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

Heartburn relief with mineral water

(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

Heartburn relief with mineral water

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)

Heartburn relief with mineral water

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

Heartburn relief with mineral water

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.

Heartburn relief with mineral water

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

Heartburn relief with mineral water

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*.

References

1 Anonymous. Mineral and Table Water Regulation of 1. August 1984 (BGBl. 1036), as last amended by Article 1 of the Regulation of 22 June 2008. October 2014 (BGBl. I p. 1633), last modified by Art. 1 V v. 22.10.2014 I 1633 (https://www.global-regulation.com/translation/germany/388259/regulation-on-natural-mineral-water%252c-spring-water-and-bottled-drinking-water.html, accessed 15 Oct 2021). 1984.