15 February 2011
EMA/131448/2011
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on the evaluation of drugs for the treatment of Gastro-oesophageal reflux disease' (EMEA/CHMP/EWP/342691/2009)

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

Stakeholder no.	Name of organisation or individual
1	EISAI
2	Montreal Consensus Group
3	Movetis NV
4	XenoPort, Incorporated
5	Paediatric Consensus Group

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1.	Eisai fully endorses the definition and classification of GERD and the possible targets of treatment. We also support the overall requirements and recommendations for clinical study design when evaluating the efficacy and safety of a new drug in adults, children and adolescents with GERD. However we have some comments on the necessity to describe the GERD symptoms, the importance of the documentation of drug-drug interactions, the primary analysis of symptoms and duration of safety data for maintenance therapy, and the need of additional specific guideline related to GERD in the paediatric population. We also wanted to show our support to the recommendation of the Los Angeles (LA) classification for grading the disease, which does not prevent the use of other classification when justified on a case by case basis. The clarification on the optional use of impedance monitoring and/or pH monitoring in phase III studies is also welcome. Some suggestions have been added to improve the readability of the text.	N/A
4	We recommend the term "acid regurgitation" be replaced by "regurgitation" as it has been shown that non-acidic reflux is associated with GERD symptoms. (Vela, et al. Gastroenterology 2001; 120;199). This is particularly relevant in discussion of developing therapies in partial responders to PPIs.	Partially agreed. The descriptions have been changed for the PPI partial responder population description.
4	Further, as indicated in our comments on Lines 204-207 and Lines 346-349, we recommend the global use of "heartburn with or without regurgitation" rather than "heartburn and acid regurgitation" through-out the Guideline.	Not agreed. The purpose of requesting both symptoms has clearly been described. No argument has been brought forward to disfavour the intention to increase diagnostic accuracy.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
lines 62 and 94	1	**Comments:** For better readability the introduction could be divided into 2 sections, one general (definition of GERD) and one specific on GERD in children (before the last 3 paragraphs of Introduction). Proposed change (if any): *"1.1. Definition of GERD" (before line 62)* *"1.2. GERD in children" (before line 94)*	Agree to this formal comment. Changes have been implemented.
line 111	1	*"Children with secondary GERD (i.e. associated with underlying disorders such as neurodevelopmental delay or congenital* Comments: A typo (missing bracket) should be corrected. **Proposed change (if any):** *"Children with secondary GERD (i.e. associated with underlying disorders such as neurodevelopmental delay or congenital abnormalities**)** form a separate sub-group of the paediatric GERD population […]*	Agree to this formal comment. Changes have been implemented.
line 239-240	1	*"Because the typical GERD symptoms heartburn and acid regurgitation translate poorly into several languages, the symptoms have to be defined with a description."* **Comments:** Eisai does not agree that these terms translate poorly and that the description is always necessary. This sentence should be deleted.	Not agreed. The difficulties with the translations and with the meaning of the term "heartburn" are described in the Montreal consensus paper.

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		Proposed change: ~~*"Because the typical GERD symptoms heartburn and acid regurgitation translate poorly into several languages, the symptoms have to be defined with a description."*~~	
lines 168-169, 172-173 line 337 lines 441-442	1	*"Reflux oesophagitis has to be diagnosed by endoscopy, using the best validated classification, which is, at the moment, the Los Angeles classification:[…].* *The use of other classifications is no longer recommended, but may be justified on a case by case basis."* *"For endoscopic grading, the Los Angeles classification should be used (see 4.1.1. and 6.2.2.)."* *"The use of the "Los Angeles classification" is recommended for inclusion or exclusion of patients and as efficacy criterion in clinical trials for erosive disease (see 4.1)."* **Comments:** Eisai strongly supports the recommendation of the LA classification for grading the disease for diagnosis, inclusion and exclusion into clinical trials and for efficacy criteria. We also support the use of other classification when justified on a case by case basis.	Comment in agreement with draft guideline. No further comment, nor changes necessary.
line 257-358	1	*"The selection of "typical" GERD patients should be based on the evaluation of overall severity (or "bothersomeness")."* **Comments:** The word "bothersomeness" does not translate well into all EU languages and is redundant in this sentence.It	Agreed. Generally, the draft guideline uses "bothersomeness" and "troublesomeness" interachangeably. This is changed to uniformly use "troublesomeness" throughout.

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		should be deleted. **Proposed change:** *"The selection of "typical" GERD patients should be based on the evaluation of overall severity ~~(or "bothersomeness").~~"*	
Line 343	1	*"…previously diagnosed reflux oesophagitis should be re-checked for healing at the time of inlcusion, and …"* **Comment:** Typo for 'inclusion'. **Proposed change:** *"…previously diagnosed reflux oesophagitis should be re-checked for healing at the time of ~~inclusion~~ **inclusion**, and …"*	Agreed. Typo is corrected.
Line 350	1	*"Both symptoms regarded as being "typical" of GERD, acid regurgitation and heartburn, have displayed a relatively weak performance in the stringent sense of diagnostic accuracy."* **Comment:** This sentence does not read well. **Proposed change** Both ~~symptoms regarded as being "typical" of GERD,~~ acid regurgitation and heartburn, **symptoms regarded as being "typical" of GERD**, have displayed a relatively weak performance in the stringent sense of diagnostic accuracy.	Agreed. Changes implemented.
lines 402-403 lines 414-415	1	*"pH monitoring may be used as inclusion criterion for clinical trials but is not regarded to be compulsory due to high diagnostic burden on the patients."* *"An inclusion of the technique [impedance monitoring] for inclusion or assessment of treatment response in*	No further comment.

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		phase III trials is not recommended for reasons of impracticability." **Comments:** Eisai fully endorses that impedance monitoring and/or pH monitoring is not recommended in phase III studies.	
line 514	1	***"**However, due to the high prevalence of the disease, increased requirements for the documentation of drug-drug interactions might apply.**"* **Comments:** Drug-drug interactions are important as they state but should be considered on a case by case basis only, ie not with class labelling. **Proposed change :** ***"**~~However, d~~**D**ue to the high prevalence of the disease **and the increased probability that patients will be taking concomitant medications, careful evaluation of potential** ~~increased requirements for the documentation of~~ drug-drug interactions ~~might apply~~ **should be conducted**. **However, this should be dealt on a case by case basis taking into consideration the pharmacological characteristics of the drug product."***	Partly agreed. The first part of the sentence is implemented. However, the purpose of the sentence was to express a higher general need for DDI studies because of the high prevalence of the disease (and, hence, the high potential for different concomitant medications). The fact that DDI studies are always a case by case decision does not have to be stated here. The following sentences already included describe the necessary approach to a sufficient extent.
line 487, line 552	1	*"The primary analysis of efficacy should be established on a responder analysis based on the evaluation of the two cardinal symptoms of reflux disease, heartburn and acid regurgitation (See also 6.2.3)…"* **Comments:** Firstly it is unclear if this refers to responders based on symptom frequency and/or responders based on symptom severity (eg, 75% of the all weeks and/or at least 2 –point decrease of heartburn severity scores based on a 4-point Likert scale). Secondly, it is unclear	Not agreed. However, to account for the question whether frequency or severity (or both) should be evaluated, a sentence is included to state that ideally frequency and severity should be evaluated.

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		if this refers to responders for the primary symptom (ie, heartburn) or responders for both cardinal symptoms (ie, heartburn and regurgitation). Thirdly, it is difficult to identify diary-based responder endpoints that are clinically meaningful, sensitive and reproducible from studies to studies since there are inherent variations in baseline disease characteristics as well as patient reported treatment-related outcomes. These variations also present challenges in adequately predict sample sizes. Therefore Eisai believes that although responder analyses provide clinically meaningful information as related to efficacy, they should be considered as optional in defining the primary analysis. The decision of the primary analysis should be based on the study design (eg, treatment duration, effect size, comparator(s) and the validated scales used for assessing symptoms). **Proposed change:** *"The primary analysis of efficacy should be established on **an analysis of an endpoint that is clinically meaningful, sensitive and reproducible based on the study design. Where appropriate,** responder analysis based on the evaluation of the two cardinal symptoms of reflux disease, heartburn and acid regurgitation, **should be considered** (See also 6.2.3)"*	
line 563	1	*"At least one year comparative treatment data are, however, necessary to appropriately document safety (see section 8.)."* **Comments:** Eisai would endorse this statement if this statement is	Agreed. The 1 year safety data requirement applies to new chemical entities only.

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		specific to a new drug product for which no prior human safety data are available. One year comparative treatment data should not be mandatory for a drug product that contains the same drug substance as in a marketed drug for which there are substantial safety data , **Proposed changes:** *"..At least one year comparative treatment data are, however, necessary to appropriately document safety* ***for a drug*** **for which no prior human safety data are available** *(see section 8)"*	
line 635	1	*"Studies in the paediatric population are encouraged. The need to develop appropriate formulas for children is emphasized."* **Comments:** It seems that 'formulations' would be more appropriate than 'formulas'. **Proposed change:** *Studies in the paediatric population are encouraged. The need to develop appropriate* ~~*formulas*~~ ***formulations*** *for children is emphasized."*	Agreed. Language correction implemented.
line 639	1	*'As there are important differences between GERD in infants and in older children and adolescents and due to different pharmaceutical forms, drug development in these 2 populations will be addressed separately.'* **Comments:** Eisai endorses that drug development in infants and older children should be addressed separately. To that purpose more recommendations in clinical studies, including age-appropriate primary objectives, is needed in the paediatric populations and a specific guideline dealing with infants would be very helpful. For that matter we would like also to draw your	Not agreed. The former mandate of the EWP clearly requested the inclusion of a paediatric part in an overall guideline.

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		attention to the FDA advisory committee meeting, planned for November 2010 (date to be determined) , which should discuss this issue and may bring new insight to the utility of PPIs in the pediatric populations - which is intended to focus on the less than 12 month old group. **Proposed change:** *'As there are important differences between GERD in infants and in older children and adolescents and due to different pharmaceutical forms, drug development in these 2 populations will be addressed separately.* ***Recommendations on the drug development in infants will be dealt in a specific guideline****.'*	
Item 4.1.2: line 201	2	**Comments:** The concept of double dose needs to be clarified further. Double dose can mean twice the regular dose given at one time e.g. omeprazole 40 mg or could mean two doses of regular strength given in split doses (before breakfast and before dinner). As the regulatory approval differs for different drugs and indications, this should be clarified	A clarification is not deemed necessary. Lines 196-198 explain why – as lines 199 – 202 propose – the choice is up to the company, whether a "standard dose" or a "double dose" is chosen. It is not considered necessary to exactly describe the timing of the dose, as the proposal to double the dose is expert opinion only, no matter whether a single dose (usually in the morning) is doubled, or if the standard dose is given 2 times daily.
Item 4.1.2 Line 203-205:	2	**Comments:** While heartburn and regurgitation are cardinal symptoms, it is possible that heartburn may resolve with acid inhibition and newer drugs that target sphincter relaxation have only the symptom of regurgitation to address. This needs to be considered in the regulatory guidance for these drugs because this may be a significant unmet need in patients treated with acid inhibitory agents	Agreed. Whereas the available data suggest that "sensitivity" for the "true" diagnosis of GERD patients could be increased when requiring both, heartburn and regurgitation, this is indeed unclear in the case of a population of partial responders to PPI therapy. Therefore, it is agreed that – in the case of this special patient population – either of the two (or both) symptoms should be allowed to be present.
Item 6.1.2 Lines 373-	2	**Comments:** It has been shown that almost one-third of patients	Agreed.

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388		with erosive esophagitis will report mild dysphagia when questioned and presumably if they are asked for this symptom on a questionnaire. It may be wise to qualify the dysphagia symptom further. Troublesome dysphagia would be an alarm symptom while mid dysphagia would not.	"Severe dysphagia" is added as alarm symptom. Mild and moderate dysphagia are mentioned as possible additional symptoms.
6.2.1.1: Lines 392-5	2	**Comments:** It would be important to include wireless 48 hour pH testing as an acceptable alternative method of measuring pH as it has now been satisfactorily validated.	Agreed. Appropriate changes have been implemented (Chapter 6.2.).
6.2.14.	2	**Comments:** The Bilitec device is no longer available. The Italian manufacturer went out of business and therefore this device is of questionable use. It may be mentioned in case it ever comes back but it would need re-validation	Agree. See changes in 6.2.1.4.
6.3.3.1	2	Acute treatment Line 551: Rebound is a phenomenon described with acid inhibition. The guidance should consider other agents such as motility agents. Is it intended that they should evaluate patients for rebound as well?	Agreed. Clarification included. However, rebound should also be investigated with agents other than acid suppressants.
6.3.3.1: Line 574	2	The group agreed with the conservative and careful approach of the agency to on demand therapy and the need for a study that documents the lack of development of erosive esophagitis.	Comments welcomed. No changes necessary.
Line 191	3	**Comment:** Does the classification imply that you first chose for NERD vs. EE, and subsequently target the PPI refractory patients within either NERD or EE? Or does it include all PPI refractory patients, regardless of the	This is a clarification request only. From the further wording of the draft guideline, and the described necessity to document the further fate of (remaining) oesophagitis in partial PPI responders/refractory patients, it becomes clear that the partial responder/refractory PPI population can be recruited

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		endoscopic status?	regardless of endoscopic status.
Line 346-349	3	**Comment:** Initial diagnosis of GORD is commonly based on symptoms (heartburn/regurgitation) only. There is strong support that each symptom is equally and independently typical of GORD [1], but their sensitivity is considered to be poor compared to physiological assessments such as pH-metry [2]. Currently, there still is a lack of gold standard for the diagnosis of GORD and as such, it is difficult to assess the overall sensitivity of both symptoms. This lead CHMP to propose that the presence of both typical symptoms (heartburn and regurgitation) has to be required for inclusion of subjects with GORD in clinical trials (official (draft) EMA guidelines [3]), as they believe that this would increase the diagnostic accuracy. Importantly, when focussing on a subpopulation of subjects with GORD, i.e. those that experience symptoms despite PPI treatment, the symptom profile might have changed. The first pH/impedance study in this refractory patient population indicated that heartburn was replaced by regurgitation, which became predominant in these subjects who failed PPIs twice daily [4]. Zerbib et al. (2008) obtained similar results in a population representative for GORD with persisting symptoms [5]. Although most subjects (60%) had both symptoms, 30% had regurgitation only and 10% had heartburn only. These so-called refractory patients remain one of the	Not agreed in general. The purpose of including both, heartburn and regurgitation as inclusion criterion is clearly described in the draft guideline. No need for change is seen in general. However, regarding the partial responder/refractory to PPI population, changes have been implemented (See also comments of Montreal Group).

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		most challenging problems in the management of GORD. As acid secretion is adequately suppressed in most of these patients, it can be reasoned that causes other than exposure to acid are in play [4]. Several studies have shown that GORD patients may suffer from underlying dysmotility, indicating a potential therapeutic target for prokinetic agents [6]. As such, it has been shown that the rate of gastric emptying might determine the acidity and proximal extent of reflux: the slower the emptying, the higher the pH and proximal extent of the refluxate [7]. Moreover, it could be hypothesized that patients that predominantly suffer from regurgitation might benefit more. In that same study from Zerbib et al., [5], it was found that compared with regurgitation, reflux episodes associated with heartburn were more frequently pure liquid and acidic, had a lower nadir pH, were more frequently preceded by acid reflux episodes and had a longer reflux bolus clearance time. Regurgitation can thus be associated with more mixed reflux. When comparing symptomatic reflux events with asymptomatic events, both Zerbib et al. [5] and Tutuian et al. [8] found that symptomatic reflux events more likely have a high proximal extent. Both volume and refluxate content contribute to the proximity of a reflux event [9]. As the rate of gastric emptying might determine the acidity and proximal extent of reflux (the slower the emptying, the higher the pH and proximal extent of the refluxate [7]), prokinetics might be more effective in patients that mainly suffer from	

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		regurgitation. **It has been suggested to develop prokinetics in an add-on to PPI setting (i.e. the PPI refractory patients). However, the symptom profile in these refractory patients might have shifted, with reflux parameters (proximal extent, volume, content, clearance time) still being the cause of the symptoms (i.e. true GORD). It is probably more accurate to include all groups (i.e., subjects having heartburn *and/or* regurgitation).** 1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006; 101:1900-20; quiz 1943. 2. Richter JE. The many manifestations of gastroesophageal reflux disease: presentation, evaluation, and treatment. Gastroenterol Clin North Am 2007; 36:577-99, viii-ix. 3. EMA-CHMP. Draft Guideline on the Evaluation of Drugs for the Treatment of Gastroesophageal Reflux Disease. EMEA/CHMP/EWP/342691/2009 2009. 4. Vela MF, Camacho-Lobato L, Srinivasan R, Tutuian R, Katz PO, Castell DO. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. Gastroenterology 2001; 120:1599-606. 5. Zerbib F, Duriez A, Roman S, Capdepont M, Mion F. Determinants of gastro-oesophageal reflux perception in patients with persistent symptoms despite proton pump inhibitors. Gut 2008; 57:156-60. 6. Farre R SD. Regulation of basal tone, relaxation	

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		and contraction of the lower oesophagel sphincter. Relevance to drug discovery for oesophageal disorders. BRr. J Pharmacol 2008; 2008:858-869. 7. Emerenziani S, Sifrim D. Gastroesophageal reflux and gastric emptying, revisited. Curr Gastroenterol Rep 2005; 7:190-5. 8. Tutuian R, Vela MF, Hill EG, Mainie I, Agrawal A, Castell DO. Characteristics of symptomatic reflux episodes on Acid suppressive therapy. Am J Gastroenterol 2008; 103:1090-6. 9. Sifrim D, Mittal R, Fass R, Smout A, Castell D, Tack J, Gregersen H. Review article: acidity and volume of the refluxate in the genesis of gastro-oesophageal reflux disease symptoms. Aliment Pharmacol Ther 2007; 25:1003-17. Proposed change (if any): Allow inclusion of all groups (i.e., subjects having heartburn *and/or* regurgitation)	
Line 532	3	**Comment:** The requirement to have a 4 week wash-out period in case of PPIs before the start of the trials is inconsistent with the assumption in line 221 that the treatment is assumed to be an 'add-on" to existing PPI therapy. Proposed change (if any): Remove wash-out period	Partially agreed only. The wash-out phase requirement is, of course not applicable in the add-on setting. This has been added (lines 541-542).
Line 563	3	**Comment:** The statement that "At lest one year comparative treatment data are, however, necessary to appropriately document safety (see section 8)." is not clear. Section 8 refers to ICH guideline E1, which requires 6 months data on 300-600 patients, and 12	Agreed. The requirements have been specified. The minimum requirements are 6 months for efficacy, and 12 months for safety (referring to ICH E1).

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		months data on 100 patients, but allows registration in the EU based on 6 months data (paragraph 8). It is therefore unclear whether it is necessary to continue the large double blind trials for 6 or 12 months Proposed change (if any): Specify in guideline whether 6 or 12 months data are needed for registration in EU	
Line 524	3	**Comment:** The requirements for PPIs as add-on are not clearly described. **Proposed change (if any):** Please specify whether in the pivotal trials it is necessary to have all patients using the same PPI at the same dose, or whether it is acceptable to allow the patients to continue using the PPI regimen they were using before the trial.	Agreed. The use of different PPIs is allowed. Clarification has been included (see chapter 4.1.2.)
Line 607, 613, 630	3	**Comment:** Please clarify whether the intention is to have placebo controlled trials in PPI-add on design or whether a true placebo arm is envisaged.	Not agreed. No need to include a clarification. Chapter 6.3.3.2. includes a clear description: PPI comparator in reflux oesohagitis, placebo in non-erosive disease, and other classifications mention the need to give placebo in addition to the PPI treatment.
Line 166	4	**Comment:** There are typos or missing words that would need revision as "5.4.4" does not currently exist in the Guideline.	Agreed. Changes have been implemented.
Line 184	4	**Comment:** There are typos or missing words that would need revision as "5.1.2" does not currently exist in the Guideline.	Agreed. Change has been implemented.
Lines 189-	4	**Comment:**	Not agreed.

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190		It would be useful to clarify what class of erosions are acceptable for a symptomatic GERD claim and what is considered "adequate justification" for inclusion of such patients in pivotal trials of symptomatic GERD. **Proposed change (if any): (Lines 189-190)** The inclusion of mild oesophagitis patients (defined as Grade LA-A) and subsequent claim of "Symptomatic Gastroeosphageal Reflux Disease" is considered acceptable.	The proposed clarification is already included (see lines 192-195) in the revised version.
Lines 204-207	4	**Comment: Proposed change (if any): (Lines 721-722)** The text following the heading "PPI partial responders" (Line 203) does not clearly address how PPI partial response is defined. We suggest adding clarifying language and reference to section 6.1.1 (inclusion criteria). The text (Lines 204-207) addresses symptom burden for inclusion and not partial response to PPI therapy. Furthermore, while the requirement for both heartburn and regurgitation (Line 205) seems reasonable, there are insufficient data at this time to make this recommendation. The study by Arts et al cited elsewhere in the draft guidance (Arts et al. Digestion 2007;76:207), had two important limitations: 1) diagnosis of GERD was not definitively established, and 2) a standard definition of regurgitation was not used. Studies in subjects with documented reflux disease have shown that	Agree as regards the necessary reference to section 6.1.1. Not agreed as regards the definition of partial response, as the term appears to be clear enough per se, and the problems in defining "partial" as opposed to complete "non-response" are described in the following paragraph already. Not agreed as regards the request to define the patients suffering from either heartburn or acid regurgitation (see above)

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		substantially fewer patients report regurgitation as compared to heartburn. (Savarino et al. Gut 2009;58:1185). We recommend the use of "heartburn with or without regurgitation" be inserted here, and through the Guideline (as recommended as global change in Item 1). **Proposed change (if any): (Lines 204-207)** Partial responders should be defined analogously to the general inclusion criteria. This means that a significant, and "typical" (heartburn with or without regurgitation, with one of them being the most troublesome or severe symptom) symptom burden should exist at inclusion that is considered to be troublesome by a patient receiving an adequate course of a PPI (see 6.1.1).	
Line 207	4	**Comment:** There is a typo or missing words that would need revision as "5.1.2" does not currently exist in the Guideline.	Agreed. The paragraph has been changed.
Line 244	4	**Comment:** There is a typo or missing words that would need revision as "5.1.2" does not currently exist in the Guideline.	Agreed. The reference to the inclusion criteria paragraph has been changed.
Line 289	4	**Comment:** There is a typo or missing words that would need revision as "5.1.2" does not currently exist in the Guideline.	Agreed. The reference to the inclusion criteria paragraph has been changed.
Lines 346-349	4	The contemporaneous presentation of both heartburn and regurgitation in GERD patients has not been clearly established in population based studies (Vakil et al. Am	Not agreed. The purpose of requesting both symptoms as inclusion criterion has been described sufficiently. For PPI non- or partial

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		J Gastro 2006;101;1900). Until such data are published, we believe it is appropriate to require heartburn only, which is supported by the literature (Wiklund et al. Am J Gastroenterol. 2006 Jan;101(1):18-28). The circumstance with GERD patients partially responding to PPIs is more uncertain, as there are virtually no published data on symptom experience in an unselected population of PPI partial responders. **Proposed change (if any): (Lines 346-349)** As the cardinal symptoms of GERD are regarded to be heartburn with or without regurgitation, the presence of heartburn is required for inclusion of GERD patients in clinical trials in which recruitment of patients is based on symptoms only, no matter whether the primary endpoint refers to endoscopy or symptoms only.	responders, the description has been changed.
Lines 357-360	4	**Comment:** The term "troublesome" is preferred over "bothersome" for linguistic reasons (Vakil et al. Am J Gastro 2006;101;1900). In addition to "bothersomeness" or "troublesomeness" as a basis for entry into clinical trials, frequency and severity of heartburn (i.e., mild symptoms on two or more days per week) have been shown to significantly reduce quality of life. Thus, we agree that frequency and severity are appropriate criteria for study inclusion (Vakil et al. Am J	Agreed. Terminology has been changed.

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		Gastro 2006; 101; 1900; Shaw et al. Gastroenterology 1998;114:G1166; Aro et al. Gastroenterology 2003;124;A168). **Proposed change (if any):** (Lines 357-360) The selection of "typical" GERD patients should be based on the evaluation of overall severity (or "troublesomeness"). This may be done with either the criterion of rating the "troublesomeness" or severity on a global level, or with defining and rating the symptoms with a validated scale by frequency and severity, at the time of inclusion.	
Lines 364-367	4	**Comment:** As indicated in Comment regarding Lines 346-349 and mentioned as a recommended global change, we believe the guidance should not require the presence of both heartburn and regurgitation. **Proposed change (if any): (Lines 364-367)** For inclusion, in addition to requiring heartburn with or without regurgitation to be present, it should furthermore be required that the overall severity and frequency of all symptoms as well as the severity and frequency of at least one of the typical symptoms are above a certain threshold to be defined in advance, and which may depend on the instrument used (see also 6.2.3.).	Not agreed See above.
Following Line 367	4	**Comment:** In trials of partial responders to PPI therapy, it is particularly important to document PPI compliance	Agreed. The need for a run-in period in trials with patients having insufficient PPI response has not been sufficiently emphasized

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		before inclusion, as poor compliance is considered the single most common cause of PPI failure (Fass et al. APT, 2005;22;794). Furthermore, in a large population based survey, only 55% of GERD patients took their PPI once-daily for 4 weeks (The Gallup Organization. Gallup Study of Consumers' Use of Stomach Relief Products. Princeton, NJ: The Gallup Organization, 2000). Accordingly, we suggest the addition of the following paragraph after Line 367 [and prior to Line 368 (Health related quality of life)]. **Proposed new paragraph following Line 367:** In trials of PPI partial responders, compliance with PPI therapy should be documented prior to treatment with study medication as non-compliance is an important cause of PPI failure.	before. However, the proposed paragraph (and additional requirements) have been included in chapter 4.1.2. which is more specific to the population, whereas chapter 6.1.1. has been left more "unspecific".
Prior to Line 368	4	**Comment:** We suggest that partial response should be defined within Section 6.1.1, Inclusion Criteria, and offer the following definition be inserted as a separate paragraph, prior to Line 368. **Proposed change (if any): INSERT NEW paragraph prior to Line 368:** Partial response should be based on medical history indicating a reduction in "typical" (heartburn with or without regurgitation) symptoms with an adequate course of PPI therapy.	Agree. Changes have been implemented in section 4.1.2. (section 6.1.1. left almost unchanged as this describes a more general population. However, a cross-reference has been included.
Lines 468-469	4	**Comment:** Absent specific regulatory guidance on patient reported	Agreed. Full sentence has been implemented unchanged.

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		outcomes, it is important that sponsors involve patients during instrument development and that symptom frequency and severity are recorded using tools that assure accuracy of data collection and minimize recall bias (Patrick et al. Value in Health 2007;10 (suppl 2):S125 and Stone AA, et al. Control Clin Trials. 2003 Apr;24(2):182-99 and Dent et al. Aliment Pharm Therap 2008;28:107-126). We recommend (1) that the text currently in Lines 468-469 be deleted, and (2) the proposed new text be used for Lines 468-469. **Proposed change (if any): INSERT this NEW TEXT for Lines 468-469** In the absence of specific regulatory guidance on patient reported outcomes, sponsors are encouraged to involve patients during instrument development and to record symptom frequency and severity using tools that assure accurate data collection and minimize recall bias.	
Lines 479-482	4	**Comment:** We suggest that the Guideline clarify that the VAS or Likert scales should be utilized for evaluating symptom severity. **Proposed change (if any): (Lines 479-482)** The symptom questionnaires should use the visual analog scale (VAS) or several point Likert scales for evaluating the severity or intensity of GERD symptoms. The number of rating points (in the Likert scales) within	Partially agreed. The use of VAS and Likert scales is not more clearly recommended.

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		these scales may vary between the tools, however, they should include at least 5 points. The main symptoms of GERD, identified to be heartburn with or without regurgitation should be included in the scales.	
Lines 485-490	4	**Comment:** It is not clear why "freedom from all reflux-related symptoms", i.e., complete resolution, may not be suitable as a primary endpoint (refer to Lines 485-486), as this is the ultimate aim for symptomatic therapy. Furthermore, it has been shown that complete resolution of heartburn is consistently associated with improvement in health-related quality of life (Revicki et al. Aliment Pharmacol Ther 1999; 13: 1621-1630.) Additionally, the definition of a responder should be based on patient perspective rather than what is "considered clinically relevant", as the latter is often determined by expert opinion and may not substantiated with data. **Proposed change (if any): (Lines 485-490)** The evaluation of freedom from the main reflux symptoms, heartburn with or without regurgitation, or freedom from all reflux-related symptoms, should be included as efficacy endpoint(s). The primary analysis of efficacy should be based on a responder analysis of the two cardinal symptoms of reflux disease, heartburn with or without regurgitation. The protocol should define clearly a treatment response that is clinically relevant, such as 50% decrease in or	Partly agreed. Whereas the wording is not taken into the guideline directly, the possibility of choosing "complete resolution" as primary endpoint has been included additionally (see chapter 6.2.3.).

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		complete resolution of reflux symptoms, from a patient perspective.	
Lines 530-532	4	**Comment:** It should be clarified that the recommendation (Lines 530-532) applies to monotherapy trials and not adjunctive studies in patients who are partial responders to acid suppressive (e.g., PPI) therapy. **Proposed change (if any): (Lines 530-532)** Prior to the start of monotherapy trials that include patients pre-treated with acid-suppressive medication, usually an appropriate wash-out period should be part of the protocol (e.g. one week in case of H2-antagonists, and 4 weeks in the case of PPIs.	Agreed. Appropriate changes have been implemented.
Lines 552-556	4	**Comment:** We suggest that the responder definition used in the responder analysis of a "Main therapeutic trial" should be based on patient's overall benefit from treatment. **Proposed change (if any): (Lines 552-556)** The primary analysis of efficacy should be based on a responder analysis of the two cardinal symptoms of reflux disease, heartburn with or without regurgitation (see also 6.2.3.). The time course of response should be sufficiently taken into consideration with regular assessment of symptoms (e.g. weekly). Responders would be defined by two criteria: A level of symptom improvement and the time course of the response (e.g. in the example given above: being a responder e.g. 75% of all weeks).	Agreed. Appropriate changes have been implemented in chapter 6.3.3.1.

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Lines 562-564	4	**Comment:** As this comment appears to pertain to maintenance of healing of esophageal erosions, we suggest further clarification. **Proposed change (if any): (Lines 562-564)** The duration of trials in maintenance therapy of healed erosive esophagitis should be at least 6 months to sufficiently document long-term efficacy. At least one year comparative treatment data are, however, necessary to appropriately document safety (see section 8.).	Not agreed. The lines following the proposed amendment make clear that the 6 months requirement is applicable to both erosive and non-erosive disease. Also, the requested endpoints make it clear that both "entities" are included by the request.
Lines 619-622	4	**Comment:** It should be clarified which subset of NERD subjects this section refers to. At present, there are not adequate data to justify routine follow up endoscopy in patient with non-erosive GERD who are on a PPI (i.e., as in an adjunctive therapy trial). Available information are from studies that are small and/or retrospective in nature and do not routinely employ PPI therapy (Fullard, et al. APT 2006; 24:33-45). Furthermore, routine endoscopy is "recommended against" by the AGA in subjects with non-erosive reflux disease to monitor for disease progression (Kahrilas, P., Shaheen, N., Vaezi, M., Gastroenterology 2008; 135;1383-1391). **Proposed change (if any): (Lines 619-622)** For placebo controlled trials in non-erosive disease without background acid suppression, the (possible) development of reflux oesophagitis in relevant numbers	Not agreed. The paragraph lists the principal requirements for studies in NERD patients. The following paragraph refers to add-on treatment. A clarification is therefore not needed.

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		of patients while on active treatment should be properly investigated and excluded during phase II. Otherwise this would have to be documented in phase III. Appropriate rescue procedures (medication and facilitated trial exit) should be in place.	
Lines 721-722	4	**Comment:** While the PPIs are generally regarded as safe, recent data highlight that long term use is associated with an increased risk of community acquired pneumonia (Gulmez SE, et al. Arch Intern Med 2007; 167: 950-955) and hip fracture (Corley DA, et al. Gastroenterology. 2010 Mar 27 [Epub ahead of print] and de Vries et al. Osteoporos Int (2009) 20:1989–1998). Recent data also suggest an interaction with the anti-platelet drug clopidogrel must be considered (Trenk D et al. Int J Clin Pharmacol Ther 2009; 47: 1–10). Regarding efficacy, in well controlled trials of PPIs for the treatment of non-erosive GERD, the responder rates for active treatment were approximately 35% as compared to placebo rates of 20% (Scott et al. Drugs. 2002;62:1503-38). Furthermore, inadequate response to therapy with PPIs, ranging between 30 and 40%, has been documented in a large, well controlled population-based survey of GERD patients (American Gastroenterological Association Institute/Harris Interactive. GERD Patient Study: Patients and Their Medications. 2008. http://www.gastro.org/user-assets/Documents/13_Media/ GERD_Survey_Final_	Agreed. The statement on available medication has been "weakened".

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		Report_2.pdf. Accessed on May 2008). Such patients experience a significant decrease in quality of life and are at risk of developing complications such as esophageal stricture, Barrett's esophagus and adenocarcinoma; thus, it cannot be asserted that safe and effective medications are available for GERD patients inadequately responding to PPI therapy. While the safety of any new therapy is of utmost importance considering its approvability, the balance between benefit and risk must be considered in the specific population for which the treatment is intended. Accordingly, we recommend the statement (Line 722) be qualified, as proposed below. **Proposed change (if any): (Lines 721-722)** GERD is a non life-threatening disease. Therefore, the safety of any therapeutic intervention is regarded to be of utmost importance. Medications that are safe and effective are available for a substantial number of GERD patients.	
635	5	**Comments:** I assume "formulations" is meant; "formulas" is ambiguous.	Agreed. Wording has been changed.
660	5	**Comments:** This sentence may be gratuitous. "Active comparators" are presumed efficacious, but unless they have themselves been tested against placebo, this cannot be presumed, particularly in infant studies (where the natural history of symptoms is clearly to improve), and particularly with symptomatic (i.e., non-erosive)	There have been difficulties in demonstrating efficacy of PPI s, especially in infants. Placebo controlled trials are acceptable. Wording has been changed accordingly. It is agreed that for studies that include an endoscopy baseline, biopsies should be performed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		outcomes. (See Orenstein SR, et al, Multicenter, double-blind, randomized, placebo-controlled trial assessing efficacy & safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. J Pediatr 154:514-20, 2009.) Infants and children deserve at least the same rigor of study that is afforded to adults, not less. l. 678-680: Because of the necessity of excluding eosinophilic esophagitis, and because this requires biopsy, it should be mandatory to include histology in any study of GERD in which endoscopy is performed--i.e., all studies based on endoscopy. (Although erosive esophagitis is unlikely to be eosinophilic, the majority of children endoscoped for possible inclusion in such trials because of their symptoms will probably not have erosions.) And if biopsies are performed, ideally provisions should be made for them to be of adequate size and orientation to assess morphometric parameters and be sure of not missing eosinophils clustered at a particular level (e.g., juxtaluminal). (Although it would not be the primary aim of such studies, these biopsies could add further information to the debate on their diagnostic role in symptomatic GERD.)	
698-9	5	**Comments:** The I-GERQ/I-GERQ-R should not be mentioned in this section on children 6-12 years, as it is only relevant to infants.	Agreed. Mentioning of the I-GERQ/I-GERQ-R has been moved to the section on infants.
713-4	5	**Comments:** To exclude EoE and allergic esophagitis requires a run-in switch to an elemental formula in infants, and	Exclusion of eosinophilic oesophagitis can be made clinically and/or by endoscopy. This has been clarified.

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		requires endoscopy in those young children beyond infancy who are consuming a more complex diet. If this is what the document intends, it should probably be explicit. These diagnoses cannot be reliably (i.e., for the purposes of a rigorous study) made by history and physical exam.	
716	5	**Comments:** This is where the I-GERQ/I-GERQ-R could be specified. The sentence from l.698 that it "has been validated for diagnostic purposes but may not be sensitive to intervention" is incorrect. The diagnostic validations are the most "iffy," as the I-GERQ was validated using subjects who were pH probe/biopsy positive compared with *asymptomatic* normal controls (thus no controls with symptoms *not* due to GERD were evaluated), and the I-GERQ-R had a weaker gold standard of clinician diagnosis. But the I-GERQ-R was specifically and rigorously validated for responsiveness to clinical change, and its ability to detect such change was clearly demonstrated.	Agreed. The wording has been changed accordingly.
66-70	5	**Comments:** the pediatric consensus should be mentioned here in this paragraph.	The paper published by the Paediatric Consensus Group is already referred to in the Introduction
Line 73-75	5	**Comments:** Mention that history in children is not reliable under 8-12 years.	Agreed. Wording changed.
Line 94-102	5	**Comments:** Not sure at all that this is true. The epidemiologic data from Susan Nelson and from Martin et al suggest the opposite: infants that regurgitate "frequently" are still different from those who did not at the age of 3-5 years although regurgitation disappeared... The onse study	Partly agreed as some children may need longer time before resolution. In particular difficulties may remain. Wording amended.

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		from susan Nelson (the only data available) gets too much attention.	
Line 105	5	**Comments:** To y recall we did not say that "not troublesome" equals "without complications". I agree that reflux symptoms that are not troublesome should not be diagnosed as GERD. I am not convinced that reflux symptoms need to be WITH complications to be regarded as GERD.	The wording has been changed to better clarify the definition by the Montreal group.
Line 114-118	5	**Comments:** mixtures of ages!! I think that in "infants", reflux treatment starts (always) with dietary treatment (= different meaning than "feeding changes") and positional treatment (although..... There is only the AMC/Australia data switching right and left position - but still increased risk for SIDS and thus not applicable) and our "AR-Bed" that certainly needs confirmation from other centers/studies before "recommendable". Thus, in practice: there is NO positional treatment to recommend today.	Partly agreed. Concerning positioning, although strictly speaking not evaluated in a rigorous manner, it is part of clinical practice and thus should be included.
Line 116-117		**Comments:** "relapse is rare": i wonder where the evidence is for this statement. There is no such evidence. In stead: the data from Susan suggest that "untreated esophagitis persists" although symptoms disappear!	Agreed. There is not much known about the relapse rate. Text has been amended accordingly and moved to the section 7.2.
117		Comments: surgery: not only in atresia, but in life-threatening symptoms, chronic medication-dependent reflux disease (neurologic patient).	Not agreed to change the text. Atresia is only mentioned as one example and the text does not have to be more detailed.
160		**Comments:** severity acid exposure: there is no evidence that more	Not applicable. This text belongs to the adult part of the

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		acid exposure causes more severe esophagitis a(least not in kids: there is no relation between reflux index and severity of esophagitis).	guideline.
162-166		**Comments:** it means that all the children need several endoscopies... And we know that "severe esophagitis" as seen in adults is rare in children - so, we know from before that 90% will no have mucosal breaks... Again: this seems not adapted to children.	NA. Belongs to adult part
175-184		**Comments:** it means all children needs endoscopies! A problem (at least in the health care structure I am working in...) is that only severe cases are referred to centers and "general paediatricians" take care of the mild / moderate cases. In other words: enters that do endoscopies see a biased because of the selected population. "First line approach" should be tested in the correct population.	NA. Belongs to adult part.
193-8		**Comments:** how do you know it is resistance / unresponsiveness to the drug and not idiosyncrastic adverse event (such as stomach pain, etc). In children : very difficult to know!. So: documentation of unresponsiveness before doubling the dose seems very reasonable in kids. We need pK/pD studies, and treat with "right" dose. And if symptoms do not improve, exlcude adverse events before doubling the dose.	NA. Belongs to adult part.
263		**Comments:** what is important in "clinical relevant improvement".	NA. Belongs to adult part.
306-318		**Comments:**	NA. Belongs to adult part

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		I do not agree that "agents influencing motility" should be "add-on" medication. Indeed, the basic mechanism are TLESRs. So, any drug that changes this.. Should be first treatment option. Especially for the upcoming evidence that also non-acid reflux may cause symptoms such as chronic coughing, etc.... Agree that "prokinetics" are probably not first option to treat esophageal symptoms but they are maybe first option in extra-esophageal symptoms. And even for the esophageal symptoms: why would it not be logic to consider thet PPI as "add-on" (healing of the mucosa) but consider the prokinetic as "fundamental" (doing something to the cause...). It is not becasue today there is no effective prokinetic on the market that the "option" is not attractive.	
Line 440, 331		**Comments:** Seems to be written for adults	NA. Belongs to adult part
Lines 530-532		**Comments:** wash-out periods.... : it all depends. If a "new PPI" needs to be tested, I think it is not ok to include patients who do not improve on other treatment options. That would induce a negative bias.	NA. Belongs to adult part
Line 612		**Comments:** NERD: May also be an indication for non-acid reducing medication such as prokinetics?	NA. Belongs to adult part
632		**Comments:** Children and adolescents.	
692		**Comments:** Helicobacter: eradication of H pylori is not recommended in chidlren taht are just Hp positive... So they have to remain symptomatic ???	Partly agreed. Children should be tested for Hp. Very little is known about the relationship of Hp to GERD in children. As long as this is an unresolved issue, it is recommended only to exclude patients with Hp associated gastroduodenal disease.

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708		**Comments:** To take up the discussion of "comparator": I think we all agree that reassurance and "dietary treatment" (I definitively prefer this wording to "dietary change") should be first option. I made my comments on the limitations of positional adaptations elsewhere. But for sure "observation and practical recommendations" are first approach. But then, symptoms persist in a subgroup. This is the group to test for "new drugs". But if the design is "compared to placebo", there is a group of infants with symptoms not improving on "conservative treatment" and they are going to receive placebo.... I will have difficult to convince parents and the ethical committee that I am not going to give a chance to any medication now on the market (PPI, H² blocker, alginate, domperidone...) even in the absence of any evidence (I fully agree that there is no evidence for efficacy. But that is what the "standard of care" is - and yes again, I agree that the "standard of care" is likely wrong....). Many of these infants will have had an endoscopy and have some polynuclear infiltartion, and the data from Susan suggest this persists.. So it will be difficult to state that "nothing needs to be done to this"...	Partly agreed. However, for shorter trials, it is not considered to be unethical to compare with placebo, in particular since efficacy of acid-inhibitors has not been convincingly demonstrated.
Line 389		**Comments:** pH-impedance shoudl become the investigation of choice, and symptom-association the way to go. But: we have no data on "SAP" cut-offs in chidlren.	Agreed. Impedance monitoring is recommended in addition to pH-monitoring