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GUIDELINE ON THE EVALUATION OF DRUGS FOR THE TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE

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EXECUTIVE SUMMARY

This guideline intends to address the EU regulatory position on the main topics of the clinical development of new medicinal products in the treatment of patients with gastroesphageal reflux disease (GERD).

1. INTRODUCTION (background)

Gastroesophageal reflux disease (GERD) has been identified as the most common gastrointestinal diagnosis during visits in outpatient clinics. Estimations suggest that up to 20% of adults are affected (weekly complaints over an observation period of 1 year).[1] An analysis of time trends revealed that an overall increase during the last 2 decades has taken place and may still be ongoing.[2]

According to the most recent consensus definition of GERD[3], the disease is defined as a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications. According to this definition, "troublesome" symptoms are those that adversely affect an individual's well-being. Typical symptoms (such as heartburn and acid regurgitation) and their frequency in order to be "troublesome" have also been defined.

Other, earlier definitions put the focus quite similarly on complications (including oesophagitis) but also on the impairment of Quality of Life [45].

The typical symptoms, heartburn and acid regurgitation have been defined by consensus only and do currently lack adequate validation. Accompanying symptoms are regarded to be epigastric pain, sleep disturbances, dyspepsia, dysphagia, odynophagia, nausea, vomiting and others.

The main complications of GERD can be regarded to be reflux esophagitis, the development of strictures, Barrett's oesophagus (intestinal metaplasia and dysplasia) and esophageal adenocarcinoma. In rare cases, oesophagitis may also lead to clinically significant bleeding and/or perforation.

However, despite the possible serious consequences, GERD usually presents as a relatively benign condition, not leading to a relevant increase in mortality[6]. GERD has traditionally been seen as a non-progressive disease (as regards the progression from non-erosive to erosive disease, to more severe erosive disease and to Barrett's oesophagus and other complications), with progression occurring in only a small proportion of patients. However, conflicting evidence is available on this topic, indicating higher progression rates than previously thought. [7].

The pathophysiological factors causing GERD can be divided into those inducing greater exposure of the oesophagus to stomach contents, and those providing increased mucosal damage or increased perception of reflux. Key elements representing these factors have been identified to be transient lower oesophageal sphincter relaxations, and oesophageal hypersensitivity as a result of visceral neural pathways dysfunction. Risk factors associated with the development of GERD have been identified to be largely environmental/demographic in nature, such as smoking and alcohol consumption, age and high body mass index. Although it has long been known that family history is significantly associated with GERD, the search for genetic susceptibility and identification of specific loci has only just begun[8].

The current knowledge of the prevalence and natural history of GERD in children and adolescents is limited. Physiological gastroesophageal reflux (GER) is found in up to 70% of healthy newborns and infants resolving without intervention in 95% of cases by 12-14 months of age while the incidence of gastroesophageal reflux disease (GERD) in infants and children has been found to be between 0.47 and 0.9 per 1000 person years. In the adolescent population, up to 3.3% of adolescents reported heartburn occurring a few times per week. Prevalence of oesophagitis is low at infancy and early childhood, increasing to adult values only during adolescence. It is important to distinguish between GER and GERD in children, as medical treatment is seldom warranted in the former and thus it is not expected that GER would be the focus of drug development.

The definition of GERD in children is neither consistent nor homogeneous. A recent consensus document, however, defined GERD in the paediatric population based on troublesome symptoms in a similar way as adult GERD, i.e. reflux symptoms that are not troublesome (and without complications in infants) should not be diagnosed as GERD[9]. Definition of "troublesome", however, remains a challenge, particularly in infants. Symptoms associated with GERD in the younger paediatric

population range from regurgitation, vomiting, abdominal pain, arching and irritability, to feeding refusal, and/or poor growth. Extra-oesophageal symptoms, e.g. respiratory symptoms, occur in children as well as adults. Children with secondary GERD (i.e. associated with underlying disorders such as neurodevelopmental delay or congenital abnormalitiesform a separate sub-group of the paediatric GERD population as they are more prone to severe and chronic forms of GERD with complications.

Conservative management of mild GERD consists of positioning and feeding changes. Pharmacological options for moderate to severe GERD include acid inhibitory agents and prokinetic agents. Relapse following successful treatment of erosive oesophagitis in children with primary GERD is rare. Surgical treatment is usually reserved for special circumstances, such as children with oesophageal atresia.

2. SCOPE

This guideline is intended to assist applicants during the development of products for the treatment of GERD in adults and children, where no current regulatory guidance exists in the EU.

The guideline does not address drug development in the indication functional dyspepsia which is defined differently from GERD or eosinophilic oesophagitis. It does not address the specific requirements for the development of OTC products in the treatment of symptomatic GERD or heartburn and it does also not address generic drug development in GERD.

3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) and Part I and II of the Annex I to Directive 2001/83 as amended. Applicants should also refer to other relevant European and ICH guidelines (in their current version), particularly those on:

- Note for Guidance on General Considerations for Clinical Trials (CPMP/ICH/291/95).
- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).
- Note for Guidance on Dose Response Information to support Drug Registration (CPMP/ICH/378/95).
- Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96).
- Note for Guidance on Choice of Control Group in Clinical Trials (CPMP/ICH/364/96).
- Reflection paper on the extrapolation of results from clinical studies conducted outside Europe to the EU-population (Draft; CHMP/EWP/692702/08).
- Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95) (Along with: Concept Paper/Recommendation on the need for revision of (CHMP) Note for guidance on the investigation of drug interactions (CHMP/EWP/297931/08).
- Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (CHMP/ICH/2711/99).
- Note for Guidance on Population Exposure: The Extent of Population Exposure to assess Clinical Safety (CHMP/ICH/375/95).
- Reflection Paper on the regulatory guidance for the use of Health-Related Quality of Life (HRQL) measures in the evaluation of medicinal products (CHPM/EWP/139391/04).
- Guideline on the Choice of the Non-Inferiority Margin (CHMP/EWP/2158/99).
- Guideline on conduct of pharmacovigilance for medicines used by the paediatric population (CHMP/PhVWP/235910/05).

4. DISEASE CLASSIFICATION/POSSIBLE CLAIMS

The following paragraph describes several "disease classes" into which GERD has been subdivided. However, not all of these subgroups are considered suitable to base indication labelling claims upon, for which the reasons will be displayed in detail in the following.

4.1 "Disease classes" possibly leading to treatment claims:

4.1.1 Subdivision based on endoscopic findings:

The development of acid-suppressive agents has been based on the primary evaluation of reflux oesophagitis patients, followed later by the inclusion of non-erosive disease, based on symptomatic evaluations "only". This "traditional" subdivision is still considered valid, as it expresses the severity of the disease, not in terms of severity of symptoms and impairment of quality of life, but severity regarding acid exposure and the risk of pre-malignant and malignant changes in the oesophageal mucosa.

The possible indication claims are therefore erosive disease ("reflux oesophagitis") and "Non-Erosive GERD". The indication "Symptomatic GERD" is also possible and may include mild forms of reflux oesophagitis, see below. A global indication "GERD" may be possible if the two distinct populations are both studied in the pivotal trials. However, the two populations should be tested in separate trials (see 5.4.4.).

Erosive disease (reflux oesophagitis):

Reflux oesophagitis has to be diagnosed by endoscopy, using the best validated classification, which is, at the moment, the Los Angeles classification. The L.A. classification is described in the following table:

Table 1: Los Angeles classification of reflux oesophagitis

Grade A	One (or more) mucosal break(s) no longer than 5 mm, that does not extend between the tops of two mucosal folds
Grade B	One (or more) mucosal break(s) more than 5 mm long, that does not extend between the tops of two mucosal folds
Grade C	One (or more) mucosal break(s) that is continuous between the tops of two or more mucosal folds, but which involve(s) less than 75% of the oesophageal circumference
Grade D	One (or more) mucosal break(s) which involve(s) at least 75% of the oesophageal circumference

The use of other classifications is no longer recommended, but may be justified on a case by case basis. The presence of mucosal breaks in these patients is therefore regarded to be the main disease feature.

Non-erosive disease:

Non-erosive disease is per definition a "diagnosis of exclusion" based on the absence of mucosal breaks. Non-erosive disease is basically not distinct in terms of symptom pattern and severity from reflux oesophagitis, but has a lower frequency in patients with hiatal hernia, lower acid exposure, and higher rates of "functional comorbidity", like functional dyspepsia, IBS, and psychological disorders[10]. Whether such a diagnosis can be based on further criteria, like micro-endoscopic diagnosis, has currently not been established and can therefore not be recommended for the purpose of drug registration trials at the moment.

If studies in this patient population are conducted, data on endoscopic diagnosis (exclusion of mucosal breaks) are required before inclusion (see 5.1.2.).

The condition “Symptomatic Gastroesophageal Reflux Disease” is slightly different from pure “non-erosive disease” because mild reflux oesophagitis (defined as grade A of L.A classification) has traditionally been included in trials in the “non-erosive” population leading to the claim “symptomatic GERD” or “symptomatic treatment of GERD”.

The inclusion of mild oesophagitis patients and subsequent claim of “Symptomatic Gastroesophageal Reflux Disease” is considered acceptable on the basis of adequate justification.

4.1.2 Further Subdivision/claims based on the response to acid suppressive medication, especially PPIs:

In recent years, there have been a growing number of reports suggesting that about 30% of GERD patients treated with PPI are partially or completely unresponsive to standard dose and duration of PPI therapy. These failure rates may even be higher in patients with an (additional or only) atypical symptom burden[11,12,13,14]. For these patients, it is usually suggested – as a first step – to increase (usually double) the dose and duration of therapy with a PPI [15,16]. The recommendation, however, is based on expert opinion only, and not supported by clinical data.

For the inclusion of patients with typical symptomatology while on PPI therapy into clinical trials, it is therefore considered likewise acceptable that patients are included on the basis of a non-response or insufficient response to standard dose PPI, or to double-dose with appropriate treatment duration of at least 4 weeks in patients with non-erosive, and 8 weeks in those with erosive disease.

PPI partial responders

Partial responders should be defined analogously to the general inclusion criteria. This means that a significant, and “typical” (both heartburn and regurgitation, with one of them being the most bothersome or severe symptom) symptom burden should exist at inclusion that is considered to be troublesome by the patient (see 5.1.2.).

PPI non-responders:

The definition of PPI non-responders may be difficult, as this would require a standardised comparison of symptom burden before and after PPI therapy, which is usually not available in clinical practice. Therefore, a group of “primary” non-responders may not be reliably identifiable unless a second treatment trial with a PPI (with standardised symptom recording at inclusion and during and after end of therapy) is performed.

Similarly, the clear identification of patients initially (partly) responding to PPI therapy and subsequently experiencing a complete relapse of symptoms (“secondary failures”), may be as difficult as for the “primary” failures.

However, if “non-response” can be accurately demonstrated, the creation of such a subgroup of patients with additional indication claims may be possible.

It is therefore recommended that an indication claim may – aside from the indication mentioned above - include terms such as “only partially responsive to PPI” or “insufficiently responsive to PPI”.

It is assumed that the treatment will be an “add-on” to existing PPI therapy.

For these subpopulations – apart from the patients with “residual” oesophagitis – the requirements for clinical trials for the “non-erosive” disease population will be applicable (see 6.3.).

4.2 “Disease classes” not leading to treatment claims:

4.2.1 Typical and atypical GERD

This subdivision based on the characteristics of symptoms has been introduced more recently. However, in the following, it is shown why this distinction is – at the moment – not considered suitable for labelling claims. It is considered that only a “typical GERD” population can lead to one of the indications mentioned in chapter 4.1.

"Typical" GERD

The typical symptoms of GERD according to the scientific literature are considered to be heartburn and acid regurgitation. However, the attempt of the Montreal process, to define an overall sensitivity and specificity of the two symptoms for the diagnosis of GERD, has failed[17], for the most part due to the lack of a gold standard and non-homogeneity of the trials. Therefore, the diagnosis of typical GERD and its definition by its main symptoms is only based on expert consensus. However, in the situation with an overwhelming consensus and the lack of practicable alternatives, this definition of a "typical" symptom spectrum is considered to be acceptable for the purpose of development of new compounds in the therapeutic area.

Because the typical GERD symptoms heartburn and acid regurgitation translate poorly into several languages, the symptoms have to be defined with a description. This description should be included in all studies requiring the recruitment of GERD patients based on symptoms only.
Other symptoms, such as dysphagia, epigastric pain, or features of "atypical GERD" may or may not be present in the patient populations included, however, at a lower level than the main symptoms (see also 5.1.2.)

"Atypical GERD"

Syndromes considered to be associated with or caused by gastroesophageal reflux (disease) are considered to be the following:

- Non-cardiac chest pain (or "reflux chest pain syndrome");
- Chronic cough (especially nocturnal cough);
- Chronic laryngitis;
- Asthma.

The association of these symptoms/syndromes with the symptoms of GERD or with endoscopic or pH-metric diagnosis of GERD is usually relatively weak. Likewise, the treatment success of acid suppressive medication in these syndromes appears to be rather modest[181920] or is mainly based on the suppression of oesophageal symptoms only[21]. Therefore, reflux (disease) is usually seen as an "aggravating" factor of the underlying condition only.

The investigation and subsequent claim of treatment of "atypical GERD" would therefore need to comprise a rather elaborate diagnostic work-up, showing that (acid or other) reflux is present to a pathological extent and is associated with the respective symptoms in the patients to be investigated.

On the other hand, the treatment of these complaints would have to show that not only the reflux related symptoms are positively influenced but that also the "atypical" symptoms get better in a consistent manner (and, needless to say, both "parts" of the disease should be shown to improve in a statistically significant and clinically relevant manner).

Therefore, the conduct of trials for regulatory purposes with the goal to claim an indication other than GERD, by defining a sub-population based on the nature of such "atypical" symptoms, can currently not be recommended. For such development programs, companies should seek Scientific Advice in order to receive individual feedback/guidance.

The investigation of patients suffering mainly from associated symptoms (such as asthma, chest pain, chronic cough, or laryngitis) without proof of a relevant "typical" symptom burden or clear pathological (acid) reflux cannot not lead to labelling claims for GERD.

Further research, including the possible links between disease and symptoms, pathophysiology and mechanisms of disease interplay appear to be warranted before clear regulatory decisions can be taken on these issues.

4.2.2 Functional heartburn

Based on the outcome of pH-monitoring, NERD patients have been further subdivided into "true" NERD (with pathological increased acid exposure in the oesophagus) and those with normal acid exposure in pH testing, subsequently diagnosed to be suffering from "functional heartburn". Functional heartburn (FH) has been included into the list of functional GI disorders in the Rome III criteria[22], and is, in these criteria, defined as:

1. burning retrosternal discomfort or pain,
2. absence of evidence that gastroesophageal acid reflux is the cause of the symptom and
3. absence of histopathology-based motility disorders.

This definition is, however, clearly in conflict to the Montreal definition of GERD, which would include functional heartburn patients into GERD, as the pH of the refluxate is not a criterion for diagnosis. The exact diagnosis of FH patients would therefore have to be based on exclusion of mucosal breaks, exclusion of pathological acid exposure, and the exclusion of symptom associations (in e.g. impedance investigations) [2324].

As the inclusion of patients into GERD therapeutic trials is usually only based on nature and severity of symptoms (see 5.1.2.), the inclusion of this kind of patients into clinical trials in non-erosive disease or "symptomatic GERD" appears to be inevitable and is regarded as being fully acceptable.

Any claim for the treatment of FH for an investigational product is however, currently not considered acceptable because of insufficient validation of this concept at the present time.

5. POSSIBLE TARGETS OF TREATMENT:

Acid suppression

Acid suppressive agents, particularly PPIs are currently the mainstay of therapy in GERD, with good efficacy and tolerability. However, a need to optimize acid suppression with regard to the daily course of acid secretion, especially during the night, has been identified. Also, lower healing rates of the more severe forms of reflux oesophagitis or a faster onset of full treatment effects may constitute a further potential for optimisation. Therefore, attempts to develop compounds with a longer duration of action (longer half-life, different release characteristics, and different way of binding to the proton pump) or with a faster onset of action are under way[2526]. Whether these will lead to clinically relevant improvements in efficacy, however, is currently unclear[27282930]. It is considered self-evident that, even if superiority to existing PPIs can be shown in specific features (such as night-time reflux complaints, better control in on-demand medication), this will most likely not lead to a different indication in the labelling, as the disease to be treated will essentially not change.

Agents influencing motility

Agents acting on the basal lower oesophageal sphincter (LOS) pressure, on transient lower oesophageal sphincter relaxations (TLOSR) frequency and magnitude/duration, and on (at the same time) gastric emptying are regarded as potential candidates for drug development in GERD [3132]. These agents would usually be developed in an "add-on" setting to existing acid suppressive medication. Such claims would therefore be mainly based on symptoms rather than on mucosal healing. This is considered acceptable, even if patients with remaining (mild) reflux oesohagitis are included in the studies. However, in these circumstances, patients with reflux oesophagitis should be endoscoped at inclusion (or an appropriate result of endoscopy within a certain time frame be known).If unhealed mucosa is found, this should be included as secondary endpoint. If the influence on mucosal injury can sufficiently and reliably be characterised within the early development of the compound (e.g. in phase II of the development), confirmatory trials may also be conducted in a more "naturalistic setting" without further endoscopy.

Other options:

Modulation of visceral pain has been suggested to be a possible further option for the optimisation of therapy, based on the similarities and associations of GERD with the functional syndromes IBS and functional dyspepsia regarding visceral hypersensitivity. Because hypersensitivity has been shown to be involved in the generation of symptoms in GERD, this approach may be considered to be promising.

Further options may include agents for mucosal protection. Other mechanisms and targets such as TRPV 1 [33], ASIC 1-3 [34], P2X 1-7, and others have been discussed as a potential mechanisms to enter clinical development.

The same requirements as for the agents influencing motility regarding the inclusion of reflux oesophagitis patients and the conduct of endoscopies would most likely apply in these cases.

6. CLINICAL STUDY DESIGN

6.1 Patient selection

6.1.1 Inclusion criteria

Endoscopic appearance:

Patients may be included on the presence of mucosal breaks if the indication "reflux oesophagitis" or "erosive reflux disease" is being proposed. The phase III trials should include a relevant proportion of all severities, unless a restriction of the indication (e.g. to less severe inflammation, or most severe inflammation only) is being sought. For endoscopic grading, the Los Angeles classification should be used (see 4.1.1. and 6.2.2.).

For substances where a "symptomatic claim" only is being sought, endoscopic status should nevertheless be documented. To this end, either pre-inclusion endoscopy results should be available, which should not be older than 1 year, or – in pre-treated patients (e.g. as "add-on" to acid suppressive therapy), previously diagnosed reflux oesophagitis should be re-checked for healing at the time of inlcusion, and if unhealed, also be followed-up after the end of the trial. For the requirements for patients with mild reflux oesophagitis included in such trials, see 4.1.1.

Symptoms:

As the cardinal symptoms of GERD are regarded to be heartburn and acid regurgitation, the presence of both symptoms are 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.

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[35] However, the gold standard for these comparisons, which has been endoscopic diagnosis has presumably not been the most adequate. An adequate gold standard may therefore be lacking completely. Therefore, in the absence of an accurately defined gold standard, consensus definitions are considered acceptable for the time being. The proposed requirement of both symptoms to be present is expected to increase the diagnostic accuracy.[36]

The selection of "typical" GERD patients should be based on the evaluation of overall severity (or "bothersomeness"). This may be done with either the criterion of rating the "bothersomeness" or severity on a global level, or with defining and rating the symptoms with a validated scale by frequency and severity [37] at the time of inclusion.

Typical GERD patients should have the greatest bothersomeness and/or highest symptom burden on one of the two symptoms heartburn or acid regurgitation (to be defined in the protocol) as opposed to other concurrent symptoms, and both symptoms should be present.

For inclusion, in addition to the requirement of both symptoms having 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.)

Health related quality of life:

As it has been shown that a relevant symptom burden indeed decreases quality of life, inclusion criteria defining a qualification of patients based on the evaluation of a certain degree of decrease of quality of life is not warranted.

6.1.2 Exclusion criteria

"Alarm symptoms"

Patients with so-called "alarm features" in symptomatology, like odynophagia, bleeding, weight loss, anaemia, and blood in stool, pointing to a possible malignant disease of the GI tract should not be

allowed into clinical trials in GERD. The exclusion can be based on symptoms only. Patients displaying "alarm symptoms" additionally to the "typical" GERD symptoms may be included based on endoscopic exclusion of malignancy.

Eosinophilic oesophagitis

Eosinophilic oesophagitis is a clinical entity increasingly diagnosed in adults as well as in children[38]. The main features of the disease are the complete unresponsiveness to acid suppressive therapy, the presence of histological eosinophilia in histological probes of the oesophageal mucosa (although the overall validity is unclear[39]), and a normal pH profile of the distal oesophagus. It is typically associated with the symptoms of dysphagia and food impaction. The exclusion of patients based on a predominance of the "typical" eosinophilic oesophagitis symptoms only (as above) is considered acceptable. However, in patients with a predominance of "typical" symptoms and co-existing significant dysphagia and food impaction, the syndrome should be excluded by endoscopy with biopsy[40].

6.2 Diagnostic methods/Methods to assess efficacy

6.2.1 Methods for the investigation of pharmacodynamics of drug candidates

6.2.1.1. pH Monitoring.

PH monitoring can be done on ambulatory basis and is therefore considered suitable for an outpatient setting. Usually 24 hours recordings of the pH are used and a maximum time for which pH is allowed to fall below the threshold of 4 is defined as being pathologic. Thresholds (for percentage of time pH<4) and duration of observation should be defined and justified in advance. [41 4243].

The method is suitable to detect acid reflux only.

The method is recommended for the documentation of the pharmacodynamics of acid suppressive substances or those influencing the LOS/oesophageal pressure in phase I and II of the development, when a full elucidation of pharmacodynamics and dose response is required.. In a situation where acid suppression is used as basal therapy, and additional substances are used in addition, the method may not be fully appropriate and is therefore not recommended.

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.

6.2.1.2. Impedance monitoring

pH and impedance monitoring can be combined, which is the preferred method in a highly experimental setting. Whereas pH monitoring can only detect acid reflux, impedance pH-monitoring is a technique that can be used to detect all types of GERD (acidic, weakly acidic, and weakly alkaline).

Impedance monitoring or pH-impedance monitoring is considered to be the method of choice in patients unresponsive or only partly responsive to acid suppressive therapy. The method is recommended for use especially in substances which aim to influence the motility and/or pressure of the oesophagus/oesophageal sphincter in order to fully document the pharmacodynamic properties and dose response in phase I and II of the clinical development (in addition to the documentation of the pressure changes).

An inclusion of the technique for inclusion or assessment of treatment response in phase III trials is not recommended for reasons of impracticability.

6.2.1.3. Pressure monitoring and other motility assessment methods

Methods to measure oesophageal pressure (including sphincter pressure) have traditionally been used to evaluate patients with symptoms of oesophageal obstruction ("swallowing disorders") or atypical symptoms, such as non-cardiac chest pain or in the pre-operative work-up for patients undergoing antireflux surgery44.45.

The evaluation by manometry is currently not sufficiently standardised, and should be justified on an individual basis.

Combination with impedance and pH-impedance monitoring is possible.

Manometry, however, is especially considered useful and necessary for substances aiming at altering the motility of the oesophagus. However, as certain manometrically diagnosed abnormalities might also be influenced by substances reducing the symptom burden by a different mechanism of action (e.g. acid suppression, influence on mucosal sensitivity), manometry may also add to the full elucidation of pharmacodynamic properties in other substance classes.

A routine performance of manometry studies in phase III of the drug development will not be required.

6.2.1.4. Bile reflux monitoring:

In patients with a suspicion of duodeno-gastro-oesophageal reflux, a method to prove the exposure of the oesophageal mucosa to bile acids (Bilitec 2000) has been introduced.[46].

This method may be especially useful in the evaluation of patients with persisting symptoms despite adequate PPI therapy[47]. It may provide additional information in patients diagnosed with non-acidic reflux during impedance pH measurements. The method is therefore not recommended for routine diagnosis but may be useful in the full elaboration of pharmacodynamic properties of a new substance.[48]

6.2.2 Endoscopic imaging

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).[49]

A truly sensitive and simple diagnostic tool, however remains an unmet need for non-erosive reflux disease.

Magnification endoscopy[50], narrow band imaging[51], and confocal laser endomicrosopy have been proposed to be used as diagnostic tools for non-erosive reflux disease. However, these methods can currently not be recommended to reliably differentiate patients suffering from reflux related symptomatology from those with "normal" exposure to gastric contents of the esophageal mucosa.

Development of a new and fully validated tool for the diagnosis of NERD [5253] remains an important task. Further research on such tools is encouraged to be part of the development programmes of new drugs in the field. It is, however, considered undesirable that validation of diagnostic or efficacy tools and their use as outcome measures takes place in the same trial (see also 6.2.3).

6.2.3 Quantification of symptoms

The evaluation and quantification of symptoms of gastro-oesohpageal reflux disease is the main tool for the selection of patients and for the evaluation of efficacy. Therefore, whenever patients are included or evaluated based on symptoms, a thoroughly and sufficiently validated tool for the assessment of symptoms should be used.

Symptoms should always be assessed by the patients themselves because symptom evaluation by physicians/investigators is considered less reliable[54]. However, symptom assessment done by the investigator may be useful as a secondary endpoint.

The symptom response should already be used for evaluation of the properties of possible drug candidates at relatively early stages of the development in order to be able to relate the pharmacodynamic response (e.g. acid suppression, change in motility or sensitivity) to symptomatic response at the time when a substantial diagnostic workup (see 6.2.1.1. to 6.2.1.4) is required.

For the later phases of drug development (phase IIb and phase III), symptom based evaluation forms the primary basis of proof of efficacy, if the claim is not related to endoscopic healing of (concurrent) inflammation of the oesophageal mucosa.

Evaluation and quantification of symptoms are within the scope of patient reported outcomes, for which – at the moment – no general European regulatory recommendations exist.

For GERD, a substantial number of partly, or even almost fully validated symptom based outcome measures/scales do exist[555657]. It is recommended to use fully validated GERD specific instruments that are focused on symptom evaluation only. The assessment of Quality of Life should be kept separate from symptom assessment. Symptom evaluation should include severity and frequency of symptoms. Availability and validity in different languages is to be considered crucial for the use in multi-national trials. Part of the validation work of symptom questionnaires might be done during the development programme of possible drug candidates. This may concern also subgroups of patients (e.g. PPI non-responders) that were insufficiently included in the previously performed validation studies. However, confirmative clinical trials should not be used for the validation of such a tool.

The symptom questionnaires usually include VAS or several point Likert scales for different domains of complaints. The number of rating points (in the Likert scales) within these scales may vary between the tools, however, they should include at least 5 points. The main symptoms of GERD, identified to be heartburn and acid regurgitation should be included in the scales.

Symptom scales open to deterioration are preferred to dichotomous modes of answers (e.g. like "satisfactory relief" or "adequate relief") as the latter have not been validated nor used in GERD.

The evaluation of freedom from the main reflux symptoms, heartburn and acid regurgitation, or freedom from all reflux-related symptoms, should be included as secondary endpoint(s).

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. The protocol should define clearly a treatment responder, i.e. the amount of improvement that is considered to be clinically relevant.

A minimal clinically relevant change in the overall symptom scale (and its definition) should be included in the validation of such scales and a minimally clinically relevant change in responder rates should be pre-defined.

6.2.4 Quality of Life

In reflux disease, it has been shown that Health-Related Quality of Life is significantly impaired[58]. The impact of GERD on Quality of Life has found to be similar to other chronic diseases such as ischemic heart disease.

Quality of Life has therefore to be regarded as an important secondary endpoint in trials not explicitly investigating the healing of oesophagitis (where the symptom evaluation is the main secondary endpoint).

Only validated health-related quality of life questionnaire should be used. Partly or even fully validated scales are already available[59]. For validation the same rules do apply as for the symptom questionnaires.

To be used as a main secondary endpoint, disease specific questionnaires are preferred to generic instruments.

For claims derived from the evaluation of Quality of Life, reference is made to the Reflection Paper on Health-Related Quality of Life" (EMEA/CHMP/EWP/139391/2004).

For both "Quality of Life" and symptom evaluation scales, a global, generic scale of change (e.g. CGI-I) is recommended to be used as internal validation measure during the trials.

6.3 Design of Clinical Trials

6.3.1 Pharmacokinetic documentation:

The general recommendations for exploration of pharmacokinetics in humans also apply for products intended to be developed for the treatment of GERD. However, due to the high prevalence of the disease, increased requirements for the documentation of drug-drug interactions might apply. A risk based approach based on in-vitro and animal data and the assessment of prescription data of (co-

(prescribed)) drugs is recommended. Regarding drug-drug interactions, the "Note for Guidance on the investigation of drug interactions" (CPMP/EWP/560/95 and CHMP/EWP/297931/08) should be taken into account.

6.3.2 Pharmacodynamic trials/phase 1 and 2

As mentioned earlier, early phase trials should investigate the pharmacodynamic properties of the drug with a variety of diagnostic tools, usually in comparison to placebo. In case of acid suppressive drugs, active comparators may be included additionally. The correlation of the pharmacodynamic parameters with the change of symptoms should also be explored at this early phase of the development.

6.3.3 Main therapeutic trials

6.3.3.1. Trial duration, endpoints and general design issues:

The treatment of GERD, being chronic in nature, can be subdivided into acute treatment during which healing of oesophageal lesions or primary symptom control is the aim, and a maintenance phase, during which the maintenance of healing and/or symptom control should be achieved.

Large randomized, double-blind treatment trials are required for the proof of efficacy.

Prior to the start of trials that include patients pre-treated with anti-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).

A possible rebound effect after the end of treatment should be evaluated during an appropriate follow-up period.

Acute treatment:
Reflux oesophagitis

The treatment duration in these trials has traditionally been 4-8 weeks. A trial duration of 8 weeks will be regarded as the minimum requirement for the documentation of healing of reflux oesophagitis.

The primary endpoint is the complete healing of all mucosal breaks (see also 6.2.2.) at the end of the trial period.

Other endpoints, such as the recently proposed "complete remission[60]", which is a composite of a validated symptom questionnaire and mucosal healing may be acceptable, depending on justification.

Non-erosive disease:

Trial durations in non-erosive GERD have traditionally been shorter, in the range of 2-4 weeks. However, treatment durations shorter than 8 weeks will only be acceptable in the future, if either efficacy in repeated cycles of treatment, maintenance treatment, or in the so-called "on-demand" treatment can be shown at the same time. The choice of the length of this primary treatment cycle (and possible further treatment cycles) should be based on the pharmacodynamic properties and the success rates achieved in phase II, which might bring up the need to explore different treatment durations.

A possible rebound effect after the end of the trials should also be evaluated during an appropriate follow-up period.

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.). The time course of response should be sufficiently taken into consideration with regular assessment of symptoms (e.g. weekly). Responders would then be defined also considering the time course of response (e.g. in the example given above: being a responder e.g. 75% of all weeks).

If patients with erosive disease (grade A) are included into trials focusing on symptomatic treatment only, full documentation of mucosal healing should in these cases be included as secondary endpoint (in the subgroup).

Maintenance therapy:

Continuous treatment:

The duration of trials in maintenance therapy 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.).

Possible rebound effect after long-term use may also be considered an issue and should be investigated.

If the maintencance of effect in patients with previous erosive disease is investigated, the endpoint should be the maintenance of complete oesophageal healing over the complete duration of the study.

For maintenance treatment in non-erosive disease, the maintenance of "response" (according to the definition used in the acute studies) over the whole duration of the trial is proposed as the primary endpoint.

The corresponding time-related endpoints (time to "failure") are considered to be a main secondary endpoint.

"On-demand" treatment or "repeated treatment cycles":

On demand treatment (take the medication whenever symptoms occur) has been documented for PPIs and other acid suppressant medication[6162] for patients suffering from non-erosive disease and mild oesophagitis and is regarded to be an appropriate mode of handling the chronic nature of the disease, where symptoms fluctuate in a more inconsistent and short-term basis.

The problem with the assessment of these trials has been identified to be two-fold:

Firstly, the chosen endpoint ("willingness to continue treatment" in most of the trials) was not validated and not directly related to the symptom burden of the patients. It is furthermore obvious, that patients waiting for symptoms to re-occur and in which the symptoms do indeed re-occur are per definition worse-off than those treated continuously in which a continuous freedom from symptoms is maintained.

Secondly, the problem of worsening of the disease over time, and eventually developing reflux oesophagitis has also not been widely addressed by these studies.

Therefore it is recommended for these studies, either to use a newly developed validated primary endpoint, or use Quality of Life evaluations and/or treatment satisfaction as an additional primary endpoint that might outweigh the anticipated increased symptom burden. Furthermore, at least one study in a development programme for this treatment regimen should document the exclusion of the development of reflux oesophagitis. In this special case, when continuous (active) treatment is compared to an on-demand or intermittent (also active) treatment, blinded studies might be too difficult to conduct and open studies are considered acceptable. However, blinded evaluation of the endoscopies is mandatory in this case.

Repeated treatment cycles (otherwise called "intermittent treatment") may form the alternative basis of approval. This may be considered for appropriate patient populations with a more "undulating" nature of their disease course, with longer periods of "off symptoms". It is not recommended for patients with a history of frequent relapse (be it symptomatic or endoscopic). At least two treatment cycles should be documented for repeated short term treatments of 4 weeks. For shorter periods, an appropriate higher number of treatment cycles are recommended. The need for long-term safety data should appropriately be considered.

6.3.3.2. Choice of comparator:

<u>Studies in Reflux oesophagitis:</u>

In reflux oesophagitis a specific medication with high success rates (around 85-90% of the patients are expected to have healed oesophageal mucosa after 8 weeks) and acceptable tolerability is available for the treatment of typical reflux disease. Therefore, the use of placebo in the investigation of a typical GERD population appears ethically not justifiable and an appropriate PPI should be used as comparator.

For candidate drugs being investigated in comparison to PPIs proposing similar efficacy the non-inferiority margin chosen should not only take into account the magnitude of superiority of the PPIs to placebo, but also to other substances used in the treatment of GERD (e.g. H2-antagonists).

Studies in non-erosive disease:

Trials in "non-erosive" reflux disease should be conducted in comparison to placebo. This can be justified by the lower response rate of acid suppressive medication in NERD in comparison to erosive disease on one hand [63], and the benign, and, mainly non-progressive nature of the disease entity. However, before inclusion in such trials, the existence of erosive disease should be excluded, e.g. by historic endoscopy/current endsocopy combined (for the inclusion of Grade A LA classification oesophagitis: see chapter 6.2.2.).

For such a programme in non-erosive disease, the (possible) development of reflux oesophagitis in relevant numbers 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.

Possible other classifications:

For other subgroups of patients, the comparison to a placebo group is generally considered to be mandatory, especially in those patients insufficiently treated with proton-pump inhibitors, for which the medication is given in addition to PPI treatment.

Maintenance therapy:

Whereas the above relates to the drug development in the acute treatment, a differentiation for erosive and non-erosive disease is not necessary for the maintenance parts of the clinical trials regarding the comparator. For the maintenance parts, placebo is the recommended comparator throughout. An active comparator may be included additionally.

7. STUDIES IN CHILDREN AND ADOLESCENTS

Notice should be taken of the NfG on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99).

Studies in the paediatric population are encouraged. The need to develop appropriate formulas for children is emphasized.

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.

As the (symptom and pathophysiological) differences between adult GERD and paediatric GERD decrease with the increasing age of the paediatric population and the relative prevalence of secondary GERD also becomes lower with increasing age, the extrapolation of adult efficacy data in certain situations may be possible, if adequately justified.

If the treatment of adolescents for a compound previously only used in adults is proposed, the efficacy and safety of the substance in adults should be well-established, and possible specific safety problems (e.g. with long-term use) should be addressed.

7.1 PK/PD studies

As pharmacokinetics may be different in children with GERD, separate PK studies in the different age-groups are necessary. Dose-finding has to be performed in children as well.

For pharmacodynamic studies of acid suppressive agents, pH monitoring is currently recommended as gold standard. Adding impedance monitoring to standard pH monitoring may improve the accuracy of reflux-symptom associations.[64] Especially for products that are not acid suppressive, impedance monitoring could be recommended. Validated parameters for impedance monitoring, however, have to be established in children before a general recommendation for its use in drug development can be made.

7.2 Phase III studies in children

For the indication of paediatric GERD, clinical efficacy and safety data are needed in addition to PK/PD data. Confirmatory studies should be double-blind, randomised controlled trials (RCT). An active comparator is generally recommended to be used in paediatric trials.

7.2.1 Studies in erosive GERD

Children with secondary GERD (i.e. associated with underlying disorders such as neurodevelopmental delay or congenital abnormalities) should preferably be studied in separate trials.

Alternatively, it has to be ensured that sufficient proportions of patients are represented in studies combining primary and secondary GERD in order to allow meaningful interpretation of results for the sub-populations. Stratification is recommended.

The primary endpoint should be complete healing of the oesophagitis. Endoscopy is needed to confirm the presence and severity of erosive oesophagitis and to exclude other diseases. Healing should likewise be confirmed by endoscopy.

Especially in infants, symptom severity does not correlate with presence of oesophagitis. No specific and validated classification for evaluation of erosive oesophagitis in children exists. The Hetzel and Dent classification is commonly used but also the LA classification. Both are acceptable.

Secondary endpoints include symptom assessments. There exist currently no validated symptom questionnaires for erosive GERD in children and development of such a tool during the earlier phases of development are strongly encouraged, see also symptomatic GERD below. Future questionnaires that might result in a reduction of the need to perform control endoscopies in this population would be welcomed.

Microscopic oesophagitis and the value of histology in paediatric GERD has been questioned recently and it is therefore not mandatory to include a biopsy for purposes other than to diagnose or exclude other conditions, e.g. eosinophilic oesophagitis.

Recommended duration of trials is 8-12 weeks with 2-4 weeks of follow-up. Relapses are uncommon following successful healing of erosive oesophagitis in children and therefore, studies on maintenance treatment would normally not be required, with the exception of children with secondary GERD with oesophagitis, where maintenance treatment should be addressed in the developmental programme.

7.2.2 Studies in symptomatic GERD

7.2.2.1. Studies in older children (6-12 years)

In children with typical symptoms of adult GERD where heartburn and regurgitation are the predominant symptoms, drug development could basically follow the same recommendations as for adults.

In trials for the symptomatic treatment of GERD in children, erosive oesophagitis and eosinophilic oesophagitis should be excluded by previous or baseline endoscopy. A test for Helicobacter pylori (Hp) should be performed at baseline and children with Hp associated gastroduodenal disease should not be included in the trial. Children with alarm symptoms such as bilous vomiting should be excluded.

The primary endpoint should be symptom based, measuring change in frequency and severity of symptoms. However, there is a lack of a globally accepted validated symptom-based questionnaire for children. Furthermore, PRO may not be reliable in the younger age-group, i.e. below the age of 8 years. The I-GERQ/I-GERQ-R has been validated for diagnostic purposes but may not be sensitive to intervention. As regards individual components of questionnaires, especially for vomiting and respiratory symptoms, the association with GERD is highly variable. It is acknowledged that at the time of writing this guideline, much work has to be done as regards the development of good patient reported outcome questionnaires for children with GERD. Questionnaires for parents are also needed as well, see studies in infants and younger children below.

Secondary endpoints proposed include individual PRO items as well as investigators assessment and use of rescue medication.

Recommended trial duration is at least 4 weeks. A follow-up evaluation period off treatment is recommended.

7..2.2.2.Studies in infants and younger children (0-5 years)

Physiological GER is common in the age-group below 2 years and should not be the target of drug development. GERD diagnosis should be made using validated symptom-based questionnaires, such as the I-GERQ with or without pH measurements to confirm gastroesophageal reflux. Only those children in whom changes in feeding and positioning have not resulted in a satisfactory reduction of symptoms should be included in trials of new drugs for GERD. Eosinophilic oesophagitis and food allergy (e.g. cow milk) should be excluded.

The primary endpoint should be symptom-based, however, reliable parent-reported outcome measures need to be developed. Secondary endpoints include individual symptoms such as episodes of regurgitation/vomiting and irritability.

The risk for GI infections following profound acid inhibition with new acid suppressive agent is an issue that is a special concern in this age-group.

8. SAFETY

GERD is a non life-threatening disease. Therefore, the safety of any therapeutic intervention is regarded to be of utmost importance. Safe and efficacious medications are already available. The requirements of the ICH E1 guideline for symptomatic benign disorder will be applicable, as GERD is regarded as a chronic disease and this makes it necessary to appropriately document the long-term safety of such compounds (see also 5.4.3.).

Depending on the results of pre-clinical evaluations and on the overall safety profile, a comparison of long-term pharmacological treatment with surgery based methods of the treatment of GERD post-approval is recommended.

Safety data collected in sub-populations may not necessarily support the authorisation in a wider patient population.

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