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ORIGINAL ARTICLE

Double-blind, randomized, 8-week multicenter study of the efficacy and safety of STW 5-II *versus* placebo in functional dyspepsia

Bettina Vinson,* Careen Fink,* Manfred Wargenau,† Nicholas J Talley‡ and Gerald Holtmann§

*Bayer Consumer Health, Steigerwald Arzneimittelwerk GmbH, Darmstadt, †M.A.R.C.O. GmbH & Co. KG, Institute for Clinical Research and Statistics, Düsseldorf, Germany, ‡School of Medicine and Public Health, University of Newcastle, Callaghan, New South Wales and §University of Queensland and Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia

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Correspondence
Gerald Holtmann, Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, Woolloongabba, QLD, Australia.
Email: g.holtmann@uq.edu.au

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Abstract

Background and Aim: Herbal products are widely used to treat patients with disorders of gut brain interaction but clinical efficacy and safety data for treatments lasting >4 weeks are widely lacking. We evaluated the efficacy and safety of 8 weeks of treatment with the herbal combination product STW 5-II for patients with functional dyspepsia (FD) meeting Rome II criteria. We also conducted a post hoc analysis including patients meeting Rome IV criteria for FD and evaluated the effect of the G-protein beta 3 (GNB3) subunit polymorphism (C825T) on therapeutic response.
Methods: This multicenter, placebo-controlled, double-blind study included 272 FD patients meeting Rome II criteria in the intention-to-treat cohort and 266 meeting Rome IV criteria. We used the validated Gastrointestinal Symptom Score (GIS) to assess GI symptoms, defining response rate as the proportion of patients with ≥50% GIS improvement in at least three of four assessments.
Results: After 8 weeks, the response rate was significantly higher in the STW 5-II group *versus* placebo (61.2% *vs* 45.1%, $P = 0.008$). Mean GIS non-significantly improved with STW 5-II treatment (7.9 ± 4.41 *vs* 6.7 ± 4.91 with placebo; $P = 0.07$). In the Rome IV subgroup analysis, STW 5-II yielded a better response rate ($P = 0.01$) *versus* placebo and greater postprandial distress symptom improvement ($P = 0.04$) *versus* placebo. Safety parameters did not differ between groups, and GNB3 status was not linked with therapeutic response.
Conclusion: STW 5-II is efficacious, with no observed safety signals at up to 8 weeks of treatment in patients with FD meeting Rome II or IV criteria.

Provisional Patent NTU (Ref: TD/129/17 "Microbiota Modulation Of BDNF Tissue Repair Pathway"), as well as a 1998 copyright for the Nepean Dyspepsia Index (i.e. NDI). Editorial: Medical Journal of Australia (editor in chief), Up to Date (section editor), Precision and Future Medicine, Sungkyunkwan University School of Medicine, South Korea, Med (Journal of Cell Press). Nicholas J Talley participates or has participated on the following committees: Australian Medical Council (AMC; Council Member 2016–2019), MBS Review Taskforce (2016–2020), National Health and Medical Research Council (NHMRC) Principal Committee, Research Committee (2016–2021), Asia Pacific Association of Medical Journal Editors (APAME; current), GESA Board Member (2017–2019). Misc: Avant Foundation (judging of research grants, 2019). Community and patient advocacy groups: Advisory Board, International Foundation for Functional GI Disorders (i.e. IFFGD). Nicholas J Talley acknowledges funding from the NHMRC for the Centre for Research Excellence in Digestive Health. Nicholas J Talley holds an NHMRC Investigator grant.

Author contribution: Bettina Vinson contributed to the study design, secured funding for the work, corrected the first draft, and revised the final draft. Careen Fink corrected the first draft and revised the final draft. Manfred Wargenau performed the post hoc analysis and revised drafts. Nicholas J Talley contributed to interpreting data, revising the draft, and finalizing the paper. Gerald Holtmann supervised the study as coordinating investigator and finalized writing the paper.

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Introduction

Functional gastrointestinal (GI) disorders (FGIDs), now termed disorders of gut–brain interaction (DGBIs), are highly prevalent.[1] Functional dyspepsia (FD) is a gastroduodenal disorder characterized by chronic or recurrent upper GI symptoms, including epigastric pain and early satiety.[2] Traditionally, these symptoms were related to disturbed motility or hypersensitivity of the stomach,[3] although recent evidence suggests that symptoms may often arise from duodenal dysfunction, which has been linked to immune activation, low-grade inflammation,[3–5] or small intestinal dysbiosis.[6]

Although FD does not cause excess mortality, patients frequently experience severely reduced health-related quality of life (QoL).[7] FD imposes a considerable economic burden on society[8] by repeated diagnostic testing following negative findings and a lack of effective therapies. Proton pump inhibitors and histamine H2 receptor antagonists are the most commonly used evidence-based medications for FD, but the overall gain over placebo is limited.[2,9]

Herbal medications have been frequently used for FD and other FGIDs for decades[10] and are acknowledged for their beneficial effects in GI complaints by the Committee on Herbal Medicinal Products of the European Medicines Agency. It has been argued that these medications should comply with regulatory standards similar to those for chemically defined therapies.[11] In the treatment of FD, a combination of different herbs may be appropriate, allowing the targeting of several symptoms and underlying pathomechanisms.

The Rome IV consensus guidelines for diagnosis and treatment of FD list the herbal combination preparation STW 5 as a potential treatment option.[2] For decades, the original STW 5, which contains nine plant, has been the only commercially available standardized herbal combination product in many countries for treatment of FD and other FGIDs. Over time, various modifications of this preparation have been tested for efficacy, and the modified STW 5-II has been introduced to the market for FD treatment arousing scientific interest on evidence of STW

5-II. STW 5-II contains only six herbal extracts (*Iberis amara*, *Carum carvi*, *Glycyrrhiza glabra*, *Matricaria chamomilla*, *Melissa officinalis*, and *Mentha piperita*). In pharmacological studies, STW 5-II and its herbal components have shown a broad spectrum of mechanistic actions, including anti-inflammatory effects, mucosal protection, and modulation of upper GI tract motility.[12–17] Placebo- and active-controlled clinical studies in FD patients have yielded clinical evidence for the efficacy of STW 5-II. Two of these studies addressed efficacy up to 4 weeks.[18,19]

This placebo-controlled phase III clinical study (study code STW 5-II/ 212-D-03-III-V) aimed to assess the efficacy and safety of STW 5-II during an 8-week trial, providing efficacy data for a longer period compared with earlier studies. Diagnostic parameters have evolved over time from Rome II to Rome IV, so we included a post hoc analysis to evaluate the efficacy of STW 5-II in patients meeting the current Rome IV criteria for FD. Previous studies have hinted at a link between FD and G-protein beta 3 (GNB3) subunit polymorphism (C825T),[20] which has been replicated in *Helicobacter pylori*–negative FD patients.[21] Based on these earlier findings, we explored the association between this polymorphism and therapeutic response to STW 5-II.

Methods

Study design. This multicenter, placebo-controlled, double-blind study was conducted from January 2004 to February 2005. After a wash-out period of 7 days, patients were treated for 8 weeks with 3×20 drops STW 5-II or placebo during a double-blind treatment phase followed by a 28-day single-blind follow-up with placebo treatment. FD symptoms were documented using the Gastrointestinal Symptom Score (GIS)[22] at baseline and every 2 weeks for 2 months.

The study was conducted in accordance with the standards of the International Committee on Harmonization on good clinical practice and the revised Declaration of Helsinki rule, approved by the ethics committee of the University Hospital Essen (approval number 03-2300) and registered by the German local authorities (submission number 4021138) in 2003 before the European clinical database was fully established. No EudraCT number is available. Written informed consent was obtained from all patients prior to inclusion in the trial. The conduct of the study and reporting of the data are in accordance with the CONSORT guidelines (Fig. 1).

Study participants. Patients aged 18–85 years and diagnosed with FD meeting Rome II criteria were recruited for this study. Typical symptoms of FD, such as epigastric pain or discomfort in the upper abdomen and at least three symptoms of "moderate" severity listed in the GIS were required. The absence of clinically relevant organic disease was confirmed by endoscopy within the 12 weeks before inclusion. Exclusion criteria were psychiatric illness, HIV-positive status or medical history, presence of drug or alcohol abuse or narcotic drug addiction, pregnancy, or breastfeeding. *H. pylori* status was evaluated via serological or breath tests and a positive *H. pylor*i status was not an exclusion criterion (Fig. 1).

Randomization and blinding. Randomization was conducted by sequential numbered method in chronological order of admission in each site without stratification and with respective code breaking cards available. The randomization list was generated using the randomization program IDV-Rancode 3.6.

For blinding, a placebo (31% volume by volume [v/v] alcohol) identical to the verum in organoleptic properties without active substances was developed.

Efficacy variables. The primary efficacy criterion was the response rate. A responder was defined as a patient reporting at least 50% improvement of the GIS at a minimum of three of the four assessments on days 14, 28, 42, and 56 compared to the baseline GIS ratings. The secondary efficacy criterion was the change in the sum score (GIS score) at the end of treatment. Further secondary parameters were assessment of efficacy by the patients and physicians at every visit on a 6-point Likert scale and time to response evaluated on a visual analogue scale (VAS) in the patient's diary. For this purpose response was defined as an improvement of 2 cm on the VAS or to 0 without further re-increase.

QoL was evaluated using the Nepean Dyspepsia Index (NDI).[23–25] Relapse during the follow-up phase was defined as recurring complaints reported by patients defined as responders before.

Safety and tolerability were assessed by the occurrence of adverse events (AEs), clinically relevant changes in laboratory parameters, and the global assessment of tolerability on a 6-point Likert scale by both patients and physicians.

GIS. The GIS comprises 10 items: epigastric pain/upper abdominal pain, abdominal cramps, fullness, early satiety, loss of appetite, sickness, nausea, vomiting, retrosternal discomfort, and acid eructation/heartburn,[22] each graded on a validated 5-point Likert scale (0 = no problem; 1 = mild problem [can be ignored when you do not think about it]; 2 = moderate problem [cannot be ignored but does not influence daily activities]; 3 = severe problem [influences your concentration on daily activities]; and 4 = very severe problem [markedly influences your daily activities and/or requires rest]). The validated German version was used.

GNB3 subunit polymorphism and response to therapy. As an additional study component, patients were offered to participate in an independent sub-project to explore the potential influence of the GNB3 subunit polymorphism on the response to therapy. After providing informed consent, buccal swabs were collected and analyzed via polymerase chain reaction and restriction fragment length polymorphism, as described previously.[20]

Statistical analysis. The confirmatory analysis of the primary target parameter was based on a logistic regression model including "treatment" and "center" as effects in both intention-to-treat (ITT) and per-protocol (PP) populations. Odds ratios (ORs) for response rates are reported as STW 5-II over placebo, whereas OR was originally calculated as placebo over STW 5-II. The two-sided hypothesis that STW 5-II would not differ from placebo was tested at an α level of 0.05. For the secondary

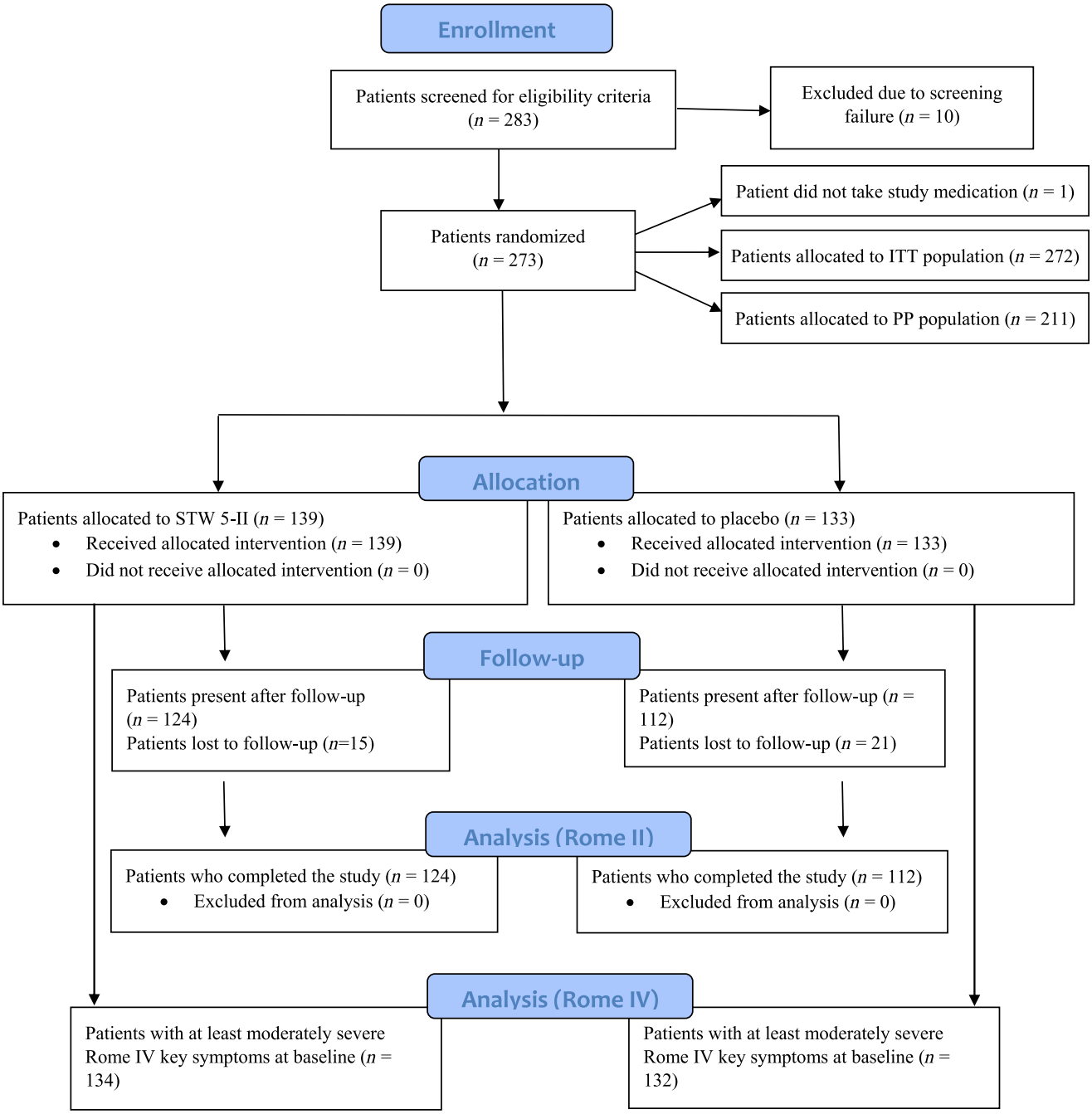

Figure 1 CONSORT flow diagram of the trial.

target parameter, an analysis of covariance model was used for both the ITT and PP populations. The additional target parameters were analyzed using the same test strategy as described for the primary and secondary parameters. The time to response (patient diary) was analyzed using statistical models for survival data (proportional hazards regression model).

Treatment response was defined as a 50% reduction in the GIS sum score from baseline in at least three out of four visits (not using last observation carried forward for week 8). Response rates were calculated based on the percentage of patients per treatment group, and differences between treatment groups were tested using logistic regression with response as the dependent variable and treatment as the independent variable. The Fisher's exact test was used if at least one expected cell count was ≤5. Analysis of the efficacy of single symptoms was based on an ANCOVA model with the last observation carried forward to replace missing values on day 56.

We used factor analysis to evaluate efficacy within four independent symptom clusters of the GIS defined in a factor analysis in the validation of the symptom score, as follows[22]: nausea, vomiting, and sickness for factor 1; early satiety, bloating, and loss of appetite for factor 2; retrosternal discomfort and acid eructation/heartburn for factor 3; and epigastric/upper abdominal pain and abdominal cramps for factor 4. Participants were included in the factor analyses if they had a positive symptom score at baseline (>0) for the respective factor. All post hoc analyses were performed using SAS version 9.4.

A post hoc analysis was conducted to analyze efficacy after 8 weeks when applying the latest FD definition according to Rome IV,[2] which is relevant for current physicians. We applied "Fullness," "Early satiety," and "Epigastric or upper abdominal pain" as key symptoms according to Rome IV. The GIS corresponds closely with symptoms listed for diagnosis in the current Rome IV criteria and covers symptoms of all FD subtypes. The analysis set for the post hoc analysis comprised all patients from the full analysis set of the database, with at least one moderate key symptom at baseline and at least one efficacy assessment post-baseline. Symptoms rated as "moderate" severity in the GIS were considered as "bothersome symptoms" fulfilling the Rome IV requirements. Although no full diagnosis according to Rome IV criteria was retrospectively possible, as no minimum frequency of symptoms was defined in Rome II, the symptom duration of 3 months (12 weeks per Rome II) is comparable. Consequently, this post hoc analysis of the original study population can be considered reasonably representative of FD patients meeting Rome IV criteria in clinical practice. The effects of GNB3 status on the therapeutic response were tested independently.

For all tests, $P < 0.05$ was considered significant. Demographic and baseline variables were analyzed exploratorily regarding differences between treatments. The assessment of safety variables was descriptive, with laboratory data and vital signs described by statistical characteristics for all visits and for changes from baseline. AEs were presented as frequency and percentage. Statistical analyses were performed using SAS version 8.1.

Power calculation. With an overall treatment response according to the GIS of 50% for STW 5-II and 30% for placebo treatment, a sample size of 268 (134 in each treatment group) was calculated to provide a power of 90% with an α level of 0.05.

Results

Study participants. A total of 283 FD patients aged 18–78 years were screened and 273 patients were randomized. The ITT population comprised 272 (STW 5-II: $n = 139$; placebo: $n = 133$), and the PP population 211 patients (STW 5-II: $n = 109$; placebo: $n = 102$). Of the total 272 patients, 266 met the Rome IV criteria (STW 5-II: $n = 134$; placebo: $n = 132$) and were included in the post hoc analysis. During the study, $n = 15$ patients in the STW-5 group dropped off compared to 21 patients in the placebo group (Fig. 1).

Demographic and other baseline patient characteristics. No significant differences in demographic variables were observed between groups (Table 1). Most of the study population was female and median duration of dyspepsia prior to inclusion was 33.5 months.

Primary efficacy endpoint: Response rate. The overall response rate (ITT population) was 61.2% in the STW 5-II group, compared with 45.1% in the placebo group after 8 weeks of treatment. The difference in the response rates revealed a significant treatment effect of STW 5-II over placebo (OR 0.502; 95% confidence interval [CI] 0.302–0.835, $P = 0.008$; Figure 2). The evaluation of the PP populations revealed a response rate of 63.3% in the STW 5-II and 46.1% in the placebo group ($P = 0.02$).

Secondary efficacy endpoint: Change in GIS. In the STW 5-II group (ITT population), the mean GIS score (standard deviation [SD]) decreased from 11.9 (3.66) at baseline to 4.2 (4.86) at the end of treatment (difference 7.9 ± 4.41). In the placebo group, it decreased from 12.1 (4.00) to 5.3 (4.82) at the end of treatment (difference 6.7 ± 4.91). ANCOVA revealed a difference between the two groups (STW 5-II minus placebo) of 1.0 (95% CI −0.1 to 2.1) in favor of active treatment that did not reach significance ($P = 0.072$).

Post hoc analysis based on ROME IV criteria. This secondary analysis of the response rates also demonstrated a significant difference in favor of STW 5-II ($P = 0.01$), with 65% responders in the active group compared to 48.7% in the placebo group. The logistic regression model revealed an OR 1.945 (95% CI 1.161–3.26, $P = 0.012$) for the subgroup analysis, which was comparable to the first endpoint of the study (reciprocal OR 1.992). ANCOVA revealed significant improvement in the single symptoms of early satiety ($P = 0.042$) and loss of appetite ($P = 0.042$) after 56 days.

In the factor analysis, there were 185 datasets for factor 1 (STW 5-II: 89; placebo: 96), 264 datasets for factor 2 (STW 5-II: 133; placebo: 131), 174 datasets for factor 3 (STW 5-II: 93; placebo: 81), and 264 datasets for factor 4 (STW 5-II: 132; placebo: 132). GI symptoms within factor 2 (early satiety, fullness, loss of appetite) showed significant improvement in favor of STW 5-II (least square [LS] mean difference 0.6, 95% CI 0.02–1.18, $P = 0.042$). GI symptoms within the other factors did not improve significantly in favor of STW 5-II: factor 1 (nausea, vomiting, sickness), LS mean difference 0.1 (95% CI −0.48 to 0.67, $P = 0.735$); factor 3 (retrosternal discomfort, acid eructation/heartburn), LS mean difference 0.13 (95% CI −0.28 to 0.53, $P = 0.54$), and factor 4 (epigastric or upper abdominal pain, abdominal cramps), LS mean difference 0.28 (95% CI −0.14 to 0.70, $P = 0.188$).

Assessment of efficacy, response and time to response, and QoL. Global assessment of efficacy by 6-point Likert scale revealed that 64.7% of participants self-assessed as "very good" or "good" in the STW 5-II *versus* 54.9% in the placebo group. Investigators assessed the efficacy of STW 5-II in 64% as "very good" or "good" *versus* 52.6%

Table 1 Demographic data for both treatment groups (ITT population)

	STW 5-II ($n = 139$)	Placebo ($n = 133$)	Total ($n = 272$)
Age (years)			
Mean (SD)	47.7 (14.27)	48.5 (14.61)	48.1 (14.42)
Min–max	20–78	18–78	18–78
Sex, *n* (%)			
Female	83 (59.7)	84 (63.2)	167 (61.4)
Male	56 (40.3)	49 (36.8)	105 (38.6)
Height (cm)			
Mean (SD)	169.47 (8.431)	169.65 (9.249)	169.56 (8.824)
Min–max	152–187	143–193	143–193
Weight (kg)			
Mean (SD)	73.32 (14.080)	73.17 (14.587)	73.25 (14.304)
Min–max	42.0–118.2	45–136	42–136
BMI (kg/m^2)			
Mean (SD)	25.47 (4.363)	25.36 (4.388)	25.42 (4.368)
Min–max	17.5–44.9	16.9–48.2	16.9–48.2
Ethnicity, *n* (%)			
White	139 (100.0)	133 (100.0)	272 (100.0)
Duration of FD (months)			
Mean (SD)	61.4 (89.29)	64.8 (85.72)	63.1 (87.42)
Median	25.0	36.0	33.5
Min–max	3–600	3–600	3–600
Medical pre-treatment, *n* (%)			
No	75 (54.0)	77 (57.9)	152 (55.9)
Yes	64 (46.0)	56 (42.1)	120 (44.1)
Total	139 (100)	133 (100)	272 (100)
Helicobacter pylori status, *n* (%)			
Missing	0 (0.0)	1 (0.8)	1 (0.4)
Negative	129 (92.8)	118 (88.7)	247 (90.8)
Positive	10 (7.2)	14 (10.5)	24 (8.8)
Total	139 (100)	133 (100)	272 (100)

FD, functional dyspepsia; ITT, intention-to-treat.

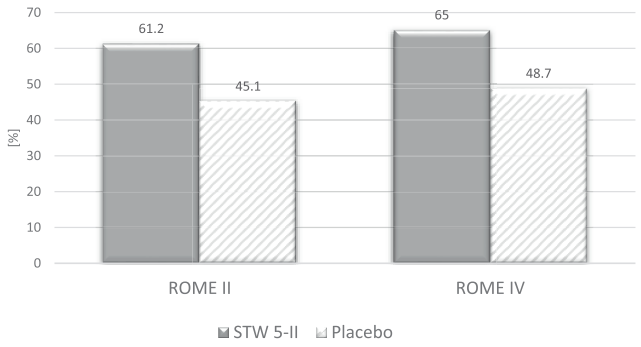

Figure 2 Response rates for STW 5-II or placebo treatment after 56 days by patients with functional dyspepsia per the Rome II or Rome IV criteria.

with placebo (logistic regression model: patients $P = 0.021$; investigators $P = 0.024$).

Efficacy assessment using the VAS showed a positive, nonsignificant trend of efficacy towards STW 5-II for the response rate and time to response as did the assessment of QoL by NDI. Relapse rates were higher after active treatment *versus* placebo, but not significantly (Table 2).

Evaluation of safety and tolerability. A total of 103 AEs were reported, with equal distribution between the two groups (STW 5-II: 49; placebo: 54); 22.3% of patients in the STW 5-II group and 29.5% of the patients in the placebo group reported at least one AE (Table 3). AEs with severe intensity were reported by 6.8% of all patients (STW 5-II: five AEs in four patients; placebo: two AEs in two patients). AEs leading to discontinuation of study medication were documented for nine patients (STW 5-II: four; placebo: five). During the study, three serious adverse events (SAEs) occurred (STW 5-II: one SAE, cardiovascular disorder; placebo group: two SAEs, respectively, hospitalization for mental disorder and anemia). None of the SAEs were rated as having a causal relationship to the study medication. Laboratory parameters and vital signs showed no clinically relevant changes or relevant differences between treatment and placebo groups during the study.

Both patients and investigators assessed the tolerability of the study medication and placebo. Among physicians, 86.3% assessed STW 5-II as "good"/"very good" *versus* 76.7% for placebo at week 2, 82.0% *versus* 83.4% at week 4, 81.3% *versus* 76.7% at week 6, and 80.6% *versus* 72.2% at week 8. Patient tolerability ratings were similar. An exploratory analysis (logistic regression model) showed significance for STW 5-II over placebo for the patient assessments ($P = 0.026$) at the end of treatment.

Table 2 Secondary endpoints

	STW 5-II		Placebo		*P*
Efficacy assessment (VAS), mean (SD)	Day 0 46.6 (24.45)	Day 56 23.2 (24.60)	Day 0 44.4 (24.13)	Day 56 25.9 (21.91)	0.182
Time to treatment response (days)	40.3 (22.14)		46.4 (±16.73)		0.096 point estimator hazard ratio 0.741
NDI disease-specific quality of life rating (items 2–42 rated on 5-point Likert scale)	−12.07		−9.70		0.160
NDI symptom checklist rated in three dimensions (item 1 rated on 5-point Likert scale)	−37.85		−31.69		0.073
Occurrence of relapse (%)	30.6		16.7		0.097
VAS response, proportion >2 cm	51.1%		42.1%		Not reported

NDI, Nepean Dyspepsia Index; VAS, visual analogue scale.

Table 3 Number of patients with adverse events (AEs) for the different treatment groups (ITT)

	STW 5-II		Placebo		Total	
	n	(%)	*n*	(%)	*n*	(%)
Patients with AEs (total)						
No	108	77.7	93	70.5	201	73.9
Yes	31	22.3	40	29.5	71	26.1
Total	139	100	133	100	272	100
Total number of AEs						
	49	48.3	54	51.7	103	100

Treatment-emergent AEs

	STW 5-II		Placebo		Total	
	n (AEs)	(%)	*n* (AEs)	(%)	*n* (AEs)	(%)
Intensity						
Mild	20	40.8	36	66.7	56	54.4
Moderate	24	49.0	16	29.6	40	38.8
Severe	5	10.2	2	3.7	7	6.8
Relation to medication						
Certain	1	2.0	1	1.9	2	1.9
Probable	3	6.1	0	0.0	3	2.9
Possible	0	0.0	3	5.6	3	2.9
Unlikely	10	20.4	11	20.4	21	20.4
Not assessable	0	0.0	1	1.9	1	1.0
None	35	71.4	38	70.4	73	70.9
Total	49	100	54	100	103	100

ITT, intention-to-treat.

Influence of GNB3 on treatment response

Baseline characteristics. The distribution of polymorphism subgroups (CC or CT/TT) was comparable between the placebo and treatment groups (Table S1, Supporting information) and represented the total study population. Among STW 5-II participants, response rates were 55.0% for the *GNB3* CC subgroup and 64.6% for the CT/TT subgroup. Among participants taking placebo, the response rate was 55.0% in the CC subgroup and 51.2% in the CT/TT subgroup. Results of the Wilcoxon signed-rank test revealed no significant treatment effect ($P = 1.000$ for the CC group; $P = 0.207$ for the CT/TT group). In post hoc analyses, response rates in the *GNB3* CC group were 58.5% with STW 5-II and 58.3% with placebo (chi-squared test $P = 0.967$), and in the CT/TT subgroup, response rates were 68.2% with STW 5-II and 56.8% with placebo (chi-squared test $P = 0.289$).

Discussion

The results of this randomized placebo-controlled trial demonstrate the clinical efficacy and safety of the herbal preparation STW 5-II in patients with FD in an 8-week trial. Whereas previous clinical trials with STW 5-II assessed treatment effects for up to 4 weeks,[18,26] the current trial provides evidence of effectiveness in symptom relief for the longer period of 8 weeks. We chose this time frame to reflect the natural history of FD as a chronic disorder with fluctuating symptoms and high symptom turnover.[27–29] The predefined endpoint of response rate reflects an adequate relief endpoint with clinically meaningful symptom improvement recommended for FGIDs in that time.[30] The response rate was significantly higher for the STW 5-II group (61.2%) compared with the placebo group (45.1%, $P < 0.05$, ITT population). Although this study used the Rome II criteria to select FD patients, it is reassuring that the primary endpoint was also met in a post hoc analysis using more stringent Rome IV criteria ($P = 0.01$) to define patients with FD. An additional post hoc factor analysis revealed a significant efficacy of STW 5-II associated with the meal-related FD symptoms "early satiety" and "loss of appetite." A clear trend in numerical, but non-significantly reduction in GIS from baseline was observed in the STW 5-II group compared with the placebo group at the end of the trial ($P = 0.072$), demonstrating improvement of self-reported symptoms and supporting the outcomes of the first endpoint. This secondary endpoint reflects symptom reduction measured at a single timepoint at the end of treatment. In contrast, the responder definition captures the natural course of the disorder over 8 weeks and reflects the effect over time, which may be more relevant. In addition, a constant reduction in GIS was detectable in the treatment period between weeks 4 and 8 (data not shown).

Although no subgroup analysis in *H. pylori* positive patients was performed, a previous study comparing efficacy of

STW 5-II to cisapride, no significant difference was found for the primary target parameter.[18] Therefore, it can be assumed that *H. pylori* status has no impact on the efficacy outcome of symptom relief with STW 5−II.

Visceral hypersensitivity because of central or peripheral sensitization[31,32] and fundic dys-accommodation[33,34] are possible pathomechanisms for meal-related symptoms. A mechanistic explanation of the efficacy of STW 5-II in relieving postprandial distress symptoms may be its effect on sensory afferent neuronal signaling from the GI tract to the central nervous system, reducing stimuli for visceral hypersensitivity.[35] Furthermore, region-specific effects of relaxing the proximal stomach and increasing contractility in the antrum have been described for STW 5-II,[14] offering another possible mechanistic explanation for the short-term efficacy of STW 5-II. The broad anti-inflammatory effects[12,15–17] described for STW 5-II could explain the clinical efficacy seen over the 8-week period, potentially acting against the low-grade duodenal and gastric inflammation that have been posited as a potential mechanism underlying FD.[36–38]

Multiple pharmacodynamic effects position herbal medicines as potential treatments for FGIDs and their likely complex pathomechanisms by targeting multiple symptoms. Herbal preparations have been in use for many years, with beneficial effects described for numerous herbal extracts.[39–41]

Previous studies have suggested that dysfunction in G-proteins may alter numerous intracellular signaling cascades, including brain–gut axis signaling associated with key mechanisms implicated in FGID pathogenesis, such as impaired motility, altered immunological and mucosal function, and visceral hypersensitivity.[42] The C825T polymorphism in *GNB3* is linked to enhanced G-protein activation, and genetic association studies first suggested the association of homozygous or heterozygous C or T alleles with FD.[20,21,43,44] Thus far, data are limited for this specific polymorphism and therapeutic response, and only one study has explored the effect of *GNB3* polymorphisms on the response to therapy with an antidepressant.[45] We note that the response rate during active therapy was numerically but non significantly higher in the *GNB3* CT/TT subgroup compared with the *GNB3* CC group (64.6% *vs* 55.0%), whereas the variant-stratified placebo groups showed virtually no difference (55.0% *vs* 51.2%).

We observed no significant differences between the STW 5-II and placebo groups for any assessed safety parameters (AEs, laboratory findings, vital signs, tolerability). The tolerability of STW 5-II was comparable to placebo. These results are in line with the previously reported good tolerability within STW 5-II trials in FD[18,19] and provide positive evidence in the frame of previous safety discussions on herbal products.[11]

The results of this prospective, randomized, placebo-controlled trial demonstrate that treatment with STW 5-II in patients with FD meeting the Rome II and Rome IV criteria confers significant clinical improvement for at least 8 weeks, with no SAEs causally related to the treatment.

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Data availability statement. Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing." This pertains to scope, timepoint, and process of data access. As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after 1 January 2014. Interested researchers can use www.vivli.org to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research, which can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the member section of the portal. Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Demographic data for genotype subtypes in the treatment and placebo groups.