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Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome

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Executive summary

This guideline intends to address the EU regulatory position in the main topics of clinical development of new medicinal products in the treatment of patients with Irritable Bowel Syndrome (IBS).

The main changes introduced into this guideline compared to the previous “Points to Consider on the Evaluation of Medicinal Products for the treatment of Irritable Bowel Syndrome”, refer to the following: The patient population to be selected has been changed from Rome II to Rome III criteria, and more flexibility towards possible future changes in the definition of the disease is introduced. The recommendation on primary endpoints to be used in confirmatory trials has been changed from a co-primary endpoint of global assessment and pain, to the evaluation of stool related abnormalities and pain. Moreover, dedicated chapters on special patient groups (gender, children and elderly) and on geographic region are introduced.

1. Introduction (background)

This guideline is a revision and expansion of the previous “Points to Consider on the Evaluation of Medicinal Products for the treatment of Irritable Bowel Syndrome”, which has been in operation since the year 2003.

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder in which abdominal discomfort or pain is associated with changes in bowel habits, stool consistency and other features of disordered defecation [1] [2] [3]. The pathophysiological basis of the symptoms is still incompletely understood, but it features disturbances of motor and sensory function, subclinical inflammatory changes, altered microbiome, associated psychosocial disorders, and genetics. By definition, however, in a more “conventional” sense, the diagnosis still excludes structural or biochemical abnormalities of the gut [4] [5] [6] [7] [8] [9].

IBS is considered to be one of the most frequent clinical problems in gastroenterology with an estimated prevalence in the Western world of up to 20%. The age distribution is very broad, but 40% of the patients are aged between 35 and 50 years. Symptoms begin before the age of 35 in 50% of patients. The female to male ratio in community samples has been estimated to be between 1:1 to 2:1, but a female predominance is more evident in those seeking health care. Only between 30-70% of “patients” suffering from IBS symptoms are “consulters” with symptoms experienced severe enough as to trigger a physician visit. IBS is not a life threatening condition; however, for those patients with more severe disease it does have a relatively large impact on quality of life, is leading to need for medical treatment and work absenteeism with consequent economic costs [10] [11] [12].

Contrary to the frequency of the syndrome, there is still a lack of adequately studied and more so of licensed medications in Europe, and a certain unmet medical need for IBS has still to be realised. Moreover, there is a wide history of unsuccessful drug development programmes in the field, and the number of Marketing Authorisation Applications for the indication has been very low during the past decade. Current approaches to diagnosis of IBS start with the identification of symptoms and the exclusion of organic disease (at least with the so-called “red-flags”). The treatment consists of non-pharmacological options with education, reassurance, and dietary modification up to the use of biofeedback and psychotherapeutic intervention. Pharmacological options are usually recommended if non-pharmacological methods alone have proven to be ineffective. Most of the current pharmacological therapies aim at treating the symptoms with the rationale of modulating intestinal motility and/or secretion, decreasing visceral sensitivity or treating associated disorders, such are anxiety and/or depression [13] [14] [15] [16] [17].

2. Scope

This Guideline is intended to assist applicants during the development of products for the treatment of Irritable Bowel Syndrome (IBS).

3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with Annex I to Directive 2001/83/EC as amended, as well as all other pertinent EU and ICH guidelines and regulations. Applicants should also refer to other relevant European and ICH guidelines (in their current version), particularly those one:

Note for Guidance on Dose Response Information to support Drug Registration (CPMP/ICH/378/95)

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 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)

4. Disease classification / possible claims

IBS is regarded to be a functional gastrointestinal disorder, thereby excluding a pathological correlate by definition. Whereas most disorders “without pathological correlate” have been defined as a diagnosis per exclusion, IBS has a long history of identifying symptoms or clustering symptoms only to make up a reliable diagnosis. Historically, these definitions were the Manning, Kruis, and the Rome (I-III) definitions of IBS. Currently, the Rome III criteria are regarded to be the standard diagnostic criteria, although convincing validation (in the sense of assuring the correct diagnosis) is missing, compared to the older classifications [18] [19] [20] [21].

This is even more true for the proposed sub-classification of IBS. However, at least the concordance between the Rome II and Rome III classification of patients has been reported [22].

The current Rome III criteria define the IBS population as follows:

Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months (with symptoms being present for the last three months and onset at least 6 months prior to diagnosis) associated with 2 or more of the following

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance of stool)

Sub-typing of IBS patients is performed by the predominant stool pattern present in a patient:

- IBS with constipation (IBS-C): hard or lumpy stools ≥25% and loose (or mushy) or watery stools in <25% of the bowel movements.

- IBS with diarrhoea (IBS-D): loss (mushy) or watery stools ≥25% and hard or lumpy stools <25% of the bowel movements
- Mixed IBS (IBS-M): Hard or lumpy stools ≥25% and loose (mushy) or watery stools ≥25% of the bowel movements
- Unsubtyped IBS – Insufficient abnormality of stool consistency to meet the criteria for IBS-C, D, or M.

The Rome III criteria are currently widely accepted as the scientific standard, and are therefore also currently accepted as the standard of definition in the regulatory environment. The history of constant change of the criteria, and the lesser acceptance of the criteria by primary care physicians or certain learned societies [23], however, make it necessary to also accept potential other classifications or criteria to define an adequate patient population in the regulatory field. Applicants are therefore requested – in the definition of their patient population to be included into clinical trials – either to choose the current most widely accepted standard – or to justify the definition used in the development programme by all scientific data available, and by evaluating concordance between the chosen criteria and the most accepted criteria at the time of conduct of trials.

Due to the poor validation data available, and considering clinical practice, the selection of patients should usually be done based on both, symptom-based criteria and exclusion of relevant other diseases with similar symptoms (see Chapter 6.2.).

Although sub-typing of patients has not or only incompletely been validated, the potential target of treatment may determine the adequate subgroups to be included into the clinical development programme, at least for the clearest currently valid subtypes of IBS-D and IBS-C. Examples from past development programmes are the two compounds acting on the serotoninergic system, tegaserod and alosetron, with their antagonistic or agonistic activity determining the adequate subpopulation. It is considered acceptable that the primary pharmacology of candidate compounds – or the results of studies in the early phases of development (see 6.1) – determines the selection of subgroups of patients (e.g. GC-C receptor activation for IBS-C; TPH_1-blocker for IBS-D)[24]. However, for candidates with different modes of actions such as centrally acting agents, or probiotics, a “global” development, acting on all subtypes of IBS will also be regarded to be acceptable

From the two main features of IBS, the abdominal pain and the associated defecation abnormalities, it is obvious that medicinal products influencing both, mucosal sensitivity, and at the same time motility and/or secretion appear to be the most promising candidates.

Claims based on the influence on only one aspect of the illness (e.g. for pain or defaecation abnormalities only) are not within the scope of this guideline. At the current time, sub-indications such as “diarrhoea in IBS” or “abdominal pain in IBS” are regarded to be problematic.

5. Clinical Study Design

5.1. Patient selection

The study population should generally be representative of a broad spectrum of IBS patients in the sense that patients are recruited from primary, secondary, and tertiary care settings. It is recommended to select patients with a certain severity level of symptoms and/or reduction of quality of life representative for the usual “consulter” population as part of the inclusion criteria. These parameters should be evaluated not only by history taking, but with a 10-14 days run-in period (see also 6.3.).

Depending on the sub-type of IBS, or the sub-population intended for treatment with the compound, additional characteristics should be made part of the inclusion criteria, such as a certain level of pain to be present (depending on the scale to be used for the final evaluation of pain) and – at least for the most relevant subgroups of IBS-C and IBS-D a certain level of symptoms defining constipation and/or diarrhoea. This should be based on the number of stools per week, and the form of the stools present (as measured by the Bristol Stool Form Scale).

IBS is a disease with a variable course. Whereas previously, it was considered that the majority of patients have only mild to moderate symptoms with the famous "waxing and waning" characteristics, and only a tiny minority of patients was expected to have constant and severe symptoms, newer work on the classification of symptom course and severity classification have partly come to different conclusions [25] [26] [27]. The inclusion criteria should however, still define and select the patient population also according to consistency of symptoms over time.

The general recommendation is to use the Rome III criteria for inclusion, and to add a relevant diagnostic work-up for the most relevant potential other diseases. This work-up should be made part of the in- or exclusion criteria and should comprise the following:

- The exclusion of lactose intolerance and other malabsorption syndromes (e.g. fructose malabsorption) should be based on the response to dietary changes (e.g. lactose-free diet). This can be done by history taking, or if in doubt, by a trial of such a diet and/or respective testing if available and deemed appropriate. [28],[29].
- Coeliac disease should be excluded by appropriate antibody testing.
- Basic laboratory tests (blood count, electrolytes, liver enzymes), stool cultures, blood in stool and exclusion of relevant systemic or GI inflammation (e.g. CRP and/or calprotectin), should be done for all patients. Positive faecal blood test and stool cultures would normally lead to further evaluation or exclusion of patients.[30]
- The exclusion of colorectal cancer and other structural abnormalities by endoscopy should be conducted either if any of the above laboratory tests yields a result of concern or be done according to national and/or international screening guidelines. The need to have historical endoscopic examinations available according to these guidelines should be included in the trial protocol. If not available, endoscopic examination before inclusion of the trial is necessary. However, patients with known familial colorectal cancer syndromes (Lynch, FAP) should not be included.
- Bile acid malabsorption/Bile acid induced diarrhoea: Patients with IBS-D should have received a therapeutic trial with bile acid sequestrants within the last two years before inclusion, or else undergo such a probatory treatment (e.g. colestyramine or colesevelam)[31, 32],[33]

As mentioned earlier, the symptom-based criteria can be updated according to the current state of the art, and should – if deviating from the current standard – be adequately justified.

5.2. Concomitant medication

During trials, the use of concomitant medication should be restricted. Drugs with analgesic action or with specific effects on bowel function should generally be excluded, and may only be allowed as specific "rescue medication" if adequately justified. The rescue medication should be clearly specified and evaluated as efficacy parameter (and for safety). The use of antidepressants –medication potentially used to treat concomitant psychiatric co-morbidity, but also used for the treatment of IBS – could be allowed, provided that patients are on stable doses for one single compound prior to study entry, and are maintained on that dose for the duration of the study. Lifestyle and dietary measures

for treating IBS should be stabilised prior to study entry and be maintained during the course of a clinical trial.

5.3. Early exploratory studies

Candidate compounds should – after the primary pharmacology has been characterised in the pre-clinical development – also be evaluated for their pharmacodynamic properties in humans. Although extrapolation from in-vitro and animal experiments may be acceptable if the late stage evaluation of candidates shows clinically relevant improvements in symptoms with an acceptable safety profile, the evaluation of the pharmacodynamic properties in the early development may help to understand the mode of action of a compound more clearly, and thus support the biological plausibility of the clinical effects achieved. Moreover, effects seen with evaluation of pharmacodynamic endpoints in different patient populations can be useful for the determination of the final target population.
It is therefore recommended to conduct – preferably after the human tolerability and early pharmacokinetic studies have been finalised – pharmacodynamic studies in healthy volunteers and/or in suitable IBS-patients. These studies should investigate the effects of a candidate compound on gastrointestinal motility and on intestinal sensitivity.

A wide range of potential investigations for the evaluation of motility is available and the method should be chosen based on the characterisation of the pharmacology in the pre-clinical development [34]. The potential influence of new candidate compounds on (the perception) of abdominal pain should be investigated by studies evaluating rectal distension. For these evaluations, however, a careful selection of the methods and the subjects to be included is regarded to be of high importance [35] [36,37] . All compounds, but especially those influencing central pathways of pain processing and/or perception may additionally be evaluated by the newer methods of cerebral evoked potentials, PET, or function magnetic resonance imaging, although these methods have currently to be regarded as partly still experimental [38].

The early phase of development should also encompass a full documentation of the pharmacokinetics of a compound, including the evaluation of drug-drug interactions and PK in special populations.

5.4. Main clinical studies

Late exploratory studies

In the phase II of the development, all candidate drugs should be evaluated for their dose-response relationship. These studies should already reflect the intended use of compounds (intermittent and/or continuous use) and the selection of the IBS-subtype. The treatment setting and the subgroup to be chosen should be based on the pharmacological profile of the compound, and the results of the in-vitro, animal, and early human study results.

Confirmatory studies

The design of the pivotal clinical studies is proposed to be different according to the intended use: Depending on the pharmacology of the compound, and the results of early PD trials, either a long-term continuous use, or a short-term repeated treatment may be investigated (or, if deemed adequate, even both). However, for all studies, a 10-14 days lead-in period should be part of the design, in order to adequately determine the fulfilment of the in- and exclusion criteria. A placebo treatment during this period is not recommended, and the exclusion of placebo responders is discouraged. During the run-in period, treatment of IBS symptoms should be done with a defined rescue medication only. Both types of treatment schedules should be investigated in placebo-controlled, randomised, double-blind trials. The inclusion of an active comparator can currently not be recommended, but may become adequate in the future, once a “standard pharmacological therapy” is established. Even if such a “standard

agent" has been established, placebo will still be considered to be the most adequate and decisive comparator, and in such a case, it is recommended to include active control only as a third arm.

a) Short-term intermittent treatment

Short-term treatment intermittent use of compounds should be evaluated in repeated treatment courses shorter than 8 weeks. Previously a duration of 4 weeks has been included in the "Points to Consider on the evaluation of medicinal products for the treatment or Irritable Bowel Syndrome". This is still generally regarded to be adequate, however, the duration of the treatment cycles should be justified based on the pharmacology of the compound and can be shorter (e.g. use of antibiotics or probiotics). At least one repeated treatment cycle has to be documented.

Depending on the pharmacology of the compound, and the envisaged target population, studies administering study drug "as needed", or "on demand" are also possible.

For the treatment scenarios in short-term intermittent use, generally many designs are possible, and the following features would require careful consideration:

- The patient groups to be (re-)randomised for the initial and for the repeated cycle (e.g. balanced or unbalanced first randomisation; open-label treatment in the first cycle (if first treatment cycle has been documented in a separate trial); re-randomisation of all patients or responders only)
- The number of re-treatment cycles and the duration of cycles "on" and "off" medication (e.g. fixed or flexible duration up to a completely flexible design with variable duration of "on-" and "off-treatment" cycles, counting "good days/bad days" (to be defined on the basis of the response criteria as given in 5.5) with fixed total study duration)
- The definition of relapse in the periods off active treatment (e.g. the same or different level of severity)

The patient population for such treatment scenarios would have to be selected according to the disease course and symptoms (i.e. not suitable for a population suffering from continuous symptoms).

Generally, the aim of the trials documenting repeated treatment should be to show that not only superiority of the investigative agent over placebo is achieved during its first use, but it should also be investigated whether there is a potential to maintain beneficial effects during the periods off-treatment. The aim of the repeated treatment would be whether an at least similar effect (as compared to the first cycle) can be achieved if the compound is administered after relapse has occurred. The design of such trials should be intended to better imitate "real world conditions" in which patients frequently stop medication, or grant themselves a "drug holiday".

It is generally recommended to seek Scientific Advice if such an approach is pursued.

b) Long-term continuous treatment:

Large, double-blind, parallel group, placebo-controlled clinical trials should be performed in patients intended or found suitable for long-term continuous use. The trials should be long enough to determine if any response will be sustained, and to cover a potential late drop-out, and/or change in IBS-subtype. The duration of such studies is recommended to be at least 6 months. Other study designs and/or durations will have to be justified in terms of their ability to adequately assess long-term sustained efficacy, withdrawal, and rebound, as well as safety.

All compounds should also be evaluated for the occurrence of withdrawal and/or rebound effects in studies reflecting the intended duration of treatment, which is preferentially included in at least one of the phase III confirmatory trials. A randomised withdrawal phase in such studies is currently

considered to be the best method to have available a full comparison between ongoing treatment, new onset of treatment, and withdrawal of the active compound.

5.5. Endpoints

a) Primary endpoints:

The previous "Points to consider" did include the recommendation to present two co-primary endpoints as primary outcome, namely the "patient's global assessment of symptoms" and the assessment of abdominal discomfort/pain, based on the fact that currently no validated and widely accepted outcome measures for assessing clinical endpoints in IBS were available. This has in principle not changed since and it is still recommended to combine two major IBS symptoms in the primary endpoint.

Previous controversy on the adequacy and method of global assessment tools, especially the binary "adequate relief" assessment [39] [40] [41] [42] [43] have led to the conclusion that the global symptom evaluation should no longer be part of the primary evaluation[44]. The global assessment of all symptoms, as intended in the "adequate relief" or other similar endpoint has the obvious disadvantage that it partly also covers the evaluation of abdominal pain and discomfort at the same time. A large effect on this feature of the disease might therefore lead to a huge effect even in the case where only minimal changes on the defecation related symptoms are achieved.

This guideline therefore recommends the further development and validation of PRO instruments for the use as primary outcome parameter in clinical trials in IBS. Such an instrument should be a multi-item PRO, including and reflecting the clinically important signs and symptoms in IBS. Different instruments may be suitable (or be needed) for different disease subtypes, and even for different sub-populations. An instrument to be used as primary outcome measure in pivotal clinical trials in IBS should be completely and rigorously validated. Such an instrument, however, is currently not available.

It is therefore recommended for the time being, to assess the main symptomatology in at least partially validated scales/outcome parameters. Because the main symptoms in IBS are considered to be abdominal pain/discomfort along with abnormalities in defecation (consistency and frequency of stools), and there is ongoing controversy on whether abdominal discomfort is a symptom distinctly different from abdominal pain (and whether it should be evaluated together or separately) the main endpoints are now recommended along with the Rome III definitions. The two components included in the proposed primary endpoint should therefore be the evaluation of abdominal pain and the evaluation of stool frequency for IBS-C (based on the number of complete spontaneous bowel movements (CSBMs) per week), and the evaluation of stool consistency for IBS-D, based on the Bristol Stool Form Scale. For other subtypes of IBS, and for "global" development programmes intending to treat two or more subtypes, the use of the global assessment is, however, still recommended. The primary endpoint should be evaluated primarily as responder rate. The numerical evaluation of changes in scales is regarded to be a secondary endpoint. For the evaluation of abdominal pain, the use of a 11-point NRS-scale has at least been partially validated for use in IBS, and is therefore regarded to be acceptable [45]. However, the previously recommended use of other scales for pain can also still be accepted, if adequately justified. As previously requested, scales (other than the 11-point NRS) should be open to change in both directions.

Primary endpoints are therefore recommended as follows:

A responder is defined as a patient who fulfils the response criteria displayed in the following for at least 50% of the observation time.

- a) IBS-D: A responder is defined as a patient with an abdominal pain score which has improved at least 30% compared to baseline and who experiences an at least 50% reduction in the

number of days with at least one stool that has a consistency of 6 or 7 (in the BSFS) compared to baseline. [46]

- b) IBS-C: A responder is defined as a patient with an abdominal pain score which has improved at least 30% compared to baseline and who experiences an increase of at least one CSBM per week compared to baseline.
- c) IBS-M, IBS-unsubtyped, mixed IBS-C and IBS-D populations: A responder is defined as a patient with a subjects global assessment of efficacy scale of the highest two improvement grades if a 7-point scale is used, or of the highest improvement grade if a 5-point scale is used, and with an abdominal pain score which has improved at least 30% compared to baseline.

Most of these evaluations can be based on daily ("worst abdominal pain in the past 24 hours"; "one stool per day"), however, the criterion for improvement of stool frequency can be based on weekly evaluations only. Therefore, the primary evaluation should be based on weekly responder rates in the case of b). In the cases a) and c) the primary evaluation can also be based on daily responder rates. However, in order to advocate such an approach, the evaluation of daily symptom collection should be evaluated in the phase 2 trials, in order to prove a comparable distribution of the rate of missing values across the different days of a week and an acceptable low number of missing values overall.

In cases of weekly evaluations of the primary endpoints a minimally required number of valid diary entries should be defined in order to be evaluable as responder, and define patients below this threshold as non-responders.

b) Secondary endpoints:

In development programmes, where the global evaluation of the symptomatology is not included as primary endpoint (choices a) and b)), a global symptom assessment should be defined as the main secondary endpoint. The choice of a scale measuring improvement and deterioration is clearly recommended. The global assessment can also likewise be based on daily or weekly responder rates as recommended for the primary endpoint.

Secondary endpoints in IBS are regarded to complement the evaluation of the primary endpoints and are required to be generally supportive of the primary endpoints, because the currently proposed composite endpoint is not regarded to be fully validated. The further secondary endpoints should include the following, but may not be exhaustive and can be adapted based on the disease subtype to be studied, if adequately justified:

- The responder rates for abdominal pain and stool abnormalities evaluated separately
- The numerical evaluation of stool frequency (CSBM and SBM) and stool consistency
- The numerical evaluation of abdominal pain and the evaluation of the number of pain free days
- The numerical and responder evaluation on abdominal discomfort, straining and bloating
- The evaluation of urgency of defecation, distension
- Different thresholds for the responder analysis of abdominal pain (e.g. 40% and 50% improvement)
- The evaluation of change in a defined severity scale of IBS (e.g. IBS-SSS).
- The evaluation of Quality of Life using validated generic and disease specific Quality of Life scales.

- Sensitivity analyses
    - Different thresholds as regards duration of response (e.g. 75% of the time for the primary evaluations and other responder evaluations)
    - Evaluation of the time-course of response (e.g. comparison of responder rates per month of observation; “sustained response” with at least 50% response during the last month of observation in addition to the 50% requirement for the whole study period)
    - Evaluation of different thresholds for the definition of invalid or missing data entry being defined as non-responders
    - Evaluation of different imputation of missing values, depending on the method used for the primary analysis.
    - In order to exclude a deterioration of the symptoms towards the end of the treatment period, response should also be evaluated by defining responders additionally as those who achieve response in at least 50% of the last four weeks of treatment in addition to the overall requirements for response.
- Exploratory endpoints
    - The evaluation of psychological/psychiatric co-morbidity on established scales
    - Impact on work productivity and health care utilisation if deemed relevant

6. Studies in Special patient groups

6.1. Children

IBS in children has also been characterised by the Rome III criteria. According to these criteria, IBS is clearly differentiated by definition from the other childhood abdominal pain related disorders such as functional dyspepsia, abdominal migraine, functional abdominal pain, and functional abdominal pain syndrome. The occurrence of recurrent abdominal pain in childhood, as well as IBS seems to determine the occurrence of IBS in adulthood [47] [48]. According to results from North America, IBS in childhood appears to have a high prevalence in school children [49]. Data from Europe have questioned this high frequency [50] [51], but newer data, appear to confirm the relatively high prevalence of the disease.[52] However, previous trials in the indication have suffered from very low recruitment[53].

IBS in children – for the conduct of clinical studies – should be defined on the current proposals of the Rome Committee (Rome III criteria) unless otherwise adequately justified. According to these criteria, IBS in childhood is defined as follows:

A patient must have all of the following:

- Abdominal discomfort or pain associated with 2 or more of the following at least 25% of the time:

    a) improved with defecation

    b) onset associated with a change in frequency of stool

    c) onset associated with a change in form (appearance of stool)
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms.

The diagnostic work-up in children to be included in clinical trials will have to reflect that the disease in children has not been defined on a symptom basis only, but also as a diagnosis of exclusion. Evaluation of the disease needs to include careful history taking not only from the patient but also from the caregiver, drafting of growth charts, and evaluation of recent and current growth. The omission of or need for endoscopic evaluations should be justified

Separate trials should be conducted in children in order to prove efficacy and safety of drug candidates. The age range to be included in these trials is from 4-18. Extrapolation from adults to children – even to adolescents – appears to be questionable.

Ideally, separate trials should be conducted in different age ranges according to the children's abilities to reliably express and rate symptoms (or the caregivers to do so) and the subsequent restricted availability of reliable outcome measures (e.g. 4-7 years, 8-12 years, adolescents). The development of outcome measures for IBS in children is encouraged.

Dose-response/dose finding and PK data should be generated in all age groups from 4-18 years.

Type of study:

In children prospective, multi-centre, double-blind, placebo-controlled, randomised trials are necessary, a third arm with a waiting list (patients randomised to delayed treatment) can be included into studies in children. Because the inter-rater reliability for the Rome III criteria has been shown to be rather low, special emphasis should be put on the careful selection of patients in clinical trials.[54] Withdrawal and rebound effects should also be investigated in children, or absence of such investigation be adequately justified. The study duration for the proof of efficacy should be long enough to cover a potential spontaneous change in symptom type, depending on the population included. A study duration of 2-3 months may be sufficient in children, if long-term safety and efficacy in adults has adequately been demonstrated in a population with stable symptoms. Long-term safety data should be generated in addition (see below) [55].Intermittent treatment cycles may also be adequate to be documented depending on the patient population included (See Chapter 6.3) and intent of medication.

In consideration of the uncertainties with recruitment for studies in children, the presence of reliable data as regards efficacy and safety in "neighbouring" indications, covering both, stool abnormalities and abdominal pain (e.g. chronic constipation and childhood functional abdominal pain syndrome), may alleviate the requirements for the extent of trial data to be generated in childhood-IBS.

Primary endpoint:

Similar to adults, IBS is defined to be a pain related syndrome accompanied by stool irregularities. The primary endpoint should therefore similarly be defined as a combination of pain relief and relief of stool disturbances. Global response to therapy (effect on psychosocial traits and daily well-being) should be defined as secondary endpoint. No clear guidance can currently be given whether a 30% degree of improvement in pain – as validated for adults – will be of similar clinical importance as in adults. A higher percentage (in the change in pain scale used compared to baseline) would be preferred, and the final choice should be justified. The need to develop reliable PROs adequate for the different age group is similarly obvious for children than it is in adults and is encouraged.

Safety:

Depending on the type of study drug (e.g. mechanism of action) special safety issues will have to be addressed in different childhood ages concerned. As IBS is considered a chronic disease entity even for children, long-term safety data – of at least one year – have to be collected.

In general, developmental parameters of growth and maturation have to be documented in all studies. Agents for which a potential influence on these parameters could be suspected (e.g. those acting by CNS pathways) should present a safety documentation regarding growth and development of at least 2 years. Depending on the overall safety profile and mode of action of the compound, the 2-years data may be provided post-marketing. For agents influencing gastrointestinal motility/secretion, special emphasis should be laid on water and electrolyte balance (similar to adults; see Chapter 8).

6.2. Elderly

There appears to be a paucity of data for the epidemiology of IBS in patients older than 70 years of age [56]. A slightly lower prevalence has been found for patients in people beyond 65 years of age as compared to other adults [57] [58]. On the other hand, increasing age has been identified to be a factor for higher consultation rates [59] [60], potentially outweighing the slightly lower incidence, when defining IBS patients as the "consulter" population only. With the potentially long history of symptoms in IBS, prevalence in the elderly can be assumed not to be substantially different from other age groups.

In clinical efficacy studies of new medicinal products, there has been a clear preponderance of women aged 30-50, meaning that the composition of the study groups have not fully reflected the epidemiology of the disease (see also 7.3.), and usually only a tiny proportion of elderly people have been included.

The intent to include a population reflecting the epidemiology of the disease (in terms of prevalence), and thus including a relevant proportion of elderly subjects should be part of all future development plans. Studies, and the proportion of elderly people included, should be big enough to allow a reasonable conclusion on similarity or differences in the efficacy and safety of a new compound.

New drug candidates in IBS are usually affecting gastrointestinal motility and/or secretion/absorption in one way or the other, thus influencing defecation frequency and consistency of stools with the obvious consequences of the undesirable effects constipation and/or diarrhoea, and the potentially more serious consequences thereof, e.g. bowel obstruction and disturbances of water/electrolyte and acid-based balance. Elderly people might be more prone to the dangers of these potential exaggerated effects and it is therefore considered a clear requirement from the patient's safety perspective, to allow reasonable conclusions on the safety of a new compound in the older age group [61].

6.3. Gender

The epidemiology of IBS according to sex shows an overall predominance of women with a pooled Odds Ratio in prevalence of 1.67. However, women appear to develop constipation-predominant subtype more frequently as compared to the diarrhoea predominant IBS, where a higher prevalence seems to be present in male patients [62]. Epidemiological studies have also shown that consultation behaviour appears to be different between men and women, with a higher percentage of females being consulters, and thus anticipated to have more severe symptoms. A female to male ratio of 4:1 to 5:1 is therefore been suggested to be realistic for a "real world" patient population depending on disease subtype. Gender differences are also obvious in clinical presentation of IBS, and in the pathophysiology[63] [64] [65]. Although the gender differences have historically been considered to be of minor clinical relevance, differences according to gender in the clinical effects of potential drug candidates appear to be an immanent possibility.

Potential gender differences should therefore be part of the early development, investigating the pharmacodynamic effects and proof of principle, in order to avoid large clinical trials showing reduced, and potentially negligible clinical effects in one gender. The development of drug candidates for one

gender only is considered fully acceptable, if indeed a differential therapeutic response with greatly reduced effects in one of them can be expected.

Previously final conclusions on the outcome of clinical development programmes regarding sex have been hampered by the tiny numbers of male patients included into clinical trials. Low numbers of male patients (e.g. due to recruitment problems) are hampering conclusions on the clinical effects in this gender and the interpretation of the overall dataset. Future applicants should therefore consider that it cannot readily be expected to be acceptable to narrow the indication to one of the genders during an initial marketing authorisation procedure.

If in the early development programme no gender differences are detected or anticipated, it should be aimed at including a sufficient number of male patients to allow conclusions on efficacy and safety in both, men and women. The inclusion in late clinical studies should aim at mimicking the “natural” sex distribution in the disease for the population anticipated. Potential differences between men and women should again be evaluated before the planning of phase 3 studies, and, of course for the results of the phase 3 studies.

6.4. Geographic region

Previously, many development programmes have focussed in their development on the United States or North America, and aim or aimed at inclusion of a North American IBS population only.

In general, the inclusion of a sufficient proportion of patients recruited in Europe is considered necessary unless it can be demonstrated that no relevant differences to European IBS populations can be expected. If indeed a development programme in one country or region only is planned, the respective analysis of ethnic/geographic and cultural factors according to the requirements of the respective guidance documents (ICH E 5, EMA/CHMP/EWP/692792/2008) should be presented at the time of MAA. Depending on the mode of action of a certain compound and assuming that a population with mainly European descent is included for the condition IBS, a justification of the transfer of data from the North American to a European population appears to be possible.

However, due to potential differences mainly in the perception and frequency of different IBS symptoms by patients and also the psychological co-morbidity [66] [67] , the inclusion of European patients into global development programmes is considered advantageous. .

The complete transfer of efficacy and safety from other regions of the world to Europe may also become increasingly difficult with the development of PROs in the field, which are intended to form the basis of the primary efficacy evaluations in the future. In such a situation, where a PRO has been validated in one country or region of the world only and is finally used for the proof of efficacy of a new compound as primary endpoint, it may no longer be possible to accept an application based on foreign data only.

Therefore, companies or private-public partnerships developing PROs to be used as primary outcome measure in IBS are encouraged to undertake exercises of translational and cross-cultural validation work including a variety of European countries right from the start of such a development, in order to be able to conduct future studies with a fully validated primary outcome measure (PRO) in European patients also [68] [69] [70].

The number of patients to be included in clinical development programmes for IBS should allow a reasonable comparison of efficacy and safety outcomes of populations from different regions.

7. Safety

As IBS is a non-life threatening condition, the safety of any therapeutic intervention is paramount. Similarly, because treatment of IBS will require intermittent or continuous long-term use of medication, it is necessary to have long-term safety data with an observation period of at least 12 months available in adequate numbers to accurately asses the safety of the medicinal product. For products intended for long-term continuous use, this will mean the observation of 12 months on active treatment, whereas for compounds with an intermittent use, the time on active drug can be reduced to a period of at least 6 months, with the documentation of at least 12 months of observation (whichever comes first). Safety data collected in sub-populations of IBS patients may not support authorisation in a wider patient population.

The safety evaluation in clinical trials for IBS is in general not different from other investigational products under development and should be focused according to the pharmacology of a compound.

This means that usually the main focus should be on the evaluation of gastrointestinal events, especially if these events are theoretically the consequence of the primary pharmacology of the new compound, which is usually to influence gastrointestinal motility and secretion/absorption, thus leading to different defecation frequency and stool consistency. As displayed in Chapters 7.1 and 7.2. for children and the elderly population, the evaluation of safety should focus on the induction of diarrhoea and constipation, and of their more serious consequences such as bowel obstruction/ileus and of disturbances of electrolyte-, water- and acid based balance, hypotension and syncope. The focus of the evaluations may, however, change depending on the primary pharmacology of a compound, e.g. for centrally acting substances, the main safety evaluation may be more adequate to be put on the evaluation of CNS events.

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