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Heartburn relief with bicarbonate-rich mineral water: results of the randomised, placebo-controlled phase-III trial STOMACH STILL

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ABSTRACT

Objective We assessed whether the bicarbonate-rich mineral water Staatl. Fachingen STILL is superior over conventional mineral water in relieving heartburn.

Design Multicentre, double-blind, randomised, placebo-controlled trial STOMACH STILL in adult patients with frequent heartburn episodes since ≥6 months and without moderate/severe reflux oesophagitis. Patients drank 1.5 L/day verum or placebo over the course of the day for 6 weeks. Primary endpoint was the percentage of patients with reduction of ≥5 points in the Reflux Disease Questionnaire (RDQ) score for 'heartburn'. Secondary endpoints included symptom reduction (RDQ), health-related quality of life (HRQOL, Quality of Life in Reflux and Dyspepsia (QOLRAD)), intake of rescue medication and safety/tolerability.

Results Of 148 randomised patients (verum: n=73, placebo: n=75), 143 completed the trial. Responder rates were 84.72% in the verum and 63.51% in the placebo group (p=0.0035, number needed to treat=5). Symptoms improved under verum compared with placebo for the dimension 'heartburn' (p=0.0003) and the RDQ total score (p=0.0050). HRQOL improvements under verum compared with placebo were reported for 3 of 5 QOLRAD domains, that is, 'food/drink problems' (p=0.0125), 'emotional distress' (p=0.0147) and 'vitality' (p=0.0393). Mean intake of rescue medication decreased from 0.73 tablets/day at baseline to 0.47 tablets/day in week 6 in the verum group, whereas in the placebo group it remained constant during the trial. Only three patients had treatment-related adverse events (verum: n=1, placebo: n=2).

Conclusion STOMACH STILL is the first controlled clinical trial demonstrating superiority of a mineral water over placebo in relieving heartburn, accompanied by an improved HRQOL.

Trial registration number EudraCT 2017-001100-30.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Bicarbonate-rich mineral waters have been used for decades for symptomatic treatment of gastrointestinal disturbances including heartburn.
⇒ Their beneficial effect has not been systematically investigated in a placebo-controlled trial so far.

WHAT THIS STUDY ADDS

⇒ STOMACH STILL is the first controlled trial demonstrating superiority of a bicarbonate-rich water over placebo in relieving heartburn.
⇒ Symptom relief was accompanied by improved health-related quality of life.
⇒ The mineral water was safe and well tolerated.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The mineral water is an alternative treatment option to chemically defined drugs in patients suffering from heartburn that comes along with excellent tolerability.

INTRODUCTION

Heartburn is one of the most frequent upper gastrointestinal (GI) tract symptoms[1 2] with a variety of causes: whereas many patients have gastro-oesophageal reflux disease (GORD), in some patients, the complaints are only functional without an association between reflux and symptoms or a consequence of other oesophageal diseases.[3 4] Of patients with GORD, about 60% have a macroscopically normal mucosa at endoscopy, that is, they have non-erosive oesophageal reflux disease (NERD).[5] Reported prevalence estimates of at least weekly GORD symptoms range from 18% to 28% in the USA and from 9% to 26% in Europe.[1] Affected patients have a significantly impaired health-related quality of life (HRQoL)—to an extent greater than with disorders like diabetes, arthritis or congestive heart failure. The impaired HRQoL mainly stems from features including disturbed sleep, reduced vitality and pain and has a negative impact on the affected individuals' productivity in both work and non-work settings.[6]

According to guidelines for the management of patients with GORD, symptoms

including heartburn should be primarily managed by dietary and lifestyle changes—either as initial treatment in mild cases or in combination with pharmacological treatments. However, the evidence base for the effectiveness of lifestyle measures is limited, and management options for symptom relief with proven efficacy are rare.[7–9] Recommended chemically defined pharmacological treatments mainly focus on the neutralisation of gastric acid, the reduction of acid secretion and/or the elimination of the acid pocket. These gastric-acid-directed medications include proton pump inhibitors (PPIs) as first-line option besides histamin-2 receptor antagonists, alginates and antacids.

Staatl. Fachingen STILL is a sodium bicarbonate-rich mineral water that has been used for decades for symptomatic treatment of GI disturbances. Its status as a so-called 'healing water' qualifies the mineral water as a medicinal product according to German drug law, however, so far, no controlled clinical trial had been available. Preliminary data of Staatl. Fachingen STILL and other bicarbonate-rich mineral waters showed positive effects on heartburn and associated complaints.[10–12] The mineral water is expected to exert its beneficial effects by neutralising gastric acid (antacid effect), by accelerating oesophageal clearance and gastric emptying, by increasing gut motility (prokinetic effect) and—as a consequence—by protecting the mucosa of the oesophagus from damage caused by acid reflux.[13–15] From a chemical perspective, such mineral waters have the same numerical capacity for neutralising gastric acid as chemically defined antacids.[16] The neutralising capacity of the recommended daily dose of 1.5 L mineral water is equivalent to the neutralising capacity of the recommended daily dose of antacids (eg, three tablets/day of Rennie Kautabletten: calcium carbonate/magnesium carbonate).[17]

The randomised, double-blind, placebo-controlled phase-III trial STOMACH STILL (InveStigation of efficacy and TOlerability of the healing water Staatl. Fachingen STILL in patients for symptoMAtiC treatment of Heartburn in comparison to placebo) was conducted to establish the clinical benefits of Staatl. Fachingen STILL on heartburn (primary objective) and other upper GI complaints as well as HRQoL in a heterogeneous population of patients suffering from heartburn without moderate to severe reflux oesophagitis (Los Angeles (LA) grades B–D). Hence, the clinical trial aimed at providing clinical evidence of symptomatic heartburn relief for a bicarbonate-rich mineral water to extend the therapeutic toolbox for healthcare professionals and patients.

METHODS

Study design

This double-blind, randomised, placebo-controlled trial with parallel-group design was conducted from April 2019 to June 2021 in 12 study sites in Germany in accordance with the Declaration of Helsinki (version 2013) and the requirements of the German Medicinal Products Act.

The trial was planned with an adaptive design in two stages to determine the superiority of Staatl. Fachingen Still (verum) over placebo in terms of efficacy for the treatment of heartburn. Placebo was a conventional mineral water with far lower mineralisation than verum. Verum and placebo were visually similar and packed in identical bottles with the same label. Furthermore, both study drugs had a comparable low content of carbonic acid (for composition of study drugs, see online supplemental methods). After screening, the patients went through a run-in phase during which they were advised to drink at least 1.5 L/day of water or other beverages. Only patients with an intake of at least 1.5 L/day of liquids on at least 10 days prior to baseline and with a Reflux Disease Questionnaire (RDQ) score ≥8 in the dimension 'heartburn' considering the last 7 days prior to baseline were eligible for randomisation. Patients were centrally allocated to the lowest yet unassigned random number in a blinded fashion to either the verum or placebo group (ratio 1:1, block randomisation with block size n=4). During the treatment period, each patient received for 42 days (6 weeks) either 1.5 L/day of verum or 1.5 L/day of placebo, both to be drunk over the course of the day. The volume of intake was documented in a diary and controlled by the number of empty/full bottles returned. Rescue medication was provided within the clinical trial (Rennie Kautabletten—calcium carbonate/magnesium carbonate); intake was allowed in case the patient considered the heartburn episode as not tolerable and had to be documented. Patients were advised not to change their general eating habits during the trial. Patients, investigators and trial staff remained blinded for the entirety of the trial duration and data analysis.

The trial is registered in the EU Clinical Trials Register (EudraCT no. 2017-001100-30) and the German Registry of Clinical Studies (DRKS00016696).

Patients

Adults ≥18 years of age were eligible for the trial, if they had a history of repeatedly occurring episodes of heartburn for at least 6 months (RDQ score ≥8 in the dimension 'heartburn'). An upper GI endoscopy within 5 years before screening excluded relevant erosive disease (reflux oesophagitis LA classification grades B–D) and other severe GI diseases including malignancies, ulcer, Barrett's oesophagus and oesophageal varices (see online supplemental methods for inclusion/exclusion criteria and explanation of interval between endoscopy and screening). Eligible patients provided written informed consent before enrolment.

Trial parameters: endpoints

The primary endpoint was based on a responder analysis taking into account the severity and frequency of heartburn. For this purpose, the RDQ, a fully validated and reliable instrument for symptom assessment and

treatment response in GORD, was used. Within the RDQ, frequency and severity of a symptom (=RDQ dimension) are assessed via two questions each, rated on 6-point scales ranging from 0 ('no occurrence') to 5 ('daily'/'severe').[18 19] A responder was defined as any patient showing a reduction of at least five points in RDQ score for the dimension 'heartburn' after 6 weeks of treatment. The chosen responder definition is based on the previously determined minimal important change for a perceived beneficial effect of 4.6 points in the RDQ score for 'heartburn'.[18 20] Symptom changes (RDQ dimensions 'heartburn', 'regurgitation' and 'dyspepsia') were assessed as secondary endpoints. HRQoL was characterised using the Quality Of Life in Reflux and Dyspepsia (QOLRAD), a validated disease-specific questionnaire evaluating the domains 'emotional distress', 'sleep disturbance', 'vitality', 'food/drink problems' and 'physical/social functioning'.[21 22] All parameters were assessed at baseline and after 2, 4 and 6 weeks of treatment. Furthermore, the intake of rescue medication based on diary entries was analysed. Also, patients themselves and investigators rated the satisfaction with treatment at all post-baseline visits using the Treatment Satisfaction Questionnaire for Medication version 9[23] and a 4-point verbal rating scale, respectively.

For characterisation of safety and tolerability, adverse events (AEs) on general questioning, coded according to the Medical Dictionary for Regulatory Activities V.23.0, were analysed according to frequency and severity (mild, moderate, severe).

All analyses presented were prespecified in the trial protocol.

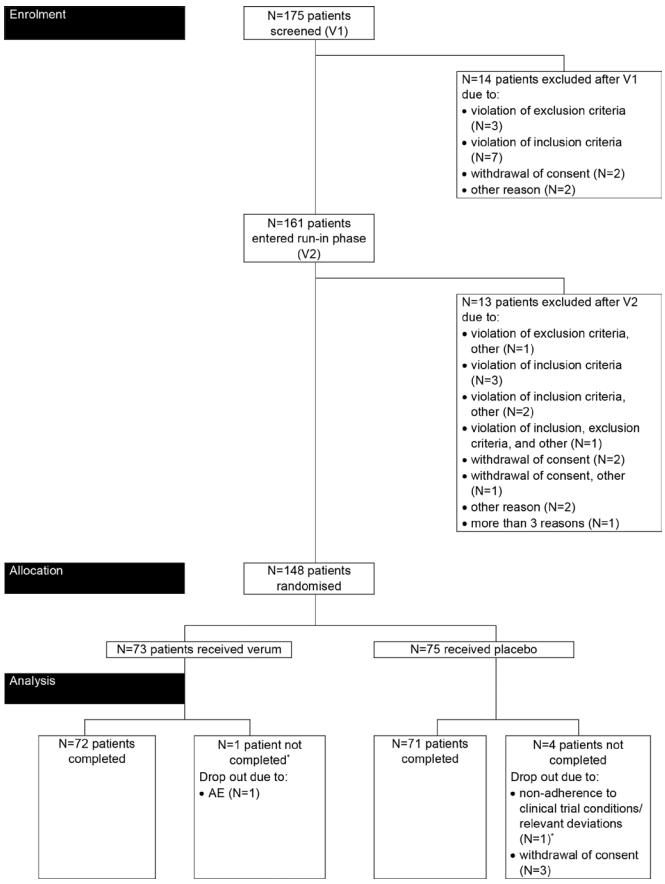

Figure 1 Disposition of patients. *Patient excluded from the FAS due to missing documentation of RDQ score at postbaseline visits V3-V5. AE, adverse event; FAS, full-analysis set; RDQ, Reflux Disease Questionnaire; V, visit.

Adaptive design and sample size

Data available in literature did not allow for a reliable sample size estimation and thus, a two-stage approach with interim analysis was planned.[24] Appropriate type-I error rates and decision boundaries for the interim (α_1=0.0233) and the final analysis (c_α=0.00870) were specified to assure control of the global type-I error rate α=0.050.

In a one-arm pilot study (EudraCT no. 2013-001256-36) in 56 patients of a comparable population treated with verum over 6 weeks, a responder rate of ~85% was calculated, and a placebo responder rate of 60% was assumed. A local type-I error rate of 0.0233 was applied at the interim analysis for the primary endpoint yielding a power of 83% for an intended sample size of 130 patients. Thus, considering a drop-out rate of about 15%, 150 patients were planned to be randomised in the first stage. Sample sizes were calculated using the software ADDPLAN, V.6.1.1 (swMATH, Karlsruhe, Germany).

Statistical methods

Efficacy was analysed for all randomised patients who received the study drug at least once, and who provided any postbaseline data for the RDQ score used for responder analysis, and who did not violate against inclusion criteria (full-analysis set, FAS).

For the primary endpoint (responder rate), a two-sided χ^2 test (global α=0.05) was used to test for superiority of verum over placebo. Missing data were not imputed; patients without endpoint assessment at study end were regarded as non-responders. Secondary parameters were analysed descriptively. To exploratively assess the treatment effect regarding symptom and HRQoL improvement, an analysis of covariance with baseline as covariate was applied ($p<0.05$ considered as statistically significant). Safety was analysed descriptively for all randomised patients who received the study drug at least once (safety analysis set, SAS). Statistical analysis was carried out using the software SAS Analyst Pro, V.9.2/0.4 (SAS Institute).

RESULTS

Patients

Figure 1 displays the disposition of patients in the trial. Overall, 148 of 175 screened patients (verum: 73, placebo: 75) were randomised. Treatment compliance was high in the trial population and comparable between the treatment groups: 77.4% of patients (verum: 80.6%, placebo: 74.3%) documented an intake of at least 1.5 L

Table 1 Patient characteristics (full-analysis set, N=146)*

Parameter	Verum (n=72)	Placebo (n=74)
Age (years)		
Arithmetic mean (SD)	54.7 (13.5)	58.2 (13.4)
Median (range)	56.0 (22–78)	61.0 (24–81)
Age group, years (n, %)		
18–30	6 (8.3)	4 (5.4)
31–40	7 (9.7)	3 (4.1)
41–50	8 (11.1)	13 (17.6)
51–64	33 (45.8)	27 (36.5)
65–74	15 (20.8)	22 (29.7)
>74	3 (4.2)	5 (6.8)
Sex (n, %)		
Female	46 (63.9)	51 (68.9)
Body mass index (kg/m^2)		
Arithmetic mean (SD)	27.9 (4.96)	26.4 (4.95)
Median (range)	27.1 (19.5–42.6)	25.9 (17.6–39.2)
Common non-GI concomitant conditions, SOC (n, %)†		
Vascular disorders	25 (34.7)	32 (43.2)
Musculoskeletal and connective tissue disorders	17 (23.6)	15 (20.3)
Metabolism and nutrition disorders	15 (20.8)	16 (21.6)

*The full-analysis set includes all randomised patients who received the study drug at least once, and who provided any postbaseline data for the RDQ score used for responder analysis, and who did not violate against inclusion criteria.
†Concomitant diseases in at least 20% of the overall trial population.
GI, gastrointestinal; n/N, number of patients; RDQ, Reflux Disease Questionnaire; SOC, system organ class.

of the study drug on each study day. Five patients (3.4%) did not complete the trial.

The baseline characteristics of all patients included in the FAS are depicted in table 1. The patients were all Caucasian, mostly female (66.4%) and had an age between 22 and 81 years; the majority of patients was aged between 51 and 64 years (41.1%). Both treatment groups did not relevantly differ from each other in demographic and anthropometric characteristics.

Primary endpoint: responder rate

In the verum group, 61 out of 72 patients (84.7%) were responders after 6 weeks of treatment, that is, had a reduction of at least 5 points in the RDQ score for the dimension 'heartburn'. In the placebo group, only 47 out of 74 patients (63.5%) responded to treatment. Hence, a placebo-corrected treatment effect of more than 20% was detected (number needed to treat (NNT) = 5). The primary objective was met: the p value of the χ^2 test for the primary evaluation of the RDQ response was p=0.0035, demonstrating superiority of verum over placebo treatment.

Notably, the interim analysis, performed with 144 patients in the FAS, already revealed superiority of verum over placebo (p=0.0034). Consequently, the trial was stopped without the need to proceed to the second stage, and the analysis presented here was then conducted including two additional subjects, who had been included while the interim analysis was done.

Symptom reduction (RDQ)

The RDQ items 'heartburn', 'regurgitation' and 'dyspepsia' as well as the total RDQ score at baseline and after 6 weeks of treatment are summarised in table 2, and the time course of the RDQ item 'heartburn' is displayed in figure 2. Baseline scores for 'heartburn' and 'dyspepsia' were slightly higher in the verum compared with the placebo group. Already after 14 days of treatment, all 4 RDQ scores were clearly reduced, that is, symptoms were improved. Within the last 4 weeks of treatment, the RDQ scores decreased further, although to a smaller degree than in the first 2 weeks. The absolute reductions of all scores from baseline after 6 weeks of treatment were larger in the verum group than in the placebo group, with the greatest difference observed for the dimension 'heartburn'.

Differences between verum and placebo group reached statistical significance for 'heartburn' (p=0.0003) and the total RDQ score (p=0.0050) (table 2). The breakdown of results according to frequency and severity of symptoms revealed that the treatment with verum reduced both characteristics of all three dimensions, although the observed positive effect was larger on the frequency than on the severity of symptoms (online supplemental table 1).

HRQoL (QOLRAD)

The five QOLRAD domains at baseline and after 6 weeks of treatment are summarised in table 3. Baseline scores were either only slightly lower (emotional distress, food/drink problems, vitality) in the verum compared with the placebo group or quite similar (physical/social functioning, sleep disturbance) in both groups. Already after 14 days of treatment, the domain scores were clearly increased, that is, HRQoL impairment was reduced (data not shown). Scores slightly increased further during the last 4 weeks of treatment. The absolute increases of all scores from baseline after 6 weeks of treatment were larger in the verum group than in the placebo group, with the following rank order of placebo-verum comparisons: food/drink problems (p=0.0125) > emotional distress (p=0.0147) > vitality (p=0.0393) > sleep disturbance > physical/social functioning (both p>0.05).

Rescue medication

During the baseline interval (comprising the run-in period), the daily average number of tablets of rescue medication (mean±SD) was slightly higher in the verum

Table 2 RDQ scores at baseline and end of treatment (full-analysis set, N=146)*

RDQ score (mean (SD))	Verum (n=72)	Placebo (n=74)	ANCOVA† Results (estimate (95% CI), p value)
Heartburn			
Baseline	13.56 (3.32)	12.59 (3.22)	−2.33 (−3.58 to −1.08), 0.0003
After 6 weeks	4.43 (4.47)	6.26 (5.42)	
Change from baseline	9.17 (4.82)	6.33 (5.07)	
Regurgitation			
Baseline	9.38 (5.54)	9.30 (5.67)	−1.08 (−2.23 to 0.08), 0.0676
After 6 weeks	4.03 (5.18)	5.04 (5.00)	
Change from baseline	5.47 (6.06)	4.17 (5.52)	
Dyspepsia			
Baseline	10.07 (5.03)	8.87 (5.56)	−1.00 (−2.27 to 0.26), 0.1194
After 6 weeks	4.43 (4.47)	6.26 (5.42)	
Change from baseline	6.09 (5.97)	3.81 (5.75)	
Total score‡			
Baseline	33.00 (10.90)	30.76 (11.59)	−4.54 (−7.69 to −1.39), 0.0050
After 6 weeks	12.41 (12.60)	16.39 (12.74)	
Change from baseline	20.65 (14.04)	14.31 (12.83)	

*The full-analysis set includes all randomised patients who received the study drug at least once, and who provided any postbaseline data for the RDQ score used for responder analysis, and who did not violate against inclusion criteria.
†ANCOVA (baseline as covariate) verum versus placebo for change from baseline.
‡Sum score of the three dimensions (max. 60 points).
ANCOVA, analysis of covariance; CI, confidence interval; n/N, number of patients; RDQ, Reflux Disease Questionnaire.

(0.73±1.15 tablets/day) than in the placebo group (0.56±0.85 tablets/day), which is in accordance with the slightly higher baseline RDQ scores in the verum group. In the verum group, the mean daily use of rescue medication decreased over time to 0.47±1.13 tablets/day in week 6. In contrast, in the placebo group, intake of rescue medication remained nearly constant throughout the trial (0.60±1.44 tablets/day in week 6).

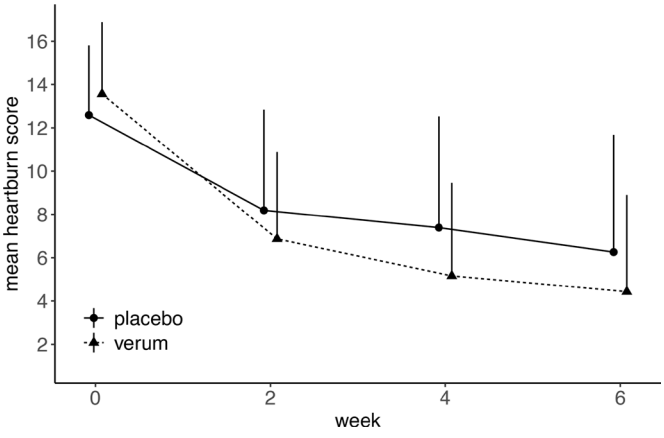

Figure 2 Time course of RDQ score for 'heartburn' (full-analysis set, N=146)* Shown are arithmetic mean values with standard deviation. *The full-analysis set includes all randomised patients who received the study drug at least once, and who provided any postbaseline data for the RDQ score used for responder analysis, and who did not violate against inclusion criteria. RDQ, Reflux Disease Questionnaire.

Treatment satisfaction

The patients rated their satisfaction with treatment in the domains 'effectiveness', 'convenience' and 'global satisfaction'. The scores for 'effectiveness' and 'global satisfaction' at all postbaseline visits were higher (= greater degree of satisfaction) in the verum compared with the placebo group. Whereas the degree of treatment satisfaction clearly increased further from week 2 to week 6 in the verum group, it remained nearly constant in the placebo group. The scores for 'convenience' were comparably high in both treatment groups and remained constant over time (table 4).

In accordance with the results of the patient-rated satisfaction with treatment, the investigator assessed the effectiveness of verum at all postbaseline visits as far better than the effectiveness of placebo. Both treatments were assessed with 'very good' or 'good' tolerability in the majority of the overall population, however, the investigator assessed the tolerability of verum at all post-baseline visits as better than the tolerability of placebo (figure 3).

Adverse events

The summary of AEs per treatment is provided in table 5. The overall incidence of AEs after study drug administration was low (39 out of 148 patients, 26.4%) and comparable between both treatment groups. Only 8 out of 91 AEs (8.79%) were assessed as related to the study drug—all of mild intensity. The related AEs concerned the system organ classes 'GI disorders' (verum: 1 case,

Table 3 QOLRAD scores at baseline and end of treatment (full-analysis set, N=146)*

QOLRAD score (mean (SD))	Verum (n=72)	Placebo (n=74)	ANCOVA† Results (estimate (95% CI), p value)
Food/drink problems			
Baseline	4.12 (1.07)	4.51 (1.14)	0.38 (0.08 to 0.68), 0.0125
After 6 weeks	5.76 (1.21)	5.50 (1.21)	
Change from baseline	1.62 (1.27)	0.96 (1.25)	
Emotional distress			
Baseline	4.90 (1.25)	5.10 (1.48)	0.35 (0.07 to 0.63), 0.0147
After 6 weeks	6.24 (1.07)	5.93 (1.02)	
Change from baseline	1.32 (1.25)	0.79 (1.22)	
Vitality			
Baseline	4.29 (1.27)	4.37 (1.34)	0.33 (0.02 to 0.64), 0.0393
After 6 weeks	5.90 (1.23)	5.50 (1.30)	
Change from baseline	1.59 (1.45)	1.13 (1.44)	
Sleep disturbance			
Baseline	4.94 (1.21)	4.99 (1.48)	0.21 (–0.09 to 0.51), 0.1604
After 6 weeks	6.10 (1.06)	5.94 (1.16)	
Change from baseline	1.15 (1.43)	0.92 (1.30)	
Physical/social functioning			
Baseline	5.38 (1.12)	5.42 (1.21)	0.19 (–0.04 to 0.42), 0.1048
After 6 weeks	6.34 (0.92)	6.16 (0.97)	
Change from baseline	0.96 (1.01)	0.73 (1.09)	

*The full-analysis set includes all randomised patients who received the study drug at least once, and who provided any postbaseline data for the RDQ score used for responder analysis, and who did not violate against inclusion criteria.
†ANCOVA (baseline as covariate) verum versus placebo for change from baseline.
ANCOVA, analysis of covariance; CI, confidence interval; n/N, number of patients; QOLRAD, Quality Of Life in Reflux and Dyspepsia; RDQ, Reflux Disease Questionnaire.

placebo: 7 cases) and 'respiratory, thoracic and mediastinal disorders' (placebo: 1 case 'throat irritation').

DISCUSSION

The present clinical trial represents the first randomised, placebo-controlled, double-blind trial that provides convincing evidence for efficacy of a mineral water in the treatment of heartburn, thereby improving different dimensions of HRQoL.

The phase-III trial was performed in accordance with international standards, the drop-out rate was low and treatment compliance was high. Only two patients were not randomised after the run-in phase due to violation of the inclusion criterion regarding RDQ score, so that a selection bias after run-in can be excluded. The primary endpoint was thoroughly selected: although no standard diagnostic tool for the assessment of the frequency and severity of heartburn is currently available, validated symptom-based patient questionnaires such as the RDQ are regarded as reliable instruments for the assessment of efficacy in clinical trials.[19 25–27] Based on the previously determined minimal important change for a perceived beneficial effect of 4.6 points in the RDQ score for 'heartburn',[18] a responder was defined as a patient with a reduction of at least 5 points in this RDQ dimension score after 6 weeks of treatment. The trial population is highly representative for the overall population of affected individuals with heartburn: according to a large UK database study including 7159 patients, the age distribution of the trial population is largely consistent with the age distribution of patients with GERD in real life.[28] Two-thirds of trial participants were female, which is in line with more frequent reports of NERD and reflux symptoms in women compared with men.[29]

The primary endpoint of the clinical trial was clearly met, demonstrating superiority of verum over placebo in heartburn relief. The detected placebo-corrected treatment effect amounted to >20%, relating to an NNT=5. In comparison, a placebo-corrected effect of 27% was found in clinical trials with the first-line treatment option of PPIs for heartburn relief in patients with NERD (NNT=3.7).[30] Consequently, the herein found 20% represent a clinically relevant effect size for a medicinal product with excellent tolerability—especially given the heterogeneous trial population with respect to the underlying cause of the symptom 'heartburn'.

The reported range of placebo response rates in randomised-controlled trials in GI disorders is broad and

Table 4 Patient-rated treatment satisfaction post baseline—TSQM-9 (full-analysis set, N=146)*

TSQM-9 domain score (mean percentage (SD))	Verum (n=72)	Placebo (n=74)
Effectiveness		
After 2 weeks	65.66 (24.99)	51.00 (23.61)
After 4 weeks	70.22 (24.10)	55.09 (26.86)
After 6 weeks	74.10 (26.87)	54.85 (28.28)
Convenience		
After 2 weeks	88.27 (15.08)	86.23 (16.52)
After 4 weeks	90.20 (13.43)	85.88 (15.00)
After 6 weeks	89.91 (14.06)	89.36 (14.20)
Global satisfaction		
After 2 weeks	69.35 (22.85)	53.17 (24.18)
After 4 weeks	75.00 (21.41)	58.63 (27.81)
After 6 weeks	79.38 (21.35)	59.18 (29.87)

*The full-analysis set includes all randomised patients who received the study drug at least once, and who provided any postbaseline data for the RDQ score used for responder analysis, and who did not violate against inclusion criteria.
n/N, number of patients; RDQ, Reflux Disease Questionnaire; SD, standard deviation; TSQM-9, Treatment Satisfaction Questionnaire for Medication version 9.

can be as high as 47% in trials involving patients with GORD[31] and even 73% in trials involving patients with functional dyspepsia.[32] The observed placebo response rate of ~60% in the present trial is within that reported range. Furthermore, the consumption of mineral water (1.5 L/day) itself—including the placebo water—may have had a certain symptom relieving effect in the present trial.

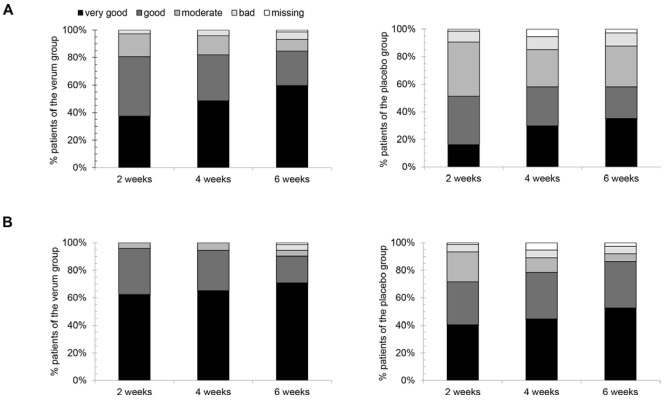

Figure 3 Investigator-assessed effectiveness (A) and tolerability (B) of treatment post baseline—Verbal Rating Scale (full-analysis set, N=146)*. *The full-analysis set includes all randomised patients who received the study drug at least once, and who provided any postbaseline data for the RDQ score used for responder analysis, and who did not violate against inclusion criteria. N/n, number of patients; RDQ, Reflux Disease Questionnaire.

The results obtained for all secondary parameters support the primary result: the extent of symptom score reduction with respect to frequency and severity after 6 weeks of treatment exceeded the previously determined minimal important changes for a beneficial treatment effect with respect to all three symptoms,[18] although a statistically significant effect over placebo was only apparent for the symptom 'heartburn'. The smaller effect of the mineral water on the symptoms 'dyspepsia' and 'regurgitation' is in line with literature data: according to Nocon *et al*, only the scores for 'heartburn' and 'regurgitation' are predictive for the assessment of a treatment response, since 'dyspepsia' represents a rather non-specific complaint, largely overlapping with reflux symptoms.[18] Furthermore, in accordance with the results of the present trial, the symptom 'regurgitation' is generally less responsive to acid suppression than 'heartburn' in patients with GORD.[33] Efficacy of the mineral water in heartburn relief is also reflected by the decreased use of rescue medication in the verum group, while this remained nearly constant throughout the trial in the placebo group.

The reduction in symptom complaints was paralleled by an improved HRQoL: the increases of QOLRAD domain scores after 6 weeks of treatment with verum exceeded the minimal important change of 0.5 points for a perceived beneficial treatment effect in all domains.[20] The observed differences between verum and placebo reached statistical significance for the domains 'emotional distress', 'food/drink problems' and 'vitality'. These results are largely consistent with the findings from the prospective cohort study ProGERD in which 6215 patients with GORD received the PPI esomeprazole: the extents of improvements in the domain scores after 2 weeks of treatment were comparable to the improvements detected in the present trial. In particular, the highest correlations between the 2-week change in the total RDQ symptom score and the change in the QOLRAD domains in ProGERD were found for 'food/drink problems' and the lowest correlations for 'physical/social functioning',[34] which is in line with the largest effect size for 'food/drink problems' and the smallest effect size for 'physical/social functioning' in the present trial.

The mineral water was well tolerated with a low AE incidence at placebo level, which is consistent with its known safety profile, as no relevant side effects are known.

A limitation of all studies focusing on symptoms only is that currently no standard diagnostic tool exists for objective assessment of heartburn. Therefore, the results of validated questionnaires based on diary entries by the patients had to be used for endpoint assessment. Furthermore, it could not be fully assured that the two treatment groups were comparable, since oesophageal physiology and factors that may have influenced symptom severity such as psychological comorbidities were not accounted for. Since the included patients had an interval between gastric endoscopy and screening of up to 5 years, patients with moderate

Table 5 Adverse events (AEs) per treatment (safety analysis set, N=148)*

	Verum (n=73)		Placebo (n=75)	
	Events	Patients (%)	Events	Patients (%)
AE	41	18 (24.7)	50	21 (28.0)
Related AE†	1	1 (1.4)	7	2 (2.7)
Serious AE	1	1 (1.4)‡	0	0
Mild AE§	32	11 (15.1)	38	19 (25.3)
Moderate AE¶	8	7 (9.6)	12	7 (9.3)
Severe AE**	1	1 (1.4)	0	0
Most frequent AEs††				
Headache	17	7 (4.7)	13	7 (4.7)
Back pain	0	0	10	6 (4.1)
Nasopharyngitis	0	0	10	6 (4.1)

*The safety analysis set includes all randomised patients who received the study drug at least once.
†At least reasonable possibility of causal relationship to study drug.
‡The patient was admitted to hospital due to 'chest pain', AE was severe but not related to the study drug.
§Mild: normal functional level not impaired or only slightly impaired.
¶Moderate: normal functional level to a certain extent impaired.
**Severe: normal functional level markedly impaired.
††Events in at least four study participants overall, all not related.

to severe reflux oesophagitis (LA grade C/D) might have been mistakenly included. In the ProGERD study (n=2721 completers), however, only 1.6% of patients with NERD and 2.7% of patients with LA grade A/B oesophagitis at baseline had progressed to LA grade C/D oesophagitis after 5 years of follow-up. Furthermore, 4.2% of patients with NERD and 8.1% of patients with LA grade A/B oesophagitis had progressed to confirmed Barrett's oesophagus after 5 years.[35]

The trial nevertheless provides the best available evidence because of appropriate internal and external validity and demonstrates a clinically relevant effect size of >20% over placebo with consistent and supportive results in all secondary analyses. Notably, the trial selected patients based on their willingness to drink 1.5 L mineral water per day over 6 weeks, thus, the estimated treatment effect may not necessarily reflect actual impact in real life, if adherence is lower.

In conclusion, the bicarbonate-rich mineral water qualitatively and quantitatively reduced heartburn symptoms in affected adult patients without moderate to severe reflux oesophagitis. The reduction in symptom complaints was paralleled by a relevant improvement in HRQoL and a reduction of the intake of rescue medication. Thus, the results of the placebo-controlled trial STOMACH STILL provide the clinical evidence for a recommendation of the mineral water Staatl. Fachingen STILL in the symptomatic treatment of heartburn. In contrast to chemically defined drugs with their associated long-term side effects, repeated administration of the healing water may result in a continuing and predictable therapeutic effect, along with excellent tolerability.

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Competing interests During conduct of the trial and preparation of the manuscript, JL received honoraria for consultancy from Fachingen Heil- und Mineralbrunnen GmbH. MA and JW were employees of SocraTec R&D GmbH. R-SW was an employee of SocraTec R&D GmbH and SocraMetrics GmbH. HW was an employee of Fachingen Heil- und Mineralbrunnen GmbH. BS was cofounder and managing director of SocraTec R&D GmbH and SocraMetrics GmbH.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the ethics committee of the Thuringian state medical chamber (ethics committee no. 35291/2018/134). Participants gave informed consent to participate in the study before taking part.

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Heartburn relief with mineral water

Supplemental Methods

Description of investigational medicinal products

The verum product Staatl. Fachingen STILL was a bicarbonate-rich mineral water with a bicarbonate (HCO^{3-}) content of 1802 mg/L (1483–2225 mg/L) and a carbonic acid (H_2CO_3) content of 1380 mg/L (1240–1860 mg/L). The water had a pH of 6.23 (5.95–6.35) and a conductivity of 2.72 mS/cm (2.57–3.14 mS/cm). Staatl. Fachingen STILL contained 2800 mg/L dissolved minerals and is thus defined as "healing water".[1] The ionic composition is summarised in **Supplemental Table 1** below.

Supplemental Table 1: Ionic composition of Staatl. Fachingen STILL (determined by "*Institut Fresenius*" in 2009)

Cations (mg/l)	Lithium	0.77
	Sodium	564
	Potassium	16.1
	Ammonium	0.48
	Magnesium	59.2
	Calcium	98.7
	Strontium	0.33
	Manganese	0.4
Anions (mg/l)	Fluoride	0.3
	Chloride	139
	Bromide	0.17
	Iodide	0.014
	Sulphate	39
	Hydrogen carbonate	1846
	Metasilic acid	30.6
	Metaboric acid	1.34
	Carbon dioxide	1510

For the production of placebo, a mineral water with low mineralisation from Bad Liebenwerda GmbH (Bad Liebenwerda, Germany) was supplemented with carbonic acid to achieve a comparable level of carbonisation between verum and placebo. The placebo water contained 27–32 mg/L (<50 mg/mL) HCO_3^- and 800-810 mg/L

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(500–2000 mg/L) H_2CO_3. The water had a pH of 4.9–5.0 (4.0–7.0) and a conductivity of 210–230 µS/cm (max. 280 µS/cm).

Both, verum and placebo, were bottled by Fachingen Heil- und Mineralbrunnen GmbH (Birlenbach OT Fachingen, Germany).

Inclusion and exclusion criteria

Included patients fulfilled the following criteria:

At screening visit:

1. history of repeatedly occurring episodes of heartburn with first manifestation at least 6 months ago
2. repeatedly occurring episodes of heartburn on at least 2 days per week within each of the last 4 weeks prior to screening visit
3. Reflux Disease Questionnaire (RDQ) score of ≥ 8 in the dimension "heartburn" considering the last 7 days prior to screening visit
4. availability of results of a gastric endoscopy within 12 months before screening visit excluding relevant erosive disease (reflux oesophagitis), i.e., assessment according to Los Angeles Classification not higher than grade A, and other severe gastrointestinal diseases including malignancies, ulcer, Barett's oesophagus, and oesophageal varices*
5. age: 18 years or older
6. willing and able to ingest at least 1.5 L water per day during the course of the trial
7. willing not to change general eating habits for the duration of the trial, i.e., no special diet planned

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8. written informed consent, after having been informed about benefits and potential risks of the clinical trial, as well as details of the insurance taken out to cover the patients participating in the clinical trial

Furthermore, at baseline visit (after run-in):

9. RDQ score of ≥ 8 in the dimension "heartburn" considering the last 7 days prior to baseline visit
10. intake of at least 1.5 L water or other beverages per day on at least 10 days over the last 14 days prior to baseline visit

Patients could not be included if they matched any of the following exclusion criteria:

At screening visit:

1. symptoms occurring after the time of gastric endoscopic examination:
    a) difficulty in swallowing (dysphagia) or painful swallowing (odynophagia)
    b) non-intended weight loss ≥5% of body weight
    c) iron deficiency anaemia
    d) experiencing episodes of persistent vomiting (at least 7 to 10 days of protracted vomiting) without causal explanation like gastrointestinal virus infection
2. signs of severe renal impairment known from medical history or reported during screening examination
3. severe heart failure (i.e., NYHA III/IV)
4. known Zollinger Ellison syndrome
5. active or known inflammatory bowel diseases (e.g., colitis ulcerosa, Crohn´s disease) or other severe chronic intestinal disease (e.g., colonic stenosis)

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6. diagnosed irritable bowel syndrome
7. patients, who rely on regular intake of medicines with pH-dependent absorption (i.e., HIV protease inhibitors, tyrosine kinase inhibitors)
8. known calcaemia (e.g., as a result of hyperparathyroidism, vitamin D overdose, paraneoplastic syndrome)
9. known nephrolithiasis due to calcium-containing kidney stones
10. known hypophosphatemia
11. known hypercalciuria
12. known hereditary problems of fructose intolerance, glucose-galactose malabsorption or saccharase isomaltase deficiency
13. patients with severe allergies or multiple drug allergies unless it is judged as not relevant for the clinical trial by the investigator
14. history of surgical intervention at esophagus or gastric and jejunal area
15. known or suspected drug or alcohol abuse within the last year
16. known or suspected eating disorders (e.g., bulimia)
17. continuous treatment with nonsteroidal anti-inflammatory drugs (NSAIDs e.g., piroxicam, ketoprofen, diclofenac, acetylsalicylic acid (ASA) or indomethacin (occasional treatment with NSAIDs or ASA 100 mg/day was permitted)
18. use of proton pump inhibitors (PPIs) within 4 weeks prior to screening visit
19. participation in a clinical trial during the last 30 days prior to individual enrollment of the patient
20. positive pregnancy test at screening examination

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21. pregnant women
22. female patients who do not agree to apply highly effective contraceptive methods
23. patients suspected or known not to follow instructions especially with regard to drinking habits and general eating habits during the study
24. patients who are unable to understand the written and verbal instructions, in particular regarding the risks and inconveniences they will be exposed to during their participation in the clinical trial
25. patients with close affiliation with the sponsor or the investigational site; e.g., close relative of the investigator or a dependent person (e.g., employee)

*The trial was started with the study protocol Amendment 02. However, the participating Principal Investigators informed the sponsor, that the request from Scientific Advice that a gastric endoscopic examination within the last year prior to enrolment has to be performed, was not in accordance with the common medical practice since the new version of the German medical guideline “S2k-Leitlinie 021/013 Gastroösophageale Refluxkrankheit” (version dated June 14th, 2014) came into effect. Thus, with Amendment 03, the inclusion criterion No. 4 was changed to “availability of results of a gastric endoscopy within 5 years before screening visit excluding relevant erosive disease (reflux esophagitis), i.e., assessment according to Los Angeles Classification not higher than grade A, and other severe gastrointestinal diseases including malignancies, ulcer, Barett’s oesophagus, and oesophageal varices”, which came into effect on 2019-11-26.

Thus, all patients included into the trial starting from January 1st, 2020 have been included according to the criteria of Amendment 03 of the study protocol.

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Furthermore, at baseline visit:

26. severe renal impairment (i.e., eGFR[1] ≤ 29 mL/min/1.73 m^2 determined from serum creatinine during screening)

27. laboratory values out of normal range unless the deviation from normal is judged as not relevant for the clinical trial by the investigator or if the following thresholds have been reached

- haemoglobin < 6.2 mmol/l

- leukocytes <2500 / µl

- platelets < 60000 / µl

28. use of PPIs within 4 weeks prior to baseline visit (during run-in period)

29. use of H_2-receptor antagonists, prokinetics, mineral waters or antacids other than the rescue medication within 2 weeks prior to baseline visit (during run-in period)

[1] Calculated via "Modification of Diet in Renal Disease" (MDRD) formula

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Supplemental Results

Supplemental Table 1: Placebo-corrected changes in RDQ dimension scores from baseline considering frequency/severity – ANCOVA (covariate: baseline) – differences of least squares mean (full analysis set, N=146)[1]

RDQ dimension	Estimate	Standard error	95% Confidence limits (two-sided)	p-value
Heartburn				
Frequency	-1.3198	0.3331	-1.9783 to -0.6613	0.0001
Severity	-0.9520	0.3290	-1.6024 to -0.3016	0.0044
Regurgitation				
Frequency	-0.6411	0.3378	-1.3088 to 0.0267	0.0598
Severity	-0.3615	0.3244	-1.0027 to 0.2797	0.2670
Dyspepsia				
Frequency	-0.7251	0.3068	-1.3316 to -0.1186	0.0195
Severity	-0.3347	0.3022	-0.9321 to 0.2627	0.2700

[1]The full analysis set includes all randomised patients who received the study drug at least once, and who provided any post-baseline data for the RDQ score used for responder analysis, and who did not violate against inclusion criteria.

ANCOVA, analysis of covariance; RDQ, *Reflux Disease Questionnaire*.

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