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POINTS TO CONSIDER ON THE EVALUATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF IRRITABLE BOWEL SYNDROME

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POINTS TO CONSIDER ON THE EVALUATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF IRRITABLE BOWEL SYNDROME

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This Points to Consider document is intended to provide preliminary guidance for the clinical investigation of medicinal products used in the treatment of the Irritable Bowel Syndrome (IBS). This document in relation to IBS will be revised in accordance with scientific advances made in this area.

This document has to be read in conjunction with directive 2001/83/ec, as amended, and all other relevant EU and ICH guidelines and regulations.

INTRODUCTION

The Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder in which abdominal discomfort or pain is associated with defecation or a change in bowel habit, and with features of disordered defecation. These symptoms represent a condition in which disturbances in motor and/or sensory function of the gut may be associated with psychosocial disorders, and the interaction leads to symptoms at several levels of the gastrointestinal tract. By definition, the diagnosis excludes structural or biochemical abnormalities of the gut. The clinical features of IBS have been formalized in the Rome II criteria which are widely accepted as the state-of-the-art criteria for research purposes. However, these criteria have limitations in that they do not encompass some clinical patterns of IBS (e.g. alternating-IBS subtype) and the requirement for abdominal pain or discomfort excludes patients whom some clinicians would classify as having IBS.

IBS is now considered to be the most common gastrointestinal disorder. Prevalence in the western world is estimated to be 15 – 20% of the adolescent and adult population and the disorder accounts for 20-50% of referrals to gastroenterology clinics. The age distribution is very broad but 40% of 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 is 1:1 to 2:1 but a female predominance is more evident in those seeking health care. IBS is not a life threatening condition; however, it does have a definite impact on patients quality of life and many patients require medical treatment with consequent economic costs.

Current approaches to management of IBS consist of identification of symptoms consistent with the syndrome and the exclusion of organic disease with a similar presentation, followed by non-pharmacological and pharmacological therapies, where appropriate. Current pharmacological therapeutic options are limited and the effectiveness of many is poorly documented. The waxing and waning of symptoms and the high placebo response rate (up to 70%) seen in some clinical trials make it difficult to assess the objective efficacy of any pharmacological treatment. Non-pharmacological options include an effective physician-patient relationship, patient education and reassurance, dietary modification (e.g. high fibre diet where constipation predominates), biofeedback and psychotherapy. Pharmacological options are not usually recommended unless reassurance, dietary measures and life style education and modifications have proved ineffective. The current pharmacological therapies aim at treating the symptoms with the rationale being either to modulate intestinal motility, decrease visceral sensitivity or treat associated disorders, particularly anxiety or depression.

I. SCOPE OF THIS GUIDANCE

This Points to Consider document gives guidance on the performance of studies involving the drug treatment of IBS only. It addresses the issue of short-term and long-term treatment of IBS, the design of pivotal phase III studies for such treatment and safety considerations in relation to this therapeutic area.

II. DESIGN OF STUDIES FOR TREATMENT OF IBS

IBS is a chronic disease whose course is extremely variable in the general population. The majority of patients have mild to moderate symptoms which tend to wax and wane in severity, while approximately 5% of patients have constant severe symptoms. It is recognised that the short-term relief of symptoms, particularly during an acute exacerbation of symptoms, would be beneficial to many patients with this condition. Similarly, it is acknowledged that a therapeutic agent which offered longterm benefit (presumably with continuous use) to patients would be desirable. The design of studies to demonstrate short-term efficacy of a treatment modality is considerably different to that which is advocated for demonstration of long-term efficacy, as outlined below.

Short-term Treatment

Given the chronic nature of IBS, it is envisaged that drugs intended for the short-term relief of symptoms would be given on an intermittent basis over months or years and that the individual time periods of treatment could be fixed or variable. The duration of active treatment during the phase III trials for such an indication may depend on the pharmacological profile of the drug and the individual patients symptoms. However, the study design and duration should allow for the adequate assessment of the effect of the treatment with repeated use and the effects of withdrawal of treatment. Studies to demonstrate efficacy should ideally adopt a placebo-controlled, double-blind, parallel group design. It is envisaged that the minimum duration of active treatment for the initial period of treatment would be 4 weeks, with efficacy assessed over the entire treatment period. A shorter active treatment period would require justification. A prospective period of baseline observation to document baseline disease activity and to allow patients to become familiar with data collection methods is recommended. The timing of intervention should be carefully considered. It is worthwhile to avoid diagnostic or other testing immediately before randomisation, which might be associated with an improvement of symptoms.

Demonstration of efficacy with repeated use would also be required to support a short-term treatment indication and it is envisaged that a minimum of 2 cycles of treatment should be included in the study design.

It may be acceptable to conduct a number of studies with different designs, which when viewed collectively, provide all of the required efficacy data, as follows.

- Dose-response studies
- Efficacy with first use (Placebo-controlled, double-blind, randomised, parallel group study design of approximately 4 weeks duration)
- Withdrawal/rebound effect (this could be examined in a blinded, placebo extension phase of the efficacy with first use studies)
- Efficacy with repeated use (A number of study designs are possible e.g. a design which includes a non-controlled initial treatment period of 4 weeks followed by a randomised, placebo-controlled second treatment assessment of efficacy in responders to the first period of therapy. An alternative design would be to conduct a placebo-controlled, double-blind, randomised, parallel group study design of approximately 4 weeks duration, followed by a variable period off-treatment with rerandomisation to placebo or active treatment in a second cycle, when symptoms warrant restarting medication.)

Long-term Continuous Treatment

Large, double-blind, placebo-controlled clinical trials should be performed in patients with well-defined IBS to establish the efficacy, safety and tolerability of a drug intended for long-term continuous use. Studies of parallel group design should be adopted. A prospective period of baseline observation to document baseline disease activity and to allow patients to become familiar with data collection methods is recommended. The timing of intervention should be carefully considered. It is worthwhile to avoid diagnostic or other testing immediately before randomisation, which might be associated with an improvement of symptoms.

The trials must be long enough to determine if any response will be sustained and to determine the effects of withdrawal of treatment. Considering the cyclic and non-life threatening nature of the disease, a duration of 6 months active treatment is considered necessary. A blinded withdrawal extension phase after the initial double-blind period should be included in order to determine the effect of withdrawal of treatment. Alternative study designs should be justified in terms of their ability to adequately assess longterm sustained efficacy, withdrawal/rebound effect and safety.

III. INCLUSION AND EXCLUSION CRITERIA FOR IBS STUDIES

Patient Population

The study population should be representative of a broad spectrum of IBS patients, therefore, patients may be recruited from primary, secondary or tertiary care settings. Men and women should be included in numbers large enough to allow meaningful sub-group analyses in order to show consistency of effect.

Patients presenting with IBS as defined by the Rome II criteria are eligible for inclusion. This requires:

At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features:

1) Relieved with defecation, and/or

2) Onset associated with a change in frequency of stool; and/or

3) Onset associated with a change in form (appearance) of stool.

The following symptoms cumulatively support the diagnosis of IBS:

- Abnormal stool frequency (abnormal may be defined as >3 bowel movements/day and <3 bowel movements/week);
- Abnormal stool form (lumpy/hard or loose/watery stool);
- Abnormal stool passage (straining, urgency or feeling of incomplete evacuation);
- Passage of mucus;
- Bloating or feeling of abdominal distension.

These symptoms can be used to subclassify patients with predominant diarrhoea or constipation for entry into clinical trials as follows:

Symptoms supportive of IBS

1. Fewer than three bowel movements a week
2. More than three bowel movements a day
3. Hard or lumpy stools

4. Loose or watery stools
5. Straining during a bowel movement
6. Urgency
7. Feeling of incomplete bowel movement
8. Passing mucus during a bowel movement
9. Abdominal fullness, bloating or swelling

Diarrhaoea-predominant

One or more of 2, 4 or 6 and none of 1,3 or 5.

Constipation-predominant

One or more of 1, 3 or 5 and none of 2, 4 or 6.

Studies which limit recruitment based on symptom subtype or other criteria (e.g. severity of symptoms) should have a clear rationale for such a strategy and it should be noted that the results of such studies may not be applicable to a broader IBS population. Patients must be able to maintain their usual diet and lifestyle during the course of the study and inclusion of patients should be done by appropriately educated and trained investigators.

Patients who do not fulfil the Rome II criteria should be excluded. In addition the following patients should be excluded:

- Patients with lactose intolerance.
- Patients with abnormal laboratory tests, positive stool cultures in patients with diarrhoea-predominant IBS or abnormal proctoscopy/ abdominal ultrasound which requires further investigation.

Patients with a family history of colorectal cancer should be properly evaluated, based on the current state of the art policy of screening.

IV. RECOMMENDED PRIMARY/SECONDARY EFFICACY ENDPOINTS

Primary efficacy endpoints: The patient's global assessment of symptoms and abdominal discomfort/pain should be used as the two primary end-points. Statistically significant changes must be found in both parameters. A statistically significant result must be justified in terms of clinical relevance. There are currently no widely accepted, validated outcome measures for assessing clinical endpoints in IBS. However, the applicant should provide justification for the choice of outcome measures. These should be easily explained and understandable by the patient, and sensitive to change in the patient's condition. Measurement of change should include deterioration as well as improvement. Measurement of discomfort/pain should use a validated scale.

Secondary (supportive) efficacy endpoints: Choice of secondary efficacy variables should be justified by the applicant and should include GI symptoms such as bloating/distension, stool frequency and urgency and quality of life parameters. Health-related quality of life must, however, be considered as the most important secondary endpoint.

Definition of a Responder

The protocol should define a priori a responder in terms of a clinically meaningful change in the primary endpoints. The study should compare the proportion of patients who achieve the stipulated amount of improvement necessary to be qualified as a responder rather than a mean change in a score. An a priori specification of the time interval over which a responder or a response occurs should be included. This should be consistent over time but usually be towards the end of the trial.

It is acknowledged that the assessment of efficacy may depend on the specific characteristics of the drug and its intended use (e.g. on demand or continuous). It is recommended that for short-term studies of about 4 weeks duration, a positive response would require a pre-specified improvement in symptoms for at least 50% of the time. The study should include measures of change for each of the symptoms that was part of the entry criteria.

V. STATISTICAL CONSIDERATION

Statistical outcome should follow ICH E9 guideline. In analysing the results of the study the estimated effects of the treatment relative to placebo together with its confidence limits should be related to the minimal effect of clinical interest. Adjustment for use of rescue medication should be pre-specified in the analysis plan as well as conservative ways to handle withdrawals in the efficacy analyses.

VI. OTHER ISSUES

Concomitant Treatment

All analgesic drugs and drugs with specific effects on bowel function should be excluded during the study period. Non-steroidal anti-inflammatory agents must be strongly discouraged. The use of antidepressants could be allowed, provided patients are on a stable dose prior to study entry and are maintained on that dose for the duration of the study. The use of rescue medication (e.g. laxatives, anti-diarrhoeals) should be pre-specified. Lifestyle and dietary measures for treating IBS should be stabilised prior to study entry and be maintained during the course of a clinical trial.

Choice of Comparator

As pharmacological options are not usually recommended unless dietary measures have proved insufficient and currently available pharmacological therapy aims at treating the symptoms, the use of placebo as a comparator in a double-blind, parallel trial design is the most appropriate at present.

Special Safety Considerations

As IBS is a non-life-threatening condition, the safety of any therapeutic intervention is paramount. Similarly, as it is likely that effective treatment of IBS will require intermittent or continuous long-term use of medication, it is necessary to have long-term safety data (12 months) in adequate numbers to accurately assess the safety of the medicinal product. Safety data collected in sub-populations of IBS patients may not support authorisation in a wider patient population.