Science For A Better Life

Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Date of study report	20-JUN-2018
Study title	A double-blind, randomised, placebo-controlled study on the efficacy of Iberogast® (STW 5) in patients with irritable bowel syndrome
Sponsor	Bayer
Sponsor's study ID	17063
NCT number	NCT01940848
EudraCT number	2011-002613-10
Study Phase	3
Indication	Irritable bowel syndrome (IBS)
Study objectives	Primary objective: • To show the efficacy of STW 5 on pain-related symptoms of subjects with irritable bowel syndrome (IBS) Secondary objectives: • The assessment of the safety and tolerability of STW 5 and to assess the effect of STW 5 on quality of life (QoL)
Test drug	STW 5 (Iberogast®, BAY 98-7411)
Active ingredient(s)	Combination of extracts from *Iberis amara totalis, Angelicae radix, Cardui mariae fructus, Carvi fructus, Chelidonii herba, Liquiritiae radix, Matricariae flos, Melissae folium, Menthae piperitae folium*.
Dose	20 drops, 3 times daily, before or during meals
Route of administration	Oral
Duration of treatment	28 days
Batch Numbers	010213KP (expiry date: JAN-2015), 010213KP (expiry date: JUL-2016), 010416KP (expiry date: MAR-2018), 010117KP (expiry date: JUL-2018)
Reference drug	Placebo
Dose	20 drops, 3 times daily, before or during meals
Route of administration	Oral
Duration of treatment	28 days
Main inclusion criteria	• Subjects of either sex aged > 18 years. • Subjects meeting the Rome III IBS diagnostic criteria. • History of pain intensity with an average of worst abdominal pain in past 24 hours score of > 30 on a daily measured visual analogue scale (VAS) scale during screening phase (a minimum of 8 VAS values, assessed on different days during screening phase, is required)
Study design	Multi-centre, randomised, double-blind, placebo-controlled study.

Methodology	Four study visits were scheduled for subjects: the screening visit (visit 1, day -14), visit 2 (day 1, randomisation), visit 3 (day 15 +/-3) and visit 4 (day 29 +/-3, end of treatment). The period between visit 1 and visit 2 served the purpose of baseline measurements to ascertain the fulfilment of the inclusion criteria. During the following treatment period (visit 2 through visit 4), subjects were treated with either STW 5 / Iberogast® or placebo in a 2:1 ratio. Primary efficacy endpoint was the efficacy of STW 5 on pain-related symptoms of subjects with IBS. Secondary objectives were the assessment of the safety and tolerability of STW 5 and to assess the effect of STW 5 on QoL. Abdominal pain intensity was evaluated by using a VAS to rate the worst abdominal pain over the past 24-hours. Stool consistency was assessed by the Bristol Stool Form Scale (BSS) which is probably more clinically relevant for IBS-D subjects. The BSS provides a pictorial and verbal description of stool consistency and form and is an appropriate instrument for capturing stool consistency in IBS trials. Stool frequency is readily defined and is probably more clinically relevant for IBS-C subjects. IBS-QoL was evaluated on baseline visit and final visit. The Birmingham IBS symptom questionnaire was used by subjects to evaluate their IBS symptoms. Safety was assessed by means of adverse event (AE) profile, laboratory parameters (haematology, blood chemistry, urinalysis), vital signs (blood pressure, heart rate, body weight) and tolerability (investigator and subject). Concomitant diseases and concomitant treatments used during the study were recorded in the case report form.
Statistical methods	All statistical analyses were appropriate to the nature and distribution of the data collected. All demographic and baseline data, as well as all efficacy and safety variables, are described by statistical characteristics for all visits, together with changes from baseline, whenever applicable. Hypothesis tests were carried out at a two-sided significance level α of 5%. The main analysis population was the full-analysis set (FAS). All analyses of the primary efficacy variable were repeated for the per-protocol set (PPS) to assess the sensitivity of the results. All analyses of secondary and further efficacy endpoints were carried out for the FAS. Only the primary efficacy variable was tested confirmatory. Other statistical tests of (secondary efficacy and safety) variables were only interpreted exploratory. Therefore, no adjustment for multiple testing was needed. For all statistical analyses, study centres with less than or equal to 10 subjects were pooled to 1 study centre. The secondary efficacy parameter responder rates for stool frequency / consistency after 4 weeks was analysed analogously to the primary efficacy endpoint. Within a Cochran-Mantel-Haenszel test controlling for centre, the odds ratio for the treatment comparison was determined together with the respective 95% confidence interval two-sided and the respective p-value. Responder rates for stool frequency / consistency after 2 weeks were analysed analogously to the primary endpoint. To assess the consistency of the results, the same analysis was repeated by imputing the missing values using LOCF approach as the sensitivity analysis.
Early termination	Not applicable

Substantial protocol changes	Not applicable, the changes in the Amendments No. 1-4 were minor and not clinically significant.
Study period	Study Start Date: 11-OCT-2013 Study End Date: 25-OCT-2017
Study center(s)	19 active study centres recruited patients in Germany
Number of subjects	Planned: 237 Analyzed: 243
Criteria for evaluation ***Efficacy***	Primary variable: • Responder during treatment period of 4 weeks as measured by pain intensity Secondary variable: • Responder during first 2 weeks as measured by pain intensity. • Responder regarding stool consistency (IBS-D) • Responder regarding stool frequency (IBS-C) • Irritable Bowel Syndrome-Quality of Life Measure (IBS-QoL): Change between visit 2 and visit 4 • Analysis of IBS-QoL for IBS-C and IBS-D subgroup: Change between visit 2 and visit 4 • Analysis of IBS-QoL on different subscore of behaviors for whole study population • Analysis of IBS-QoL on different subscore of behaviors for IBS-C and IBS-D subgroup • Stool Texture: Analysis of BSS: Change of stool consistency in IBS-C and IBS-D subjects at week 4 compared to baseline • Change of pain intensity from baseline to week 4 • Change of pain intensity from baseline to week 2 • Subgroup analysis: change of pain intensity from baseline to week 4 (week 2) in the subgroups IBS-C and IBS-D • Subgroup of subjects responding regarding pain intensity in the first 7 days (early responders) • Subgroup of subjects responding regarding pain intensity in the last 14 days (late responders) • Change of completed evacuation and of feeling of uncompleted evacuation from baseline (first 8-14 diary data) to week 4 Other variable: • Global assessment of efficacy on 5-point Likert scale by investigator and subjects • Subjects' use of rescue medication • Analysis of subjects' symptoms assessed by Birmingham IBS symptom questionnaire

Safety	• AE profile • Vital signs (blood pressure, heart rate, body weight) • Laboratory parameters (hematology, blood chemistry, urinalysis) • Global assessment of tolerability on a 5-point Likert scale by investigator and subject

Subject disposition and baseline

A total of 320 subjects were screened in Germany, of which 243 subjects were enrolled between October 2013 and July 2017 and randomised to either receive STW 5 (N = 167) or placebo (N = 76). As all subjects were exposed to at least 1 dose of study medication, the safety analysis set (SAF) comprised 243 subjects.

Six subjects were excluded from the FAS population because no post-baseline efficacy data were available, thus the FAS comprised 237 subjects; 162 were randomised to treatment with STW 5 and 75 to placebo.

Further, 39 subjects had to be excluded from the PPS due to protocol deviations leading to a PPS with 198 subjects in total. Of these, 136 subjects received STW 5 and 62 subjects received placebo.

92.2% of subjects completed the study, thereof 152 subjects randomised to the STW 5 and 72 to the placebo group. Less than 10% of subjects in the SAF discontinued prematurely due to an AE.

The mean (SD) age of subjects in the SAF was 46.8 (16.76) years, ranging from 19 to 86 years. As expected, the majority of subjects enrolled in the study were female (78.19%). All subjects were Caucasian.

Overall, treatment groups were comparable with regard to their demographic data, time from the date of first IBS diagnosis, and the distribution of the different IBS-types.

Efficacy

Pain intensity

The response rate for abdominal pain intensity after 4 weeks of treatment as primary efficacy variable did not meet statistical significance with regard to differences in the frequency of responders between treatment groups. For the FAS, slightly more subjects responded to 4 weeks of treatment placebo treatment (N = 32, 42.7%) compared with subjects treated with STW 5 (N = 66, 40.7%; [p =0 .8678, CI: 0.54; 1.68]).

There was also no significant difference in the response to 2 weeks of treatment between the STW 5 group and placebo group (p = 0.6552, CI: 0.50; 1.54).

Both treatment groups experienced a relief in their pain intensity from baseline to week 4. However, the differences were not statistically significant between treatment groups (p = 0.5943, FAS).

Subjects in both treatment groups also reported decreasing pain intensity from baseline to week 2; the difference between treatment groups was not statistically significant (p = 0.5637, FAS).

According to the VAS, approximately 1 third of subjects in both treatment groups of the FAS were early responders regarding pain intensity, they were reporting decreasing pain intensity for at least 4 days during the first 7 days of the treatment phase (STW 5: 30.2%, placebo: 28.0%).

In both treatment groups in the FAS, most subjects were categorized as late responders, they were reporting decreasing pain intensity for at least 7 days during the last 14 days of the treatment phase (STW 5: 50.6%, placebo: 53.3%). Treatment groups did not significantly differ in the frequencies of early (p = 0.5692) or late responder (p =0.7926).

Stool parameters

No significant difference was found between the treatment groups for stool frequency in subjects with IBS-C (p = 0.9753) or stool consistency in subjects with IBS-D (p = 0.2952) after 4 weeks of treatment. The numbers of stool frequency and consistency responders after 2 weeks of treatment were not statistically different between the treatment groups.

No statistically significant difference was found between the treatment groups in the change of the mean score of stool consistency during week 4 compared to the mean score of stool consistency during the baseline phase.

From baseline (first 8-14 diary data) to week 4, no statistically significant difference was found between the treatment groups regarding the subjects' feeling of completed and uncompleted evacuation.

Irritable bowel syndrome - quality of life measure (IBS-QoL)

Subjects in both treatment groups experienced an improvement in their IBS-QoL during the study, although study treatment did not significantly affect the IBS-QoL total score (p = 0.3607).

For subjects with IBS-C as well as subjects with IBS-D, the results on the ANCOVA subscale scores were comparable.

Global assessment of efficacy

The frequencies of subjects rating treatment efficacy as 'very good' and 'good' was comparable between treatment groups. The overall efficacy judgement by the subjects using the Wilcoxon rank sum test of the FAS did not reveal significant differences between the treatments at visits 3 (p = 0.6495) and visit 4 (p = 0.6116).

The same was true for the efficacy as judged by the investigators, however, the efficacy rating of subjects compared with that of investigators differed significantly at visit 4 (p = 0.0440) of the FAS.

Subject's use of rescue medication

No statistically significant difference was found between treatment groups for the weekly usage of either rescue medication at the single visits or in the change from baseline.

Birmingham IBS symptom questionnaire

As indicated by the decreasing mean Birmingham IBS symptom total score during the study, subjects in both treatment groups reported a relief in their overall IBS symptoms.

The decrease in the total score and thus, in the IBS symptoms, was slightly more pronounced in subjects treated with STW5 compared with placebo, however, the differences were not statistically significant.

Safety

No death, serious AE or suspected unexpected serious adverse reaction were reported during this study. Analysis of all reported treatment-emergent AEs (TEAEs) revealed no difference between the placebo and STW 5 group, with regard to incidence and nature of reported events and thus did not lead to any safety concerns. TEAEs leading to treatment discontinuation were reported from 6 subjects treated with STW 5. None of these TEAEs were serious or revealed unknown risks associated with the IMP and only 2 of these TEAEs were certainly related to the study drug; all other events were assessed as not related or unlikely related.

With regard to blood laboratory values, no relevant adverse treatment effect on blood chemistry, haematology, coagulation or urinalysis variables in comparison with placebo was documented in this study. Clinically significant abnormal blood test values, not present at baseline, were reported overall for 4 subjects only at visit 4 (2 of 4 in the STW 5 group and 2 of 4 in the placebo group). The abnormal values in the STW 5 group were due to a

common cold in these subjects and thus did not raise any safety concern. No subject dropped out due to an abnormal laboratory blood value.

Vital signs measurements did not reveal clinically significant abnormalities and changes from baseline were insignificant.

The tolerability of the IMP was assessed similar by both treatment groups. The majority (>80%) of subjects treated with STW 5 or placebo rated the tolerability as ‘very good’ or ‘good’ at study end.

Overall, the safety relevant results of this study confirm the known positive safety profile of STW 5.

Overall conclusions

The design criteria for studies focussing on this specific study population are to be evaluated and carefully considered to enable an accurate efficacy assessment. In future clinical studies, endpoints using patient-reported outcome measures focussing on different items of IBS, including IBS symptoms and bowel habits, would help depict a more multi-dimensional structure of the complex disease IBS.

The safety and tolerability assessments of STW 5 did not demonstrate any risks associated with the product and confirmed a favourable safety and tolerability profile of STW 5.

Publication(s) based on the study

None at the time of report creation.

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