IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Linaclotide – Benefit assessment according to § 35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment "Linaclotid – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 30 July 2013). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Matthias Breidert, Hospitals in the Altmühltal Nature Park, Kösching, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. IQWiG is solely responsible for the content of the report.

IQWiG employees involved in the dossier assessment:[2]

- Marloes Kamphuis
- Lars Beckmann
- Katharina Biester
- Gertrud Egger
- Andreas Gerber-Grote
- Tatjana Hermanns
- Beate Wieseler
- Natalia Wolfram

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[2] Due to legal data protection regulations, employees have the right not to be named.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AGA	American Gastroenterological Association
EMA	European Medicines Agency
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
IBS-C	irritable bowel syndrome with constipation
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
NSAID	non-steroidal anti-inflammatory drugs
RCT	randomized controlled trial
SGB	*Sozialgesetzbuch* (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug linaclotide. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 2 May 2013.

Research question

The aim of this report is to assess the added benefit of linaclotide compared with the appropriate comparator therapy (ACT) (medically advised dietary changes and symptom-orientated treatment [constipation, bloating, cramping, pain]) in patients with moderate to severe irritable bowel syndrome with constipation (IBS-C).

The assessment was conducted based on patient-relevant outcomes. Direct comparative randomized controlled trials (RCTs) were included in the assessment.

Results

The company did not submit any relevant study for the assessment of the added benefit of linaclotide compared with the ACT specified by the G-BA.

The company included 3 studies (MCP-103-302, LIN-MD-31 and MCP-103-202) in its study pool. In none of these 3 studies was the ACT of the G-BA implemented. In addition, the 12-week duration of the treatment phases of the MCP-103-202 and LIN-MD-31 studies was too short to assess the added benefit of linaclotide.

Appropriate comparator therapy

The ACT specified by the G-BA explicitly consisted of 2 components that must be implemented in the studies for assessing the added benefit of linaclotide: medically advised dietary changes and symptom-orientated treatment for the symptoms constipation, bloating, cramping and pain.

In 2 studies (MCP-103-302 and LIN-MD-31) the patients were expressly required not to change their previous diet. In each case, an inclusion criterion specified that on enrolment in the study, patients had to agree not to make any major alterations to their lifestyle that might affect the symptoms of IBS-C, e.g. dietary changes. The documents of the third study, MCP-103-202, contained no information about dietary advice and dietary changes. No dietary advice and any consequent change in diet were planned in the study.

It is not clear from the study documents of any of the 3 studies whether dietary advice and any resulting change in the diet – if not in the study, then at least shortly before enrolment in the study – took place. For example, the investigator did not have to confirm that dietary changes were not necessary or not possible.

Moreover, it was not made clear in any of the studies whether symptom-orientated treatment was permitted, adequate and flexible.

In all 3 studies, on entry into the study, patients were required to organize their previous and any new treatment according to the protocol requirements. For instance, patients had to discontinue their respective treatment if this was not permitted according to the protocol or to continue it at a constant dose. In particular, the following classes of drugs considered for use in the treatment of IBS-C symptoms were not permitted: non-prescription or prescription-requiring laxatives/enemas as well as herbal or natural agents for the treatment of constipation and (for Studies MCP-103-302 and LIN-MD-31) other symptoms of IBS-C; any specific treatment for IBS-C or anticholinergics, which include, e.g., the spasmolytic, butylscopolamine. The unchanged continuation, for example of fibre and bulk laxatives, was permitted. However, no change in their dosage or a first-time use, if necessary, was possible during the course of the study.

The only treatment that was explicitly allowed was for the symptom "constipation". In the MCP-103-302 and LIN-MD-31 studies, bisacodyl was used as rescue medication if at least 72 hours had elapsed since the last bowel movement, or the symptoms were intolerable. It can be assumed that these protocol requirements ensured that those patients who needed treatment for constipation received adequate and individual care. In Study MCP-103-202 the Fleet enema was also allowed in addition to bisacodyl as rescue medication, but only if at least 72 hours had elapsed since the last bowel movement. The study documents were not clear regarding the use of the rescue medication for patients for whom the symptoms were intolerable. For this reason, it remains uncertain whether patients in the MCP-103-202 study were able to react with adequate flexibility to constipation symptoms that were intolerable for them.

In contrast to the treatment of constipation, no (rescue) medication was explicitly defined or permitted in the study protocols for any of the other IBS-C symptoms (abdominal bloating, cramping and pain). The simultaneous extensive restrictions could even have led to a situation where individual treatment according to patient needs was not possible.

Duration of studies too short

In addition to the deficiency relating to the ACT, the treatment phases of Studies MCP-103-202 and LIN-MD-31 of 12 weeks were too short to assess the added benefit of linaclotide. A minimum duration of 6 months (24 weeks) is necessary for the present research question, in order to ensure an adequately long treatment and observation phase.

Taken as a whole, no studies relevant for the benefit assessment were submitted by the company. Therefore the assessment presented by the company in its dossier provided no proof of added benefit of linaclotide in comparison with the ACT specified by the G-BA.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug linaclotide compared with the ACT are assessed as follows:

Table 2: Extent and probability of added benefit of linaclotide

Therapeutic indication	Appropriate comparator therapy of the G-BA	Extent and probability of the added benefit
Symptomatic treatment of moderate to severe irritable bowel syndrome with constipation in adults	Medically advised dietary changes and symptom-orientated treatment (constipation, bloating, cramping, pain)	Added benefit not proven
G-BA: Federal Joint Committee		

The decision on added benefit is made by the G-BA.

2.2 Research question

The aim of this report was to assess the added benefit of linaclotide compared with the ACT in the symptomatic treatment of moderate to severe IBS-C in adults.

The company had requested advice from the G-BA regarding the ACT for the therapeutic indication "symptomatic treatment of moderate to severe irritable bowel syndrome with constipation". In accordance with this request, the G-BA defined the ACT as follows: medically advised dietary changes and symptom-orientated treatment (constipation, bloating, cramping, pain).

The company adopted the ACT of the G-BA for the therapeutic indication according to the Summary of Product Characteristics [3] ("symptomatic treatment of moderate and severe irritable bowel syndrome with constipation"), and described it as individual symptom-orientated treatment which included dietary changes as well as an individual, need-based treatment of the single symptoms.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1-3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

The benefit assessment of linaclotide was carried out in comparison with the ACT specified by the G-BA.

The assessment was conducted based on patient-relevant outcomes and on direct comparative RCTs.

Further information about the research question can be found in Module 3, Section 3.1 and in Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- List of studies on linaclotide (studies completed up to 24 April 2013)
- Search in trial registries for studies on linaclotide (last search on 22 April 2013)

The Institute's own searches to check the company's search results:

- Search in trial registries for studies on linaclotide (last search on 16 May 2013)

Further information on the inclusion criteria for studies in the present benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

From the above-named steps of information retrieval, 3 studies were identified that investigated linaclotide in the relevant indication: MCP-103-302 [4,5], MCP-103-202 [6,7] and LIN-MD-31 [4,8]. These studies corresponded to the study pool of the company.

The studies were checked to see whether they were suitable for deriving conclusions on the added benefit of linaclotide in comparison with the ACT of the G-BA.

None of the 3 studies of the company was suitable for assessing the added benefit of linaclotide in comparison with the ACT of the G-BA.

Table 3 and Table 4 show the characteristics of the studies and of the interventions included by the company. Table 5 contains an overview of the information on medically advised dietary changes in the studies.

Table 3: Characteristics of the studies included - RCT, direct comparison: linaclotide versus placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MCP-103-302	RCT, multicentre, double-blind, placebo-controlled, parallel, Phase III	Adults with IBS-C according to modified[b] Rome II criteria	Linaclotide 290 µg (N = 402) Placebo (N = 403)	Screening phase: 3 weeks Pretreatment phase: 2 to 3 weeks Treatment phase: 26 weeks	111 centres in the USA July 2009 to September 2010	Primary:[c] abdominal pain and CSBM (FDA); abdominal pain and discomfort, IBS degree of relief (EMA) Secondary: symptoms, health-related quality of life, adverse events
LIN-MD-31	RCT, multicentre, double-blind, placebo-controlled, parallel, Phase III	Adults with IBS-C according to modified[b] Rome II criteria	Linaclotide 290 µg (N = 406) Placebo (N = 397)	Screening phase: 3 weeks Pretreatment phase: 2 to 3 weeks Treatment phase: 12 weeks Randomization withdrawal phase: 4 weeks	111 centres in the USA, 7 centres in Canada July 2009 to July 2010	Primary:[c] abdominal pain and CSBM (FDA); abdominal pain and discomfort, IBS degree of relief (EMA) Secondary: symptoms, health-related quality of life, adverse events

(continued)

Table 3: Characteristics of the studies included - RCT, direct comparison: linaclotide versus placebo (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MCP-103-202	RCT, multicentre, double-blind, placebo-controlled, parallel, dose-finding, Phase II	Adults with IBS-C according to Rome II criteria	Linaclotide 72 µg (N = 79) Linaclotide 145 µg (N = 82) Linaclotide 290 µg (N = 85) Linaclotide 579 µg (N = 89) Placebo (N = 85) Of which relevant subpopulation: Linaclotide 290 µg (N = 85) Placebo (N = 85)	Screening phase: 4 weeks Pretreatment phase: 2 weeks Treatment phase: 12 weeks Post-treatment phase: 2 weeks	92 centres in the USA March 2007 to February 2008	Primary: change in weekly CSBM rate from pretreatment to Week 12 Secondary: symptoms, health-related quality of life, adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes contain only information on relevant available outcomes for the present benefit assessment.
b: The Rome II criteria were adapted in relation to the constipation requirements.
c: Different primary outcomes for FDA and EMA due to differing requirements of these regulatory authorities.

CSBM: complete spontaneous bowel movement; EMA: European Medicines Agency; FDA: U.S. Food and Drug Administration; IBS: irritable bowel syndrome; IBS-C: irritable bowel syndrome with constipation; N: number of randomized patients; RCT: randomized controlled trial

Table 4: Characteristics of the interventions – RCT, direct comparison: linaclotide versus placebo

Study (treatment duration)	Intervention	Comparison	Previous treatment in both arms	Concurrent medication during the treatment phase in both arms
MCP-103-302 (26 weeks)	Linaclotide 290 µg once daily in the morning, 30 minutes before breakfast	Placebo once daily in the morning, 30 minutes before breakfast	No restrictions regarding previous treatment Patients had to stop certain previous treatments before starting therapy (see next column under "Not permitted") or maintain a stable dosage (see next column under "Unchanged continuation")	Permitted: Bisacodyl[a] Not permitted: All non-prescription or prescription laxatives, suppositories or enemas and herbal or natural agents for constipation or other symptoms of IBS-C; prokinetic agents; NSAIDs for abdominal pain and discomfort; any drug causing diarrhoea; all narcotics; any specific treatment for IBS-C or CC (alone or in combination including lubiprostone, colchicine and misoprostol); drugs with pharmacological activity against (HT)4, 5-HT_{2b} or $5HT_3$ receptors; anticholinergics and cholinomimetics;[b] bile acid sequestrants; oral and parenteral antibiotics;[c] barbiturates; oral or parenteral glucocorticoids;[d] all drugs for weight loss; any drug for the treatment of diarrhoea; the antiepilectic pregabalin Unchanged continuation:[e] Fibre; bulk laxatives; stool softeners; probiotics; antipsychotic agents[f] and antidepressants; calcium channel blocker verapamil;[g] Proton pump inhibitors, iron preparations as nutritional supplement or for the treatment of iron deficiency anaemia
LIN-MD-31 (12 weeks)	Linaclotide 290 µg once daily in the morning, 30 minutes before breakfast	Placebo once daily in the morning, 30 minutes before breakfast	No restrictions regarding previous treatment Patients had to stop certain previous treatments before starting therapy (see next column under "Not permitted") or maintain a stable dosage (see next column under "Unchanged continuation")	Permitted: Bisacodyl[a] Not permitted: as in Study MCP-103-302 Unchanged continuation:[e] as in Study MCP-103-302

(continued)

Table 4: Characteristics of the interventions – RCT, direct comparison: linaclotide versus placebo (continued)

Study (treatment duration)	Intervention	Comparison	Previous treatment in both arms	Concurrent medication during the treatment phase in both arms
MCP-103-202 (12 weeks)	Linaclotide 290 µg once daily in the morning, 30 minutes before breakfast	Placebo once daily in the morning, 30 minutes before breakfast	No restrictions regarding previous treatment Patients had to stop certain previous treatments before starting therapy (see next column under "Not permitted") or maintain a stable dosage (see next column under "Unchanged continuation")	Permitted: Bisacodyl and/or Fleet enema[h] Not permitted: All non-prescription or prescription laxatives/ enemas; herbal or natural agents for constipation; prokinetic agents; antiemetics; stool softeners; all narcotics; any specific treatment for IBS-C or CC (alone or in combination including lubiprostone, colchicine and misoprostol); drugs with pharmacological activity against 5-HT_4, 5-HT_{2b} or 5HT_3-receptors; anticholinergics and cholinomimetics;[b] bile acid sequestrants; oral and parenteral antibiotics;[c] antipsychotics;[f] oral anticoagulants;[i] antihistamines;[j] calcium channel blocker verapamil[g] Unchanged continuation: Fibre and bulk laxatives;[k] antidepressants[e]

a: As rescue medication (if at least 72 hours had elapsed since last bowel movement or symptoms were intolerable)
b: Inhaled ipratropium and tiotropium and intraocular cholinomimetics (e.g. pilocarpine) were permitted
c: Oral antibiotics up to 10 days were permitted as standard therapy
d: Oral administration of glucocorticoids for 10 days or an injection were permitted
e: This concurrent medication was only permitted if it had been given in stable dosage for 30 days prior to screening. Patients were not to alter the dose of the respective medication during the course of the study.
f: Paliperidone was permitted
g: All other calcium channel blockers were permitted
h: As rescue medication (if at least 72 hours had elapsed since last bowel movement)
i: Platelet aggregation inhibitors were permitted
j: Loratadine and fexofenadine were permitted, also intranasal and ocular application of antihistamines.
k: These concurrent drugs were only permitted if they had been given in stable dosage for 30 days prior to the first dose of the study medication. Patients were not to alter the dose of the respective medication during the course of the study.

CC: chronic constipation; HT: hydroxytryptamine; IBS-C: irritable bowel syndrome with constipation; NSAID: non-steroidal anti-inflammatory drugs; RCT: randomized controlled trial

Table 5: Summary of the information on medically advised dietary changes – RCT, direct comparison: linaclotide versus placebo

Study (treatment duration)	Medically advised dietary changes
MCP-103-302 (26 weeks)	▪ Study design: ▫ Dietary changes not permitted ▫ Patients had to agree before enrolment not to make any major alterations to their lifestyle that might affect the symptoms of IBS-C, e.g. dietary changes. ▪ Study results: ▫ No information on medically advised dietary changes in the study population (before or during the study)
LIN-MD-31 (12 weeks)	As in Study MCP-103-302
MCP-103-202 (12 weeks)	▪ Study design: ▫ No information on dietary advice and dietary changes ▫ No dietary advice or any subsequent dietary changes were planned. ▪ Study results: ▫ No information on medically advised dietary changes in the study population (before or during the study)
IBS-C: irritable bowel syndrome with constipation; RCT: randomized controlled trial	

Studies MCP-103-302, LIN-MD-31 and MCP-103-202 were randomized studies with linaclotide compared with placebo. Patients with IBS-C diagnosed according to Rome II (Study MCP-103-202) or modified Rome II criteria (Studies MCP-103-302 and LIN-MD-31) were enrolled. None of the 3 studies was suitable for the benefit assessment of linaclotide, in particular because linaclotide was not compared with the ACT of the G-BA in any of them. In addition, the treatment phase of Studies MCP-103-202 and LIN-MD-31 was too short.

The detailed reasons for excluding these studies are given below.

Appropriate comparator therapy

The ACT explicitly specified by the G-BA was medically advised dietary changes and the symptom-orientated treatment of constipation, bloating, cramping and pain. The ACT thus consisted of 2 components that had to be implemented in the studies for the assessment of added benefit. Diet-related measures were to be at the forefront of IBS treatment.

The company took the advice of the G-BA and explicitly agreed that the ACT was an individualized form of therapy in which each patient was to receive, where needed, an additional pharmacological treatment of symptoms alongside dietary changes.

Lack of medically advised dietary changes

In Sections 3.1.2 (Module 3) and 4.2.2 (Module 4) of the dossier, the company stated that dietary changes can be implicitly assumed to have always taken place in the patients observed

in the studies it included. Therefore, the conditions specified by the G-BA concerning the ACT were met.

The company justified its claim firstly by saying that patients in the studies it included had suffered from a diagnosed IBS-C for an average of 13 years and dietary changes would therefore have already been carried out. Secondly, the company stated that these studies had been performed in accordance with the guidelines of the European regulatory authorities (EMA) amongst others [9]. These requirements state that the lifestyle and diet-related measures must be stable before the study and must be maintained unchanged throughout its duration. The company also argued that according to the EMA, pharmacological options are not normally recommended unless dietary measures have proved ineffective. Furthermore, the company stated that the study participants had to have met the Rome criteria that were developed by the Rome Foundation and the American Gastroenterological Association (AGA) and that, according to the AGA, dietary changes should be the first step in the therapeutic treatment of IBS.

The company's assertion that the ACT component "medically advised dietary changes" was implemented in the studies submitted in its dossier, is neither supported on the basis of the studies included by the company, nor on the basis of its further arguments.

For instance, in 2 of the studies included by the company (MCP-103-302 and LIN-MD-31) the patients were expressly required not to change their previous diet. One of the inclusion criteria in each study was that, on enrolment in the study, patients had to agree to avoid any major alterations to their lifestyle that might affect the symptoms of IBS-C e.g. dietary changes. Hence, in these studies "medically advised dietary changes" were not possible.

The documents of the 3rd study (MCP-103-202) contain no information about dietary advice and changes. Hence, dietary advice and possible resulting changes were not planned in this study.

Moreover, it is not clear from the study documents of any of the 3 studies whether dietary advice and any resulting changes – if not during the study itself, then at least shortly before it started – took place. For example, prior dietary advice was not an inclusion criterion for the studies. It was also not necessary for the investigator to confirm that dietary changes were not necessary or not possible.

It must be noted that the study design of all 3 studies did not ensure that patients were enrolled who had modified their diet in accordance with medical advice. In addition, in the studies themselves, dietary changes were either explicitly excluded (2 studies) or not explicitly planned (1 study).

The company's arguments that long disease duration implies dietary changes and that the component "medically advised dietary changes" was therefore met, is not considered valid. It is admittedly conceivable that enrolled patients had in the past changed their diet one or more

times already. However, if dietary advice and possible resulting changes were not to take place during the study, then these had to have occurred at least relatively shortly before enrolment. A consultation with a doctor was to determine whether an individual needed to change his or her diet and whether this was possible. Such information must then be obvious from the study documents. Dietary advice or changes at an unspecified time in the disease history is not sufficient for the ACT to be considered implemented. Hence, it cannot be assumed (without this being explicitly documented) that dietary habits at the time of the study corresponded to the current needs of the patient. The company did not submit such information.

The company's arguments also relate solely to the discussion of the mean disease duration of the patients enrolled in Studies MCP-103-302 and LIN-MD-31 [10]. The company did not take into account the distribution of disease duration in the study populations (median disease duration: 9.3 years, 25% quantile: 3.4 years; 75% quantile: 19.7 years) [10].

From the analyses of the company it is thus obvious that patients were also included in these two studies whose IBS-C was diagnosed after they had signed the consent form. Hence, these patients could not have received any advice about dietary changes for IBS.

If one took the above arguments of the company a step further, then it might be assumed that further opportunities for dietary advice with resulting dietary changes would be possible for a group of patients with only a few years of the disease (25% quantile of disease duration: 3.4 years). Alternatively, one might also assume that dietary changes could have taken place shortly before the study started. However, such information cannot be gleaned from the study documents.

The company's argument that the studies were conducted according to the requirements of the EMA [9] – which stated that lifestyle and dietary measures were to be stabilized beforehand and were to be maintained for the duration of the study – is insufficient evidence of adequate dietary changes prior to the studies. Instead, the proper implementation of medically advised dietary changes as a component of the ACT needs to be demonstrated directly from the study documents. It can be derived from the EMA requirements that the recommendation not to undertake any dietary changes in the studies is not because pharmacological treatment options should only be used after the possibilities of dietary changes have been exhausted. The purpose of avoiding dietary changes in the study is rather to prevent distortion of the treatment effect (versus placebo). Furthermore, the approval documents on linaclotide explicitly state that the influence of dietary changes on the study results should be kept minimal in order to avoid distortion of the results [11]. However, such an approach is not expedient for the assessment of added benefit in comparison with an established (appropriate) comparator therapy.

The company's argument that since patients had to meet the Rome criteria in order to be enrolled in the study, it can therefore be assumed that dietary changes had been carried out

prior to pharmacological treatment, is also difficult to follow. The Rome criteria are a diagnostic instrument and contain no reference to dietary advice or changes [12,13].

Lack of/inadequate symptom-orientated treatment

The company states in Section 4.3.1.2, Module 4 of the dossier that patients had the opportunity to alleviate their IBS-C symptoms in the form of individual, symptom-orientated treatment. According to its statement, patients had access to required treatment of the various symptoms. Elsewhere in the dossier (e.g. Module 3, Section 3.1.1), the company stated that at least one drug was permitted for each symptom of IBS-C if ingestion of that drug had begun 30 days before starting the study and was continued in a stable dosage during the study.

The company supports its assertion with analyses of the concurrent medications used in the studies, which, in its view, were suitable for symptomatic treatment. In Table 4-12 (Module 4 of the dossier) the company names the classes of drugs (listed using ATC codes) that it considered as symptom-orientated treatment in the studies and then summarizes for each study the proportion of patients who had taken at least one of these drugs for individual symptom-orientated treatment (Table 4-13, Module 4). The data in Table 4-13 are based on an unpublished analysis that the company quotes at the appropriate point [14] (see also Appendix A of the dossier).

The company's view that all the patients observed in the study were able to have their symptoms individually treated cannot be substantiated for several reasons and therefore remains at least unclear.

In all 3 studies, on entry to the study patients were required to organize their previous and any new treatment in accordance with the conditions stated in the protocol. These requirements concerning the concurrent medication were the same in Studies MCP-103-302 and LIN-MD-31 and similar to these first-named studies in Study MCP-103-202.

Thus, patients had to discontinue their respective treatment if this was forbidden (see Table 4, column "Concurrent medication" under "Not permitted") or to continue it at a stable dosage (see column "Concurrent medication" of Table 4 under "Unchanged continuation"). Non-permitted medication included in particular the following classes of drugs that can be appropriate for the treatment of IBS-C symptoms: non-prescription or prescription laxatives/enemas and herbal or natural agents against constipation and (for Studies MCP-103-302 and LIN-MD-31) other symptoms of IBS-C; any specific treatment for IBS-C or anticholinergics, which include, e.g., the spasmolytic butylscopolamine. The unchanged continuation, for example of fibre and bulk laxatives, was permitted. However no change in their dosage or a first-time use, if necessary, was possible during the course of the study.

Only the treatment of the symptom "constipation" was explicitly permitted. Bisacodyl was used in Studies MCP-103-302 and LIN-MD-31 as rescue medication if at least 72 hours had elapsed since the last bowel movement, or the symptoms were intolerable. It can be assumed

that this protocol requirement ensured an adequate and individual care of patients who needed treatment for constipation.

In Study MCP-103-202, the Fleet enema was also permitted as rescue medication in addition to bisacodyl, but only if at least 72 hours had elapsed since the last bowel movement. It is not clear from the study documents whether or when the rescue medication was used for patients for whom the symptoms were intolerable. For this reason, it is also unclear whether patients were able to react in an adequately flexible way to constipation symptoms that were intolerable for them.

In contrast to the treatment of constipation, no (rescue) medication was expressly defined or permitted in the study protocols for all other IBS-C symptoms (abdominal bloating, cramping and pain).

In view of the extensive restrictions specified at the time, individual treatment according to patient needs appears impossible. Furthermore, from the approval documents of the EMA, approx. 18% of patients of the approval studies MCP-103-302 and LIN-MD-31 had to discontinue their previous treatment between screening and the pretreatment phase [11]. This problem was not discussed by the company in the dossier.

In addition, the information presented by the company in the dossier (Module 4, Tables 4-12 and 4-13), together with the analyses on which this was based [14] were not comprehensible, showed several deficiencies and cannot be used.

As an example, the company's analyses [14] contain classes of drugs whose use was not permitted according to the study protocol (including non-steroidal anti-inflammatory drugs [NSAID] for pain due to IBS-C in Studies MCP-103-302 and LIN-MD-31). In Module 4 of the dossier, the company stated that in Study MCP-103-202, NSAID were not to be taken for IBS-C pain, but this was incomprehensible in comparison with the study protocol. It is equally difficult to follow that the company took account of osmotically acting laxatives when calculating the concurrent medication. On the one hand, it did not name them in the characteristics of the interventions in Table 4-12 (Module 4) and on the other, the use of these drugs during the course of the study was also largely not permitted. Although it is conceivable that non-permitted drugs were taken in spite of study requirements, it can be assumed that patients tended to receive the non-permitted drugs to a lesser degree than if these had been permitted in the studies. An example of a further deficiency is that in the case of selective serotonin reuptake inhibitors and tricyclic antidepressants the company did not differentiate whether these were used for the symptomatic treatment of IBS-C. These deficiencies, mentioned only as examples, lead to the assumption that the data in Table 4-13 tend to represent an overestimate of the proportion of patients who used at least one drug of the individual, symptom-orientated treatment.

Taken as a whole, the data given by the company in Module 4 of the dossier on drugs for symptom-orientated treatment and the proportion of patients who received symptom-orientated treatment were incomprehensible in comparison with the study reports. It remains at least unclear whether a symptom-orientated treatment of every IBS-C symptom was possible in the studies and could be used in an adequately flexible manner according to individual patient needs.

Treatment duration too short

The company considered that a minimum study duration of 12 weeks was adequate for assessing the added benefit of linaclotide.

In its arguments, the company referred to the EMA [9] and stated that the EMA recommended a study duration of at least 4 weeks for short-term treatment of IBS symptoms and that studies lasting 6 months would be required for evidence of a persistent effect. To record withdrawal effects, a blinded withdrawal phase was to follow an initial double-blind phase. In summary, the company stated that the study periods recommended by the EMA were taken into account in the studies included by the company.

Elsewhere in its dossier, the company assumed that linaclotide "had been approved for long-term therapy" (see, for example, Module 3, Section 3.1.1 of the dossier).

The statement that linaclotide is indicated for long-term treatment is understandable - unlike the company's assessment that a study duration of 12 weeks is sufficient for the benefit assessment of linaclotide.

As stated by the company, the EMA essentially draws a distinction between short-term and long-term treatment of IBS-C. However, corresponding to the respective aims of these two types of treatment, the EMA not only recommends different study durations, but also different study designs. This was not considered by the company. Short-term treatment is regarded by the EMA as the treatment of an acute exacerbation of symptoms. Several aspects must be investigated in studies on such short-term treatment, such as repeated use or withdrawal effects [9]. Treatment of an acute exacerbation of symptoms can admittedly also take place within long-term treatment, but repeated use of such treatment must be examined. However this is not the research question of the present report, because linaclotide is indicated for long-term treatment. It is clear from the European Public Assessment Report of EMA [15] that linaclotide is intended for long-term, continuous treatment. The EMA considered only one study (MCP-103-302) as a pivotal approval study [15]. The justification by the company of a minimum duration of 12 weeks is therefore not sustainable.

Particularly in view of the fluctuating course of the disease and in agreement with the EMA [9], a minimum study duration of 6 months (24 weeks) was considered necessary for this research question in order to ensure an adequately long duration of treatment and observation in the studies.

The treatment phases of Studies MCP-103-202 and LIN-MD-31 were 12 weeks long and were thus unsuitable for assessing the added benefit of linaclotide.

Summary

Table 6 shows a summary of the reasons for exclusion.

Table 6: Summary of the reasons for exclusion of the studies – RCT, direct comparison: linaclotide versus placebo

Study (Treatment duration)	Reasons for exclusion					
	Appropriate comparator therapy					Treatment duration too short
		Lack of/inadequate symptom-oriented treatment				
	Lack of medically advised dietary changes	Constipation	Bloating	Cramping	Pain	
MCP-103-302 (26 weeks)	●		○	○	○	
LIN-MD-31 (12 weeks)	●		○	○	○	●
MCP-103-202 (12 weeks)	●	○	○	○	○	●
●: Reason for exclusion; ○: Lack of clarity						

The studies included by the company were not suitable for addressing the present research question. The ACT specified by the G-BA consisted of medically advised dietary changes and symptom-orientated treatment (constipation, bloating, cramping, pain). The company explicitly stated its agreement with the ACT. Despite this, it used studies to assess the added benefit of linaclotide in which medically advised dietary changes were not implemented. In Studies MCP-103-302 and LIN-MD-31, such changes were expressly forbidden. In Study MCP-103-202, they were not planned. None of the study documents of any of the studies show whether such changes were not necessary or not possible, or had taken place at least shortly before enrolment in the study.

It was unclear whether symptom-orientated treatment for bloating, cramping and pain was possible in any of the 3 studies. In the case of Study MCP-103-202, it was also unclear whether symptom-orientated treatment for constipation was adequately flexible.

In addition, the 12-week treatment phases of Studies MCP-103-202 and LIN-MD-31 were too short for assessing the added benefit of linaclotide.

Hence, none of the studies were suitable for the assessment of the added benefit of linaclotide compared with the ACT of the G-BA.

Further information on the results of information retrieval and the study pool derived from it can be found in Module 4, Section 4.3.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment. Further information on study design and study populations can be found in Module 4, Section 4.3.1.2.1 of the dossier and in Section 2.7.2.3.2 of the full dossier assessment.

2.4 Results on added benefit

The company did not submit any assessment of linaclotide in comparison with the ACT of the G-BA in its dossier. The study pool contained no study that was suitable for comparing linaclotide with medically advised dietary changes as well as symptom-orientated treatment of constipation, bloating, cramping and pain. Since no relevant studies were submitted for the benefit assessment, there is no proof of added benefit of linaclotide over the ACT specified by the G-BA.

This result deviates from that of the company, which derived an added benefit for linaclotide from the studies it included.

Further information on the results of added benefit can be found in Module 4, Section 4.3.1.3 of the dossier and in Section 2.7.2.4 of the full dossier assessment.

2.5 Extent and probability of the added benefit

Table 7 shows the results of the assessment of added benefit of linaclotide in comparison with the ACT.

Table 7: Extent and probability of added benefit of linaclotide

Therapeutic indication	**Appropriate comparator therapy of the G-BA**	**Extent and probability of the added benefit**
Symptomatic treatment of moderate to severe irritable bowel syndrome with constipation in adults	Medically advised dietary changes and symptom-orientated treatment (constipation, bloating, cramping, pain)	Added benefit not proven
G-BA: Federal Joint Committee		

This assessment deviates from that of the company, which derived proof of a considerable added benefit for linaclotide.

The decision regarding added benefit is made by the G-BA.

2.6 List of included studies

Since, in its assessment, the company submitted no relevant studies for determining the added benefit of linaclotide in comparison with the ACT of the G-BA, this section is not applicable.

References for English extract

Please see full dossier assessment for full reference list.

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