038 (92.9)
≥ 60 days	1773 (82.6)	975 (86.4)	2743 (83.9)
≥ 120 days	1486 (69.2)	891 (78.9)	2373 (72.6)
≥ 180 days	1188 (55.4)	853 (75.6)	2039 (62.4)
≥ 240 days	702 (32.7)	798 (70.7)	1499 (45.8)
≥ 360 days	269 (12.5)	715 (63.3)	984 (30.1)
≥ 540 days	68 (3.2)	220 (19.5)	288 (8.8)
Patient-years	1177	1111	2285

Studies: LIN-MD-02 and MCP-103-305 (cut-off date of 11-Oct-2010).
CC = chronic constipation; IBS-C = irritable bowel syndrome with constipation

The overall exposure for "Group 4" sums up to 2,753 patients in the IBS-C population, and 1,627 CC patients in the CC population that were exposed to linaclotide. The mean treatment duration was 199.9 days for IBS-C, and 298.8 for CC. The number of patients treated for longer than 360 days therefore sums up to 416 in the IBS-C indication, and 745 in the CC indication.

During the assessment the applicant submitted an update of the Summary of Safety, which includes an update on the LTSs with data included until June 2011. It is stated that this includes 88% of the total exposure to be expected, which is a reasonable number and time to base the overall assessment upon.

At the new data cut-off point, an additional 63 years of exposure and 746 patients years to linaclotide in the CC and IBS-C population, respectively were recorded. The mean duration of treatment was therefore 312.9 days in the CC population, and 298.9 days in the IBS-C population. Of these, 750 CC patients, and 1293 IBS-C patients have been treated for longer than one year. After reviewing the update of the ISS, and the look at the additional events reported, CHMP considered that the additional data submitted did not generally alter the initially shown safety profile.

Adverse events

During the placebo-controlled trials in IBS-C, about 55% and 61% of the patients in the placebo and linaclotide groups experienced adverse events. The most common adverse events in these trials were related to the gastrointestinal tract, the most frequent being diarrhoea, abdominal pain, flatulence, headache, viral gastroenteritis, and abdominal distension. This was also reflected in the evaluation of events that were considered to be treatment related by the investigators. The evaluation of the company is shown in the following table:

Table 12: Treatment-emergent adverse events reported in ≥2% of linaclotide IBS-C patients in the phase 3 placebo-controlled trials and with an incidence greater than placebo.

	Number (%) of Patients	
Adverse Event (Preferred Term)	*Placebo (N = 798)*	*Linaclotide 290µg/day (N = 807)*
Any TEAE	438 (54.9)	491 (60.8)
Diarrhoea	24 (3.0)	160 (19.8)
Abdominal pain	26 (3.3)	41 (5.1)
Flatulence	15 (1.9)	35 (4.3)
Headache	25 (3.1)	33 (4.1)
Gastroenteritis viral	11 (1.4)	21 (2.6)
Abdominal distension	9 (1.1)	18 (2.2)

A more complete evaluation of the double-blind studies in IBS-C is shown in the following table. patients:

Table 13: Incidence of TEAEs by treatment group and preferred term reported in more than 1%, Study LIN-MD-31 and Study MCP-103-302; Safety population.

	MCP-103-302		LIN-MD-31		Pooled Data[a]	
	Number (%) of Patients		***Number (%) of Patients***		***Number (%) of Patients***	
Adverse Event	***Placebo***	***Linaclotide 290µg***	***Placebo***	***Linaclotide 290µg***	***Placebo***	***Linaclotide 290µg***
(Preferred Term)	*(N=403)*	*(N=402)*	*(N = 396)*	*(N = 406)*	*(N = 798)*	*(N = 807)*
Any TEAE	**228 (56.6)**	**263 (65.4)**	**210 (53)**	**228 (56.2)**	**438 (54.9)**	**491 (60.8)**
Diarrhoea	10 (2.5)	79 (19.7)	14 (3.5)	79 (19.5)	24 (3.0)	160 (19.8)
Abdominal pain	16 (4.0)	18 (4.5)	10 (2.5)	22 (5.4)	26 (3.3)	41 (5.1)
Nausea	24 (6.0)	23 (5.7)	20 (5.1)	17 (4.2)	44 (5.5)	40 (5.0)
Sinusitis	28 (6.9)	23 (5.7)	15 (3.8)	12 (3.0)	43 (5.4)	35 (4.3)
Upper Respiratory tract infection	22 (5.5)	22 (5.5)	14 (3.5)	13 (3.2)	36 (4.5)	35 (4.3)

	MCP-103-302		LIN-MD-31		Pooled Data[a]	
Flatulence	9 (2.2)	15 (3.7)	6 (1.5)	20 (4.9)	15 (1.9)	35 (4.3)
Headache	11 (2.7)	13 (3.2)	14 (3.5)	20 (4.9)	25 (3.1)	33 (4.1)
Urinary Tract Infection	22 (5.5)	17 (4.2)	9 (2.3)	7 (1.7)	31 (3.9)	24 (3.0)
Gastroenteritis viral	9 (2.2)	15 (3.7)	2 (0.5)	6 (1.5)	11 (1.4)	21 (2.6)
Abdominal distension	6 (1.5)	9 (2.2)	3 (0.8)	9 (2.2)	9 (1.1)	18 (2.2)
Nasopharyngitis	16 (4.0)	11 (2.7)	13 (3.3)	6 (1.5)	29 (3.6)	17 (2.1)
Influenza	13 (3.2)	7 (1.7)	9 (2.3)	9 (2.2)	22 (2.8)	16 (2.0)
Vomiting	7 (1.7)	8 (2.0)	3 (0.8)	6 (1.5)	10 (1.3)	14 (1.7)
Fatigue	4 (1.0)	8 (2.0)	7 (1.8)	4 (1.0)	11 (1.4)	12 (1.5)
Sinus congestion	4 (1.0)	8 (2.0)	3 (0.8)	4 (1.0)	7 (0.9)	12 (1.5)
Vulvovaginal mycotic infection	6 (1.5)	7 (1.7)	2 (0.5)	3 (0.7)	8 (1.0)	10 (1.2)
Gastroesophageal reflux disease	6 (1.5)	9 (2.2)	1 (0.3)	1 (0.2)	7 (0.9)	10 (1.2)
Dyspepsia	7 (1.7)	6 (1.5)	4 (1.0)	4 (1.0)	11 (1.4)	10 (1.2)
Bronchitis	10 (2.5)	6 (1.5)	6 (1.5)	4 (1.0)	16 (2.0)	10 (1.2)
Muscle strain	1 (0.2)	5 (1.2)	3 (0.8)	5 (1.2)	4 (0.5)	10 (1.2)
Abdominal Pain Upper	6 (1.5)	4 (1.0)	6 (1.5)	6 (1.5)	12 (1.5)	10 (1.2)
Cough	8 (2.0)	3 (0.7)	4 (1.0)	7 (1.7)	12 (1.5)	10 (1.2)
Dizziness	3 (0.7)	3 (0.7)	7 (1.8)	7 (1.7)	10 (1.3)	10 (1.2)
Oropharyngeal pain	7 (1.7)	6 (1.5)	4 (1.0)	3 (0.7)	11 (1.4)	9 (1.1)
Anxiety	8 (2.0)	5 (1.2)	4 (1.0)	4 (1.0)	12 (1.5)	9 (1.1)
Contusion	2 (0.5)	3 (0.7)	2 (0.5)	5 (1.2)	4 (0.5)	8 (1.0)
Arthralgia	5 (1.2)	5 (1.2)	4 (1.0)	3 (0.7)	9 (1.1)	8 (1.0)
Gastro intestinal sounds abnormal	0	4 (1.0)	0	4 (1.0)	1 (0.1)	8 (1.0)
Rash	4 (1.0)	3 (0.7)	4 (1.0)	5 (1.2)	8 (1.0)	8 (1.0)
Neck Pain	1 (0.2)	5 (1.2)	0	2 (0.5)	1 (0.1)	7 (0.9)
Weight increased	5 (1.2)	4 (1.0)	2 (0.5)	3 (0.7)	7 (0.9)	7 (0.9)
Insomnia	8 (2.0)	4 (1.0)	1 (0.3)	3 (0.7)	9 (1.1)	7 (0.9)
Oedema peripheral	5 (1.2)	2 (0.5)	2 (0.5)	5 (1.2)	7 (0.9)	7 (0.9)
Seasonal Allergy	3 (0.7)	6 (1.5)	0	0	3 (0.4)	6 (0.7)
Depression	5 (1.2)	6 (1.5)	3 (0.8)	0	8 (1.0)	6 (0.7)
Toothache	1 (0.2)	4 (1.0)	1 (0.3)	2 (0.5)	2 (0.3)	6 (0.7)
Back Pain	12 (3.0)	3 (0.7)	3 (0.8)	3 (0.7)	15 (1.9)	6 (0.7)
Hypertension	9 (2.2)	3 (0.7)	1 (0.3)	3 (0.7)	10 (1.3)	6 (0.7)
Defaecation urgency	0	1 (0.2)	3 (0.8)	5 (1.2)	3 (0.4)	6 (0.7)
Influenza like illness	1 (0.2)	4 (1.0)	0	1 (0.2)	1 (0.1)	5 (0.6)
Pyrexia	5 (1.2)	4 (1.0)	2 (0.5)	1 (0.2)	7 (0.9)	5 (0.6)
Hypothyroidism	1 (0.2)	4 (1.0)	0	0	1 (0.1)	5 (0.6)
Pharyngitis streptococcal	4 (1.0)	2 (0.5)	4 (1.0)	3 (0.7)	8 (1.0)	5 (0.6)
Joint Sprain	1 (0.2)	4 (1.0)	0	1 (0.2)	1 (0.1)	5 (0.6)
Muscle spasm	4 (1.0)	3 (0.7)	2 (0.5)	2 (0.5)	6 (0.8)	5 (0.6)
Decreased Appetite	0	4 (1.0)	1 (0.3)	1(0.2)	1 (0.1)	5 (0.6)
Alopecia	0	1 (0.2)	1 (0.3)	4 (1.0)	1 (0.1)	5 (0.6)
Haemorrhoids	4 (1.0)	4 (1.0)	2 (0.5)	0	6 (0.8)	4 (0.5)
Blood potassium increased	1 (0.2)	4 (1.0)	0	0	1 (0.1)	4 (0.5)
Arthritis	0	4 (1.0)	0	0	0	4 (0.5)
Chest Pain	4 (1.0)	2 (0.5)	0	2 (0.5)	4 (0.5)	4 (0.5)
Abdominal tenderness	7 (1.7)	3 (0.7)	4 (1.0)	0	11 (1.4)	3 (0.4)
Migraine	7 (1.7)	1 (0.2)	1 (0.3)	2 (0.5)	8 (1.0)	3 (0.4)
Dysuria	4 (1.0)	2 (0.5)	0	1 (0.2)	4 (0.5)	3 (0.4)
Constipation	7 (1.7)	2 (0.5)	2 (0.5)	0	9 (1.1)	2 (0.2)
Weight decreased	5 (1.2)	2 (0.5)	0	0	5 (0.6)	2 (0.2)
Myalgia	4 (1.0)	1 (0.2)	3 (0.8)	1 (0.2)	7 (0.9)	2 (0.2)
Pollakiuria	0	1 (0.2)	5 (1.3)	1 (0.2)	5 (0.6)	2 (0.2)
Procedural pain	2 (0.5)	2 (0.5)	5 (1.3)	0	7 (0.9)	2 (0.2)
Joint swelling	2 (0.5)	0	4 (1.0)	1 (0.2)	6 (0.8)	1 (0.1)

According to this analysis and after the evaluation of the material of the data provided during the assessment, additional events to be included into the SPC had to be discussed. The company was able to show that the increased frequency for the AEs headache, sinus congestion, neck pain, toothache, influenza like illness, hypothyroidism, and joint sprain would not justify the inclusion into chapter 4.8 of the SPC.

Additionally, as a consequence of diarrhoea – the adverse events hypokalaemia, low bicarbonate, dehydration, dizziness, orthostatic hypotension, and decreased appetite, have been included in the list of undesirable effects in the SmPC, based on slightly higher occurrence in the linclotide treated patients, the assessment of relatedness by the investigators, and the plausibility of the occurrence considering the mode of action and potential consequences of diarrhoea.

A quite similar profile of adverse events is reported in the phase 2, and the CC phase 3 studies.

During the LTS studies, the most frequent adverse events were again events related to the gastrointestinal tract, and obviously to the laxative effects of the compound, such as diarrhoea, abdominal pain, nausea and flatulence, however, the most frequent events also comprised urinary tract infections, and sinusitis. The evaluation of relatedness produced again diarrhoea, abdominal pain, flatulence, abdominal distension, and nausea to be the most frequent events. Similar profiles were observed in IBS-C and CC patients. The most frequent events from the LTS-studies are shown in the following table (with a threshold of 1.5%, taken from the updated Summary of Safety with data cut-off June 2011).

Table 14: TEAEs reported in ≥1.5% of all IBS-C or CC patients in the phase 3 open-label long-term safety studies (group 3) Safety Population:

	Number (%) of Patients		
Adverse Event (Preferred Term)	***Total IBS-C*** **(N = 2147)**	***Total CC*** **(N = 1129)**	***Total patients*** **(N = 3271)**
Any TEAE	**1554 (72.4)**	**849 (75.2)**	**2401 (73.4)**
Diarrhoea	693 (32.3)	358 (31.7)	1051 (32.1)
Sinusitis	137 (6.4)	71 (6.3)	208 (6.4)
Urinary tract infection	127 (5.9)	72 (6.4)	199 (6.1)
Abdominal pain	135 (6.3)	58 (5.1)	193 (5.9)
Upper Respiratory tract infection	119 (5.5)	58 (5.1)	177 (5.4)
Nausea	105 (4.9)	64 (5.7)	169 (5.2)
Headache	82 (3.8)	54 (4.8)	136 (4.2)
Abdominal Distension	78 (3.6)	48 (4.3)	126 (3.9)
Flatulence	66 (3.1)	60 (5.3)	126 (3.9)
Nasopharyngitis	70 (3.3)	33 (2.9)	103 (3.1)
Bronchitis	58 (2.7)	43 (3.8)	101 (3.1)
Constipation	76 (3.5)	24 (2.1)	100 (3.1)
Back pain	56 (2.6)	36 (3.2)	92 (2.8)
Gastroenteritis Viral	52 (2.4)	25 (2.2)	77 (2.4)
Arthralgia	50 (2.3)	27 (2.4)	77 (2.4)
Anxiety	52 (2.4)	23 (2.0)	75 (2.3)
Influenza	45 (2.1)	26 (2.3)	71 (2.2)
Gastrooesophageal reflux disease	44 (2.0)	23 (2.0)	67 (2.0)
Hypertension	41 (1.9)	26 (2.3)	67 (2.0)
Abdominal pain Upper	31 (1.4)	34 (3.0)	65 (2.0)
Vomiting	43 (2.0)	20 (1.8)	63 (1.9)
Depression	42 (2.0)	21 (1.9)	63 (1.9)
Procedural Pain	29 (1.4)	27 (2.4)	56 (1.7)
Dizziness	27 (1.3)	18 (1.6)	45 (1.4)
Fatigue	34 (1.6)	17 (1.5)	50 (1.5)
Defaecation Urgency	39 (1.8)	10 (0.9)	49 (1.5)
Cough	34 (1.6)	14 (1.2)	48 (1.5)

	Number (%) of Patients		
Haemorrhoids	23 (1.1)	25 (2.2)	48 (1.5)
Dyspepsia	31 (1.4)	15 (1.3)	46 (1.4)
Vulvovaginal mycotic infection	27 (1.3)	16 (1.4)	43 (1.3)
Weight increase	21 (1.0)	17 (1.5)	38 (1.2)
Abdominal Discomfort	13 (0.6)	23 (2.0)	36 (1.1)
Muscle Spasms	21 (1.0)	14 (1.2)	35 (1.1)
Abdminal Pain Lower	25 (1.2)	8 (0.7)	33 (1.0)
Pain in extremity	23 (1.1)	18 (1.6)	41 (1.3)
Vertigo	20 (0.9)	5 (0.4)	25 (0.8)

Most events in both indications, and in both the placebo-controlled and the LTS-studies were considered to be mild or moderate in severity only, with only about 1/6 of the events being severe in nature overall.

The evaluation of the onset of events produced a continuous reduction of adverse events over time with the highest frequencies shown at the beginning of the treatment. However, this is obviously partly an effect of discontinuations of patients due to the adverse events (especially those related to diarrhoea).

The company presents 4 different "events of interest", namely diarrhoea, the potential consequences of diarrhoea (dehydration, dizziness, and hypotension), gallbladder disease (related to a relatively high frequency in one of the LTS-studies), hypersensitivity, and aplastic anaemia (1 case documented).

Regarding diarrhoea, the company makes the case that the frequency and severity of diarrhoea is decreasing with ongoing treatment. This statement is finally accepted after re-analysis. Regarding diarrhoea it has also been shown that the frequency of diarrhoea is highest among the elderly population. Also – this being a more vulnerable population – the concurrence of diarrhoea and its consequences (hypokalaemia, low bicarbonate, dehydration, dizziness, and orthostatic hypotension) might be more frequent or more severe. Appropriate statements have been included into the SmPC.

Regarding dehydration, there is no hint of an association of dehydration with diarrhoea in the IBS-C population, whereas this association appears likely from the evaluation of the CC double-blind population. There was one case of diarrhoea associated with dehydration and orthostatic hypotension. Similar results are given for dizziness, and for orthostatic hypotension. It is concluded that an association of diarrhoea with clinically more relevant consequences such as dizziness, dehydration, and orthostatic hypotension is rare but appears to be likely (this is appropriately reflected in the SmPC).

Regarding gallbladder disease, the phase 3 double-blind studies did not suggest an increased occurrence of such events. The company substantiated that within the IBS-C population, where an increased incidence of gallstones has been reported overall, the incidence rate compared to a population not treated with linaclotide is most likely not increased.

The company has furthermore substantiated that a causal association with the occurrence of aplastic anaemia in one patient treated with linaclotide does not exist. The company has evaluated the occurrence of haematology related events, namely low neutrophil counts, low platelet counts, and decreased haemoglobin, which revealed a slightly higher incidence for these events for linaclotide as compared to placebo. However, the follow-up of these patients made a causal association with (suspected early effects in the development of bone marrow aplasia) these events unlikely, as the vast majority of patients were later continuously treated with linaclotide without further events, or with

normalisation of the laboratory values. It is concluded that there appears to be no suspicion of a causal relationship with aplastic anaemia/pancytopenia with the administration of linaclotide.

The incidence of TEAEs during clinical development of linaclotide that could potentially be related to immunogenic potential (i.e.: hypersensitivity, rash, pruritus, urticaria, asthma) was generally similar in the linaclotide and placebo groups. Linaclotide has a molecular weight of 1526 Da, which is below the generally accepted threshold for immunogenicity risk (≥10,000 Da).

Serious adverse event/deaths/other significant events

7 patients died during the course of the studies, which were all treated with linaclotide except one patient who died before receiving first dose of study drug. However, after evaluation of the patient narratives, it appears that none of the deaths can be causally attributed to the intake of linaclotide.

Table 89: List of patients who died in the linaclotide clinical development programme (Safety Population)

Study/Patient No	Age, y/ Sex	Indication/ Treatment	Day of Onset of Fatal SAE[a]	Day of Death	SAE Preferred Term
Group 1 (Phase 3 Trials)					
LIN-MD-31/ 0153115	54/M	IBS-C/ Pre Randomization	NA	NA	Cardiopulmonary arrest and ventricular fibrillation[d]
LIN/MD-01/ 0090105	66/F	CC/Linaclotide	8	98	Pancreatic carcinoma
LIN-MD-01/ 0160101[e]	49/F	CC/Linaclotide	52	52	Drug toxicity (Fentanyl)
Group 3 (LTS Studies)					
MCP-103-305/ 0872010	36/F	IBS-C/ Linaclotide	123	123	Drug toxicity (Morphine[c])
MCP-103-305/ 292004	40/F	IBS-C/ Linaclotide	351	351	Drug toxicity (Morphine and alprozolam)
MCP-103-305/ 1033022[b]	48/M	CC/Linaclotide	383	391	Esophageal squamous cell cancer stage IV
MCP-103-305/ 0093022	68/M	CC/Linaclotide	97	97	Multiple injuries

The number of serious adverse events (SAEs) has been low during the placebo-controlled phase 3 trials in IBS-C, with 9 and 6 events in the placebo and linaclotide groups. None of these events occurred in more than one patient. Therefore, it appears that no clear conclusion can currently be drawn on the occurrence of SAEs, and a causative relation to the intake of linaclotide appears to be unlikely. The occurrence of SAEs was also low in the CC placebo-controlled studies, and also none of the events occurring in more than one patient.

Table 90: Incidence of on-therapy serious adverse events in IBS-C patients in the phase 3 placebo-controlled trials (group 2) – Safety Population

System Organ Class Preferred Term	Number (%) of Patients	
	Placebo (N =798)	Linaclotide 290 µg/day (N = 807)
Any SAE	9 (1.1)	6 (0.7)

	Number (%) of Patients	
CARDIAC DISORDERS	0	1 (0.1)
Pericardial effusion	0	1 (0.1)
Pericarditis	0	1 (0.1)
EAR AND LABYRINTH DISORDERS	1 (0.1)	0
Vertigo	1 (0.1)	0
GASTROINTESTINAL DISORDERS	2 (0.3)	0
Abdominal pain lower	1 (0.1)	0
Duodenitis	1 (0.1)	0
Hiatus hernia	1 (0.1)	0
Oesophagitis	1 (0.1)	0
HEPATOBILIARY DISORDERS	1 (0.1)	0
Cholecystitis chronic	1 (0.1)	0
INFECTIONS AND INFESTATIONS	2 (0.3)	1 (0.1)
Appendicitis	0	1 (0.1)
Bronchitis	1 (0.1)	0
Gastroenteritis	1 (0.1)	0
Pneumonia viral	1 (01)	0
Urinary tract infection	1 (0.1)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (0.1)
Rotator cuff syndrome	0	1 (0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	2 (0.3)	1 (0.1)
Hodgkin's disease nodular sclerosis stage IV	0	1 (0.1)
Rectal cancer stage IV	1 (0.1)	0
Uterine leiomyoma	1 (0.1)	0
NERVOUS SYSTEM DISORDERS	1 (0.1)	0
Transient ischemic attack	1 (0.1)	0
RENAL AND URINARY DISORDERS	1 (0.1)	0
Renal cyst	1 (0.1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (0.1)
Asthma	0	1 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.1)	0
Angioedema	1 (0.1)	0
SURGICAL AND MEDICAL PROCEDURES	0	1 (0.1)
Cystopexy	0	1 (0.1)

During the LTS-studies, almost 4% of the patients experienced SAEs, the most common being cholelithiasis, chest pain, breast cancer, back pain, osteoarthritis, fall, syncope, biliary dyskinesia, and uterine prolapse without differences between the IBS-C and CC patients.

Laboratory findings

No relevant influence of linaclotide was found on laboratory parameters such as blood cell parameters, and clinical chemistry, including parameters related to electrolyte, water, and bicarbonate balance. However, as a consequence of diarrhoea, possible electrolyte dysbalances especially in elderly patient are reflected in the SmPC and included as an important identified risk in the RMP. Furthermore a PASS is planned with a safety endpoint specifically addressing complications of diarrhoea.

The evaluation of vital signs, and ECGs did not reveal any abnormalities. The ECG evaluation also comprised an extended evaluation ("triplicate ECG programme") in a controlled manner to exclude

effects on QT, which was considered appropriate to replace a TQT study due to the nature of the compound and the results of the pre-clinical investigations. No relevant influence could be found.

Safety in special populations

The evaluation of adverse events in subgroups, such as age, gender, race, and BMI revealed that there were no relevant differences in the adverse event profile for gender, race, and BMI. However, it could be shown that elderly patients appear to be more prone to the gastrointestinal effects, at least to diarrhoea as such (without the presumed "accompanying" symptoms abdominal pain, flatulence, etc). For the elderly, also the percentage of severe events was higher. These results were consistently shown in IBS-C, as well as in CC patients. The SmPC labels clearly that special attention should be given to these patients.

As regards the overall documentation of safety in the elderly population, as well as for the male population, the reported patient numbers are relatively low. The safety in the elderly population will continuously monitored in a planned PASS.

No differentiation of the adverse event profile was seen for the exploration of underlying disease subgroups, such as patients suffering from diabetes, CV-disease, and hypertension. However, as these patients are prone to a disturbance of water or electrolyte balance following diarrhoea the SmPC mentions that electrolyte control should be considered in these patients.

Safety related to drug-drug interactions and other interactions

To address the lack of drug-drug interaction studies due to the low or completely missing blood levels of linaclotide, respective subgroups of patients with concomitant medication subgroups were evaluated. In the case of antidepressants/SSRIs this evaluation revealed an overall higher occurrence in the non-gastrointestinal and non-diarrhoea related GI adverse events, which has been further explored. The company presented the additional analysis of GI events other than diarrhoea for their dependency of the total frequency on the concomitant administration of SSRIs or antidepressants. Taking the variability of the occurrence of adverse events into account, the presented numbers did not reflect a gross deviation in the occurrence of these non-diarrhoeal GI events in those with the concomitant compounds compared to the overall population. Therefore, a relevant interaction between the compounds is not suggested. Also, no further GI events were seen in this population, compared to the overall population.

The higher incidence of diarrhoea in patients treated with laxatives, and with PPIs is noted and has been taken into account for within the SmPC and the RMP. In patients taking diuretics or agents affecting the renin-angiotensin system, the incidence of TEAES with linaclotide was slightly higher than that of placebo, with a clinically relevant difference in rates of diarrhoea (19.4% vs 1.7% and 22.8% vs 4.2%, respectively). There were no clinically meaningful changes in electrolytes observed between linaclotide and placebo in hypertensive patients. However, in case of diarrhoea, special populations, either because they are treated with drugs that may modify the water electrolyte balance or because of their underlying condition, may be prone to potential relevant changes in electrolytes. In this regard, the product information acknowledges that caution should be exercised in patients who are prone to a disturbance of water electrolyte balance (e.g. elderly, patients with CV diseases, diabetes, hypertension), and electrolyte control should be considered. Furthermore further data on the alterations of electrolytes under treatment with linaclotide will be generated within the planned PASS.

A food interaction clinical study in healthy subjects showed that linaclotide was not detectable in plasma either in fed or in fasted conditions at the therapeutic doses. Taking linaclotide in the fed

condition produced more frequent and looser stools, as well as more gastrointestinal adverse events, than when taking it under fasting conditions. To take this into account linaclotice is recommended to be taken 30 minutes before a meal (see section 4.2 of the SmPC).

Discontinuation due to adverse events

Discontinuations of treatment due to adverse events were more frequent in the linaclotide groups as compared to the placebo treatment group (almost 10% in the IBS-C studies). This is mainly, and again, attributable to diarrhoea, and other gastrointestinal adverse events, such as abdominal pain, and distension, flatulence, nausea, and defecation urgency. Similar results are given for the CC studies. In the LTS-studies, about 10% of the patients discontinued due to adverse events, again by one half relating to diarrhoea, and to the main part of the other half relating to other gastrointestinal events. Differences between the two groups (CC and IBS-C) were not detected.

Post marketing experience

No post-marketing data was available during the assessment.

2.6.1. Discussion on clinical safety

Adverse events occurring with the administration of linaclotide can mostly be related to the laxative effects of the compound, namely diarrhoea and associated signs and symptoms (abdominal pain, nausea and vomiting, flatulence, defecation urgency). In pivotal trials in IBS-C, diarrhoea was reported in 160 (19.8%) of linaclotide patients compared with 24 (3.0%) of placebo patients. A total of 16 (2.0%) linaclotide patients had diarrhoea TEAEs that were reported as severe compared with 1 (0.1%) placebo patient. A total of 91 (11.3%) patients developed moderate-severe diarrhoea compared with only 6 (0.7%) placebo patients. In the 160 patients who had TEAEs of diarrhoea and continued treatment, the event resolved within 7 days in 49 (30.6%) patients, and lasted more than 28 days in 84 (52.5%) of them. Also, there appears to be an increase in gastrointestinal viral infections, also causing diarrhoea, of which the mechanism is currently unclear and which was included as a potential risk in the RMP.

The clinical studies did not suggest that the occurrence of diarrhoea did lead to potential more serious consequences, such as dehydration, acid-base and electrolyte disturbances, or dizziness, hypertension, or syncope. However, the SmPC takes into account that these events may occur in rare cases. Furthermore the planned PASS will contain a safety endpoint that will specifically address complications of diarrhoea in patients with associated risk factors.

The majority of these gastrointestinal events appears to be occurring at the beginning of the treatment. The SmPC mentions in 4.4, that, should prolonged or severe diarrhoea occur the treatment should be temporary discontinued and medical advice should be sought.

The overall long-term safety profile is not relevantly different from the short-term profile apart from this overall decreased frequency of mainly the GI events. Patients exposure and preliminary results from the ongoing Long term safety studies give sufficient assurance that this is manageable in clinical practice. The SmPC provides appropriate guidance. Furthermore, future data assessment will occur based onthe final study report which is requested from the applicant upon finalisation (as described in the RMP).

The occurrence of adverse events is not higher in relevant patient subgroups according to underlying disease, or for the different sexes, BMIs or races/ethnicities. However, the elderly population appears

to be more prone to adverse events, namely diarrhoea and its consequences. Therefore the need of periodical assessment of the benefit risk ratio in the elderly is highlighted in the SmPC. More safety data in the elderly population, for whom the available patient numbers are low, will become available with the PASS.

The higher incidence of diarrhoea in patients treated with laxatives, and with PPIs is noted and has been taken into account for within the SmPC and the RMP. In patients taking diuretics or agents affecting the renin-angiotensin system, the incidence of TEAES with linaclotide was slightly higher than that of placebo, with a clinically relevant difference in rates of diarrhoea. There were no clinically meaningful changes in electrolytes observed between linaclotide and placebo in hypertensive patients. However, in case of diarrhoea, special populations, such as patients suffering from diabetes, CV-disease, and hypertension, either because they are treated with drugs that may modify the water electrolyte balance or because of their underlying condition, may be prone to potential relevant changes in electrolytes. In this regard, the product information acknowledges that caution should be exercised in patients who are prone to a disturbance of water electrolyte balance (e.g. elderly, patients with CV diseases, diabetes, hypertension), and electrolyte control should be considered. Furthermore further data on the alterations of electrolytes under treatment with linaclotide will be generated within the planned PASS.

Serious adverse events during the trials were low, and all serious events did not occur more frequently than once. There were 7 deaths during the trials that can, however, none of these was attributed to linaclotide.

An association of the compound with the occurrence of blood dyscrasias, including aplastic anaemia has been discussed. Based on the similar incidence than placebo of TEAEs potentially related to immunogenic potential, as well as molecular weight below the generally accepted threshold for immunogenicity risk, the potential immunogenicity of the compound is considered not to be a concern.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

In summary, the safety profile of linaclotide has been adequately characterised. The compound does cause diarrhoea and associated symptoms as the most relevant undesirable effect. The data do not suggest that this does lead to clinically relevant, or serious, adverse events that could be considered a consequence of diarrhoea, namely, dehydration, electrolyte and bicarbonate disturbances, dizziness, hypotension and syncope in relevant numbers. Even if such events do occur in rare cases, they were generally mild in severity, and can be considered fully reversible and controllable. The SmPC takes these risks adequately into account. The product is considered to have an acceptable safety profile also in long-term administration.

To further elucidate the safety profile as derived from the clinical studies a PASS was requested by the CHMP to address potential and identified risks, and missing information as described in the RMP. Furthermore, the final results of the long-term safety studies will be submitted upon availability, as defined in the RMP.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan

Table 4. Summary of the risk management plan

Safety issue	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimisation activities (routine and additional)
Diarrhoea	Routine pharmacovigilance activities supported with "cases of special interest" procedure for early identification and analysis of events for further characterisation in subset of patients who experience severe diarrhoea. PASS with a safety endpoint that will specifically address complications of diarrhoea in patients with associated risk factors.	Diarrhoea is included as a very common adverse event in Section 4.8 of the linaclotide SmPC (**Annex 2**). In addition, 'abdominal pain', 'abdominal distension', and 'flatulence' are added as common adverse events in Section 4.8 of the linaclotide SmPC. 'Faecal incontinence' and 'defecation urgency' are also included as uncommon adverse events in Section 4.8 of the linaclotide SmPC (**Annex 2**). Section 4.2 (Posology and Method of Adminstration) of the linaclotide SmPC contains a statement advising that linaclotide should be taken preferably at least 30 min before a meal (to reduce the chances of experiencing diarrhoea). An advisory statement has also been added to state that physicians should periodically assess the need for continued treatment with linaclotide. Section 4.4 (Special Warnings and Precautions for Use) of the linaclotide SmPC contains a statement warning that: '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 occurs'. Should prolonged (e.g more than 1 week) or severe diarrhoea occur, temporary discontinuation of linaclotide until the diarrhoea episode is resolved should be considered and medical advice sought. Additional caution should be exercised in patients who are prone to a disturbance of water or electrolyte balance (e.g. the elderly, CV diseases, diabetes, hypertension), and electrolyte control should be considered.") Section 4.5: "Concomitant treatment with proton pump inhibitors, laxatives or NSAIDS may increase the risk for diarrhoea.") An observational study will be performed and specific ADR follow-up questionnaires will be used for spontaneous case reports of severe cases of diarrhoea

Safety issue	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimisation activities (routine and additional)
Faecal Incontinence and Defecation Urgency	Routine PV	• 'Faecal incontinence' and 'defecation urgency' are included as uncommon adverse events in Section 4.8 of the linaclotide SmPC (**Annex 2**). • As diarrhoea is the main risk factor for developing faecal incontinence and defecation urgency, risk minimisation is mainly directed at reducing the risk of diarrhoea and assuring correct handling of patients with diarrhoea. • Section 4.2 (Posology and Method of Adminstration) of the linaclotide SmPC contains a statement advising that linaclotide should be taken preferably at least 30 min before a meal (to reduce the chances of experiencing diarrhoea). An advisory statement has also been added to state that physicians should periodically assess the need for continued treatment with linaclotide. • Section 4.4 (Special Warnings and Precautions for Use) of the linaclotide SmPC contains a statement warning that: '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 occurs'. Should prolonged (e.g more than 1 week) or severe diarrhoea occur, temporary discontinuation of linaclotide until the diarrhoea episode is resolved should be considered and medical advice sought. Additional caution should be exercised in patients who are prone to a disturbance of water or electrolyte balance (e.g. the elderly, CV diseases, diabetes, hypertension), and electrolyte control should be considered.") • Section 4.5: "Concomitant treatment with proton pump inhibitors, laxatives or NSAIDS may increase the risk for diarrhoea.")

Safety issue	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimisation activities (routine and additional)
Potential for off-label use and abuse/excessive use	Routine pharmacovigilance activities PASS	• Section 4.1 (Therapeutic Indications) of the linaclotide SmPC (**Annex 2**) stating that linaclotide is indicated for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults. • Section 4.2 (Posology and Method of Adminstration) of the linaclotide SmPC contains a statement advising that physicians should periodically assess the need for continued treatment with linaclotide. • Section 4.4 (Special Warnings and Precautions for Use) of the linaclotide SmPC contains a statement warning that: "Constella should be used after organic diseases have been ruled out and after diagnosis of IBS-C is established". '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 occurs'
Viral Gastroenteritis	Routine PV PASS	Viral gastroenteritis is included as a common adverse event in Section 4.8 (Undesirable Effects) of the linaclotide SmPC.

Safety issue	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimisation activities (routine and additional)
Manifestations of Severe Diarrhoea e.g., Alterations of Electrolytes, Dehydration and/or Orthostatic Hypotension	Routine PV PASS	• Section 4.4 (Special Warnings and Precautions for Use) of the linaclotide SmPC contains a statement warning that: '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 occurs'. Should prolonged (e.g more than 1 week) or severe diarrhoea occur, temporary discontinuation of linaclotide until the diarrhoea episode is resolved should be considered and medical advice sought. Additional caution should be exercised in patients who are prone to a disturbance of water or electrolyte balance (e.g. the elderly, CV diseases, diabetes, hypertension), and electrolyte control should be considered.")

Safety issue	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimisation activities (routine and additional)
Safety data in the paediatric population	Routine pharmacovigilance activities PIP studies PASS	Appropriate statements has been added to the linaclotide SmPC (**Annex 2**). Section 4.2: The safety and efficacy of Constella in children and in adolescents under 18 years old have not yet been established. No data are available (see sections 4.4 and 5.1)." 'Constella is not recommended for use in children and adolescents." Section 4.4: "Constella is not recommended for use in children and adolescents as it has not been studied in this population. As GC-C receptor is known to be overexpressed at early ages, children younger than 2 years may be particularly sensitive to linaclotide effects."

Safety issue	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimisation activities (routine and additional)
Safety data in the elderly population	Routine pharmacovigilance activities PASS	• An appropriate statement has been added in Section 4.8 of the linaclotide SmPC (**Annex 2**) stating that elderly (>65 years), hypertensive and diabetic patients reported diarrhoea more frequently as compared to the overall IBS-C population included in the clinical trials. • Section 4.4 (Special Warnings and Precautions for Use) of the linaclotide SmPC contains a statement warning that: '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 occurs'. Should prolonged (e.g more than 1 week) or severe diarrhoea occur, temporary discontinuation of linaclotide until the diarrhoea episode is resolved should be considered and medical advice sought. Additional caution should be exercised in patients who are prone to a disturbance of water or electrolyte balance (e.g. the elderly, CV diseases, diabetes, hypertension), and electrolyte control should be considered." "There are limited data in elderly patients (see section 5.1). Because of the higher risk of diarrhoea, special attention should be given to these patients and the treatment benefit-risk ratio should be carefully assessed'.

Safety issue	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimisation activities (routine and additional)
Safety data in pregnancy and lactation	Routine pharmacovigilance activities	An appropriate statement has been added in Section 4.6 of the linaclotide SmPC (**Annex 2**) stating that There is limited amount of data from the use of linaclotide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Constella during pregnancy.
Safety data in patients with co-existing disease, e.g. hepatic/renal	Routine pharmacovigilance activities PASS	Section 4.2 (Posology and Method of Administration) of the linaclotide SmPC states that no dose adjustments are required for elderly patients or for patients with

Safety issue	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimisation activities (routine and additional)
disease		hepatic or renal impairment (see section 5.2). In addition Section 4.8 (Undesirable effects) of the SmPC states that as linaclotide is minimally absorbed, differences in the safety profile of patients with renal or hepatic impairment are not expected.
Safey data in patients with inflammatory bowel disease	Routine pharmacovigilance activities PASS	Section 4.1 of the linaclotide SmPC (**Annex 2**) contains a clear statement that linaclotide is indicated for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults. Section 4.4: "Constella has not been studied in patients with chronic inflammatory conditions of the intestinal tract, such as Crohn's disease and ulcerative colitis, therefore it is not recommended to use Constella in these patients." 'Constella should be used after organic diseases have been ruled out and after a diagnosis of IBS-C is established'.
Safety data in patients receiving concomitant medications	Routine pharmacovigilance activities	Section 4.5: "Concomitant treatment with proton pump inhibitors, laxatives or NSAIDS may increase the risk for diarrhoea." and "In cases of severe or prolonged diarrhoea, absorption of other oral medicinal products may be affected. The efficacy of oral contraceptives may be reduced and the use of an additional contraceptive method is recommended to prevent possible failure of oral contraception (see the prescribing information of the oral contraceptive). Caution should be exercised when prescribing medicinal products absorbed in the intestinal tract with a narrow therapeutic index such as levotyroxine as their efficacy may be reduced."

Safety issue	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimisation activities (routine and additional)
Safety data in male patients	Routine pharmacovigilance activities PASS	None
Safety data in patients with known or suspected mechanical GI obstruction	Routine pharmacovigilance activities PASS	Section 4.3 of Linaclotide SmPC contraindication for 'Patients with known or suspected mechanical gastrointestinal obstruction"

Safety issue	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimisation activities (routine and additional)
Safety data in patients with cardiac disorders or cardiovascular risk factors (e.g., Hypertension, diabetes)	Routine pharmacovigilance activities PASS	Section 4.4 (Special Warnings and Precautions for Use) of the linaclotide SmPC contains a statement warning that: '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 occurs'. Should prolonged (e.g more than 1 week) or severe diarrhoea occur, temporary discontinuation of linaclotide until the diarrhoea episode is resolved should be considered and medical advice sought. Additional caution should be exercised in patients who are prone to a disturbance of water or electrolyte balance (e.g. the elderly, CV diseases, diabetes, hypertension), and electrolyte control should be considered."
Long-term safety data	Routine pharmacovigilance activities Review of LTSS	None

The below pharmacovigilance activity(ies) in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Database based cohort study (PASS) to evaluate potential and identified risks and collect data on patient populations where data is missing. (RMP measure)	A draft final protocol should be submitted for assessment within 6 months after approval
Final study reports of the long-term safety studies MCP-103-305 and LIN-MD-02. (RMP measure)	The study reports and final evaluation should be submitted by October 2012.

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

In the two main studies, a statistically superior effect in comparison to placebo was shown for the overall assessment of IBS symptoms, and for a huge variety of response variables, combining the occurrence of relief of these symptoms according to various criteria. This includes the satisfactory response rates regarding abdominal pain/discomfort (combined), and regarding "IBS Degree of Response", which represented the co-primary endpoints in these trials. Several levels of "strictness" of the response criteria have also been evaluated showing highly statistically significant results in all of the evaluations. The compound was shown to exert effects not only on constipation/bowel movement related endpoints, such as frequency of bowel movements, stool consistency, severity of straining at stool, bloating, and others, but also had beneficial effects on the IBS-specific endpoints abdominal pain and discomfort; a clear dose-response relationship on these effects could be shown.

Generally, the endpoints used in the clinical trials were in agreement with the current European guidance document, and the instruments used to measure these endpoints have at least partly been validated. The patient population included in the trials has been evaluated to be fully reflecting a moderately to severely diseased population in need for a continuous treatment. Exclusion of patients with other potential diseases explaining the subjective complaints have been conducted to a satisfactory extent.

Most of the results do in fact not only represent statistically significant, but also clinically relevant results. As regards the primary endpoint response criteria, the effect of linaclotide versus placebo for the "12-Week abdominal Pain/abdominal discomfort responders" (relative increase in responders by 80%, and 14% in absolute terms) and "12-Week IBS Degree of Relief Responders" (relative increase in responders by 194% and 21% in absolute terms) was consistent across pivotal trials in IBS-C. For other variables, at least partly, pre-determined levels of clinical relevance have also been met.

The beneficial effects seen as regards all these parameters are not only seen in the two phase 3 studies after 3 months in consistent manner, but have obviously shown persistence of sustainability by showing similar, or even slightly better results in the single 6 months study for the longer treatment duration. Also, as taken from data on patient satisfaction in the ongoing long-term safety studies, the beneficial effects appear to last for even longer periods. Linaclotide has also been shown to beneficially impact Quality of Life of patients, which has been shown with a variety of these instruments.

The consistency of the effects has generally been shown for the relevant subgroups of ethnic/racial minorities, and the minority of male and elderly patients to a sufficient extent, although a higher variation was seen overall. A relevant rebound effect after cessation of treatment with the compound has not been observed in the trials.

Uncertainty in the knowledge about the beneficial effects.

The beneficial effects for periods longer than 3 months have only been demonstrated in one study. The long-term safety studies included some parameters for the evaluation of efficacy which was supportive. The fact, that only one trial has been conducted with the treatment duration of 6 months, required the efficacy demonstration in this trial to provide overall outstanding robustness of results, and full validity of the data. This overall robustness of the results has generally been shown hence the availability of this single long-term trial is accepted.

Despite the clinically relevant results it has to be noted that the rate of non-responders to linaclotide in pivotal studies was high (45.5% of non-responders for improvement in 12-week abdominal pain/abdominal discomfort and 61.7% of non-responders in 12-week IBS degree of relief). This means that approximately half patients will not adequately or fully benefit from treatment with linaclotide. To avoid that patients not responsive to linaclotide are being treated, the SmPC contains a clear guidance to physicians to assess the improvement of the symptoms after 4 weeks of treatment and should reconsider treatment if there is no improvement in symptoms.

Risks

Unfavourable effects

In the clinical studies, linaclotide was overall causing a modest but relevant increase in adverse events. This increase in adverse events as compared to placebo was mainly attributable to the induction of laxation by the compound, and its "unwanted" exaggeration, namely diarrhoea.

In association with diarrhoea, other associated gastrointestinal disturbances have been observed, which are suspected to be direct consequences of the induction of laxation, and of diarrhoea, namely abdominal pain, bloating, abdominal distension, faecal incontinence, and defecation urgency. The majority of these gastrointestinal events appears to be occurring at the beginning of the treatment. The SmPC mentions in 4.4, that, should prolonged or severe diarrhoea occur the treatment should be temporary discontinued and medical advice should be sought.

The number of serious adverse events was overall low during the clinical development. None of the events occurred more than once. Only a minority of the adverse events observed were severe in nature and were completely reversible and controllable at the same time.

From the available data it appears that the elderly are more prone to the occurrence of gastrointestinal adverse events, namely diarrhoea and its associated events. Therefore physicians should periodically assess the benefit risk ratio in the elderly (4.4 of the SmPC).

Further data on complications of diarrhoea under treatment with linaclotide will be generated within the Post-authorisation Safety Study (PASS) containing a safety endpoint that will specifically address complications of diarrhoea in patients with associated risk factors. This study is subject to the Risk Management Plan.

Uncertainty in the knowledge about the unfavourable effects

In clinical practise the occurrence of diarrhoea may lead to potential more serious consequences, such as dehydration, acid-base and electrolyte disturbances, or dizziness, orthostatic hypotension, or syncope. The SmPC - despite such events were not observed - acknowledges that caution should be exercised in patients who are prone to a disturbance of water electrolyte balance (e.g. elderly, patients with CV diseases, diabetes, hypertension), and electrolyte control should be considered. Furthermore,

additional data will be generated through the PASS which contains a safety endpoint that will specifically address complications of diarrhoea in patients with associated risk factors.

The number of patients in the elderly subgroup (65 years and older) is rather low in the double-blind phase 3 studies and the elderly population has the highest rates of adverse events. Also, the incidence of diarrhoea – and hence also the potential for the more serious consequences of diarrhoea – appears to be highest in the elderly population. This uncertainty is considered to be adequately balanced by the guidance in the SmPC. In addition further relevant post marketing data will be specifically generated with the PASS (as described in the RMP).

The evaluation of a potential influence of concomitant medication revealed that differential rates of adverse events were seen for PPIs. While the potential mechanism remains unclear this has been taken account for within the SmPC.

The overall long-term safety profile is not expected to be significantly different from the short-term profile apart from this overall decreased frequency (of mainly the GI events). Patients exposure and preliminary results from the ongoing Long term safety studies give sufficient assurance on the granting of a marketing authorisation. The applicant is requested to submit the final report of these long-term safety studies upon finalisation (as described in the RMP).

Benefit-risk balance

Importance of favourable and unfavourable effects

The observed favourable effects are generally considered to be clinically relevant. Linaclotide has been shown to exert beneficial effects in consistent manner on bowel movement related endpoints, as well as in those related to abdominal pain and discomfort. Also global measurements and the evaluation of Quality of Life are in accordance with these results. Overall, a clinical relevance of the results in comparison to placebo can be concluded. Subgroups of patients have shown an overall acceptable consistency of efficacy.

The unfavourable effects of the compound appear to be mainly restricted to effects in the gastrointestinal tract, and related to the laxative action of linaclotide, and being in accordance with the missing systemic availability. More serious consequences of the gastrointestinal effects – which is mainly diarrhoea and associated symptoms – such as electrolyte and acid base changes, as well as dehydration, dizziness, and syncope were rather rare events and of low severity. Moreover, diarrhoea appears to be controllable with intermittent dosing cessation and fully reversible. These unfavourable effects are adequately labelled and manageable with the guidance in the SmPC and appropriate risk management measures are included in the RMP.

Benefit-risk balance

Based on the robust efficacy demonstration and the manageable safety profile, in conjunction with the clearly outlined requirements for future data generation, the benefit/risk balance of the linaclotide for the treatment of IBS-C in adults is considered positive.

Discussion on the benefit-risk balance

Linaclotide is intended for the treatment of Irritable Bowel Syndrome with constipation. IBS is a functional bowel disease characterised by recurrent abdominal pain and discomfort associated with defecation irregularities, with the subgroups constipation predominant, diarrhoea predominant, mixed

or unsubtyped. IBS is an incompletely understood syndrome, for which no specifically licensed medication is available in Europe, and treatment recommendations point to a symptomatic therapy only. IBS represents a significant burden for patients, physicians, healthcare providers and employers. Patients with IBS have more days off work, have poorer quality of life, and utilize healthcare resources more frequently compared with individuals who do not have IBS. Therefore, there is an unmet medical need for therapies for alleviating symptoms and increasing quality of life in patients with IBS-C.

Linaclotide is the first drug candidate proposed for licensing in this indication for long time. Linaclotide is proposed to treat the constipation predominant subtype of IBS. The development programme for linaclotide has shown unequivocal efficacy to a statistically significant, and also a clinically relevant extent. The safety profile of the compound is considered acceptable and controllable with the relevant statements included into the SmPC and the measure defined in the RMP as described above.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Constella in the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3.0 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

The PSUR cycle for the product will follow the standard requirements until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Obligation to complete post-authorisation measures

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that linaclotide is to be qualified as a new active substance.