25 September 2014
EMA/CHMP/266108/2014
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on ' Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome' (CPMP/EWP/785/97 Rev. 1)'

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	European Society of Neurogastroenterology & Motility (ESNM); In cooperation with United European Gastroenterology (UEG)
2	Swissmedic
3	Sanofi

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	1. The patient population to be selected has been changed from Rome II to Rome III criteria. This change is logical and in agreement with evolving concepts of IBS within the scientific community (1). The patient population most likely overlaps considerably with the one according to the Rome II definition (2). 2. The recommendation on primary endpoints to be used in confirmatory trials has been changed from a co-primary endpoint of global assessment and pain, to the evaluation of stool related abnormalities and pain. Page 10, line 291: “The global assessment of all symptoms, as intended in the “adequate relief” or other similar endpoint has the obvious disadvantage that it partly also covers the evaluation of abdominal pain and discomfort at the same time.” Page 10, line 312: “For other subtypes of IBS, and for “global” development programmes intending to treat two or more subtypes, the use of the global assessment is, however, still recommended.” With this statement, the agency abandons the previously supported co-primary endpoint of global assessment of IBS symptom control (3). In support of this change, the document states that “two main features of IBS are the abdominal pain and the associated defecation abnormalities”. While it is true that these two aspects are dominant in the current	1. No further comment necessary. The GL opens the inclusion of patients to further changes of the Rome criteria. 2. The draft GL was not sufficiently clear on whether to use a co-primary or a combined evaluation of the two endpoints pain and stool abnormalities. This has now been corrected, and, in full compliance with the proposals of the FDA, a composite endpoint is recommended. The “global” evaluation, however, is not lost, as suggested by the comments, but it is given as the main secondary endpoint. Furthermore, the GL states that since the currently proposed composite endpoint is not fully validated, the secondary endpoints will be required to be supportive of the primary endpoints. Therefore, the previous concept of including a more complete evaluation of all symptoms has not been abandoned, but only the weight of the different evaluations has been adjusted. For global developments, the value of not having to develop separate protocols, or statistical analysis plans for the same trial data appears to be obvious with regard to facilitating the further drug development in the field, let alone the unsolved problem of potential unaddressed multiplicity issues.

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	definitions of IBS according to the Rome III consensus (1), the clinical and symptomatic picture of IBS is broader, and a global assessment comes closer to clinical practice. Hence, with the decision to abandon the endpoint reflecting the patient's global assessment of symptoms, treatment evaluation loses an endpoint which captures the total complexity of IBS symptoms, which is in line with clinical practice, and which distinguishes evaluation of IBS outcomes from other functional bowel disorders like chronic functional constipation and functional bloating: a) An adequate measure of treatment benefit should capture the most significant signs and symptoms of IBS. In a recent study evaluating the IBS physical experience based on a conceptual framework, it has been demonstrated that patients perceive their IBS symptoms as multi-dimensional, comprising two abdominal symptom domains (IBS pain and IBS gas/bloating), two defecatory domains (IBS-diarrhea and IBS-constipation) and one IBS extra-intestinal symptom domain (4). It is unlikely that separate assessment of pain intensity and of stool pattern captures the complexity of this symptom constellation. Especially symptoms of bloating and gas, which are consistently ranked by patients as one of the most bothersome aspects of IBS (5, 6), are explicitly not addressed when using both pain and stool pattern assessments as primary outcome variables. In contrast, it remains conceivable and even likely that the previous	a) The comments regarding the most important symptom domains are noted, and the concerns are understood. However, it is clear from what is included in the given reference, that 2 of four of the symptom domains (assuming that constipation and diarrhoea domains are mutually exclusive, at least for IBS-D and IBS-C) are covered by the new composite endpoint. The "discomfort-related" domain as given in the reference (4) will be covered by the secondary endpoints requesting a "numerical and responder analysis of abdominal discomfort, straining, and bloating". Moreover, the evaluation of the cross-cultural understanding of the term "bloating" and associated terms of gas-related complaints, has been identified by a Rome Committee Working group to be especially problematic. Therefore, the designation of this part of the symptom domain as primary endpoint can currently not be recommended (See: Sperber A et al: Final Report Rome Foundation Working Team on Conducting Multinational, Cross-cultural Research in the Functional GI Disorders and Fostering Multinational Research Networks; available at

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	binary endpoints (adequate or satisfactory relief) and the global assessment endpoint, as previously adopted by EMA, integrate multiple aspects of the IBS symptom domain as experienced by the patient. In support of this notion, in the linaclotide IBS-C program, the only one where different endpoints were directly compared, the assessment of overall symptom relief generated the lowest placebo responses while maintaining a solid therapeutic margin over placebo (7-10). The largest placebo effects and smallest margins over placebo were observed for the pain or pain/discomfort endpoints (11). b) The attractiveness of both the global relief of IBS endpoint and the binary endpoints is their closeness to what clinicians do in clinical practice. Communication with patients in terms of symptom relief addresses a broad impression of relief or lack of relief, and only secondarily will home in on individual symptom patterns and details like number of stools and their consistency. In fact, although regulatory views drove the perception that binary endpoints are no longer acceptable and lack specificity, all analyses conducted to date have confirmed their adequate performance in comparison to other endpoints (11-14). c) Another matter of concern is the loss of distinction between functional disorder diagnostic categories as a result of the change in endpoints. The recommended stool pattern endpoint for IBS-C, focusing on CSBM evaluation, is very similar to the	http://www.romecriteria.org/committees/WorkingTeamFinalReport_Jan%202014.pdf; accessed 2014-04-01. It is true that – from the separate evaluation of the two FDA endpoints, and the separate evaluation of the two EMA endpoints – the IBS-C degree of relief responder rates yielded the lowest placebo response. However, these low placebo response rates were also achieved when a combined evaluation of the FDA endpoints was performed (See Figure 1 of the reference 11). Assuming that an endpoint with the lowest placebo response rate would most accurately reflect a true picture of efficacy of a compound within a therapeutic trial, the choice of a composite of pain and bowel abnormalities – based on the linaclotide data – appears to be similarly appropriate compared to the previous IBS-C degree of relief endpoint. b) As remarked above, a complete abandonment of the global relief endpoint is not intended. However, the needs of a quick and still comprehensive evaluation of the well-being of patients in clinical practice cannot per se determine the methods for the evaluation of outcomes in clinical trials. Usually a more broad and diverse picture is needed to fully assess the benefits of a particular treatment. The proposed composition of primary and secondary endpoints is considered to give an overall most complete picture of the disease course. c) The comment is noted and considered to be well taken. However, in view of the results of the latest trial with the most “pure” laxative (PEG 3350), it is considered that the distinction between agents acting on the bowel habits only, and acting on a more comprehensive set of endpoints as requested for IBS, can clearly be made with the proposed

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	treatment efficacy evaluation approach for chronic constipation, thereby further obscuring the distinction between both conditions (11, 15, 16). It is clear from the large placebo response that the 30% improvement cut-off level for the pain relief endpoint is a relatively low hurdle. Any drug suitable for the treatment of chronic constipation is therefore likely to meet the endpoints for IBS-C (and vice versa). The difference is relevant for two reasons: 1) although a grey area exists clinically, clinicians do distinguish both entities and especially 2) reimbursement attitudes towards new pharmacological agents differ strongly when considering chronic constipation versus IBS with constipation. For all these reasons, the agency should consider "upgrading" the subjects global assessment of efficacy from a marginal position (only applicable in IBS-mixed, IBS-unsubtyped, or mixed populations) to a key endpoint, as has been the case for EMA evaluations to date.	composite (See: Chapman RW et al: Randomized Clinical Trial: Macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. The Am. J Gastroenterol 2013; 108: 1509-1515). In Summary, a change in the proposed composite primary endpoint for IBS-C and IBS-D is not agreed with.
2	Statement about measurement of stool–calprotectin for the differentiation between an inflammatory disease and irritable bowel disease is missing and can be recommended based on evidence of scientific literature.	Agreed. Calprotectin has been included as a potential laboratory parameter to be tested for exclusion of IBD.
3	Sanofi welcomes the revision of the 2003 points to consider and appreciates that this revision brings consistency with the existing 2012 US guideline.	No comment necessary.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
77	2	**Comment:** To make text more precise **Proposed change:** Add: "...treating the symptoms with the rationale of modulating *the diversity of the gut microbiota*, the intestinal motility....."	Not agreed. There may be future developments aiming at modulation of the diversity of the gut microbiota, however, currently such a medication for the treatment of IBS does not exist. Because the paragraph describes cursorily the current armamentarium, this is not included.
149-151	3	**Comment**: It is acknowledged that a medicinal product developed for IBS should target both main features of the disease. However we would appreciate a clarification whether, based on mechanism of action of the study drug, a claim on only one feature of the IBS (i.e. either pain or abnormal defecation) would also be acceptable.	Agreed. From the current European regulatory view, however, it is not considered appropriate to create "partial claims" on aspects of IBS. Clarification on this has been included.
157	2	**Comment:** Text correction **Proposed change:** Instead As part to *as part*	Agreed. Typographical error eliminated.
162	2	**Comment:** Pain scale example can be proposed. **Proposed change:** Add:"...(depending on the scale *e.g. (VAS 0-10)* to be used for the final evaluation of pain)....."	Not agreed. The clear suggestion of which scale to use for the pain endpoint is included in chapter 5.5. Because the paragraph here says that the endpoint determines the way of classifying the pain during the selection of patients, no addition is needed.
171	1	**Comment:** - The document recommends testing for lactose	Generally agreed. The paragraphs dealing with the necessary

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		intolerance prior to inclusion in a trial. This is probably over-cautious and redundant: lactose tolerance testing uses quantities of lactose that may not be reached in daily life. For this reason the test generates many false positive. Response to lactose-free diet seems sufficient as a criterion (17-20). - Procto-/sigmoidoscopy is not useful and should not be mandatory for young people, especially in IBS with constipation, and in all young people without a history of blood in the stools. Propose to use the recommendation only in IBS-D or when there is blood in the stools (18-20). - The value of abdominal ultrasound in IBS-like symptoms is not supported by the available literature, and adding it to an IBS study work-up will only increase the study burden. I propose to skip this as a recommended test (18-20). It is true that the ECCO guideline gives some support to using ultrasound to distinguish IBD from IBS, but this is a guideline for clinical application, rather than IBS trial design (21).	exclusion criteria have been revised. Lactose intolerance testing is now based on history taking of the historical response to a lactose free diet. The need for procto-/sigmoidoscopy has been deleted. Abdominal US has been deleted.
177	1	**Comment:** - This sentence is confusing, as it seems to exclude anyone with a family history of colorectal cancer; for instance also a 25-year old IBS patient with a grandfather diagnosed with colorectal cancer at the age of 82? It might be more appropriate to rephrase to 1) exclusion of patients with familial colorectal cancer syndromes (Lynch, FAP), and 2) exclusion of colorectal cancer in all patients, according to the national screening guidelines (or international if no national guideline exists) (18-20).	Agreed. Section has been revised. The GL is now referring to the screening guidelines.

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188	1	**Comment:** - The agency could consider the recommendation that only patients on a single antidepressant, on a stable dose, are included. This should minimize interactions between psychotropics and with the investigational drug.	Agreed. Single antidepressant has been included.
202 – 208	1	**Comment:** "It is therefore recommended to conduct – preferably after the human tolerability and early pharmacokinetic studies have been finalized – pharmacodynamic studies in healthy volunteers and/or in suitable IBS-patients. These studies should investigate the effects of a candidate compound on gastrointestinal motility and on intestinal sensitivity. ….. The potential influence of new candidate compounds on (the perception) of abdominal pain should be investigated by studies evaluating rectal distension". - The intent to provide scientific rationale for drugs under development for IBS is important. For drugs affecting motility, test which are technically easy to conduct with appropriate predictive value for symptom control outcomes are available (transit studies, stool consistency charts) (22). For visceral sensitivity testing, this is much more problematic. Current tests used for studying the impact of drugs on visceral (hyper) sensitivity have shown poor to absent translatability to clinical outcomes, probably because they are influenced by psychological factors such as test-specific anxiety and anticipation (23). Hence, rigorous adherence to sensitivity testing in man or in patients may eliminate potentially effective compounds at an early stage,	Not agreed. It is acknowledged that the conduct of such trials, and the interpretation of the results are not without problems. However, the non-availability of pharmacodynamic studies in a stricter sense would be seen as a deficiency (and has been interpreted as such in the linaclotide dossier). In order to take account of the concerns, a cautionary approach to these studies has been included in addition.

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		due to the deficiencies of the tests. In that respect, it is worthwhile to point out that linaclotide, which has robust effects on visceral hypersensitivity models in animals and on abdominal pain in patients, was never tested in a human visceral sensitivity paradigm (7-9, 24).	
238 and onwards	1	**Comment:** - This section would benefit from clearer guidelines. The evaluation of the tegaserod retreatment trials already generated a lot of uncertainty. If this is not clarified, the (by itself highly valuable) short repeated treatment concept is likely to never be tested. - One point of clarification regards treatment outcome expectancies. In the tegaserod retreatment trial, responder rate for the second cycle was similar to the first cycle (25). It was argued that, as only responders to the first cycle were randomized, a much higher success rate of the second cycle was to be expected. This type of details related to retreatment trial design would benefit from clarification in the document.	Agreed in Principle. However, the almost complete missing of regulatory experience with the planning or evaluation of such studies does not allow to give more detailed recommendations at this time. The listing of the potential problems with such designs and the recommendation to seek Scientific Advice is considered sufficient. With regard to the expectations to the repeated treatment cycle, a more clear wording was introduced.
324 and 328	3	**Comment:** The introduction of “at the same time” for evaluation of abdominal pain score and abdominal defecation is confusing. The understanding is that a responder should be based on improvement of both symptoms and not that the two symptoms should be improved at the exact same time. **Proposed change:** Please delete “at the same time”.	Agreed. The term “at the same time” has been deleted. The inconsistencies regarding the terms “co-primary” and “composite” endpoint have been clarified.

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330	3	**Comment:** The responder definition is given for IBS-M, IBS-unsubtyped and mixed IBS-C and IBS-D populations. However, no definition of the IBS-C and IBS-D is provided in section 4 and it is not clear how IBS-C and IBS-D populations differ with IBS-M population. **Proposed change:** Please add a definition of IBS-C and IBS-D in section 4 that should also differentiate this population from IBD-M.	Not agreed. Chapter 4 includes the definition of the subgrouping according to the Rome III criteria. No need for amendment identified.
409	2	**Comment:** Precise definition of children age **Proposed change:** Add: "...to be conducted in children *(age≤18 years)* in order to prove...."	Agreed. Age ranges have been given as examples.
419	3	**Comment:** The meaning of "a third arm with a waiting list can be included into studies in children" is unclear. Please clarify.	Agreed. Clarification has been included.
461	2	**Comment:** Text correction **Proposed change:** Change "preponderance" to "predominance"	Not agreed. The Oxford English Dictionary given the following explanation for preponderance: "The quality or fact of being greater in number, quantity, or importance: *the preponderance of women among older people"* – which is exactly what is intended to be expressed.

References stakeholder 1

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