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Technologically-Treated Polyclonal Affinity-Purified Antibodies to the Tumor Necrosis Factor-α, Brain Specific S-100 Protein and Histamine in Treatment Of Functional Dyspepsia: Results of the Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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The aim of the study was to evaluate the efficacy and safety of Kolofort® (a complex medicine containing technologically processed forms of antibodies to S-100 protein, tumor necrosis factor-α and histamine) in the management of functional dyspepsia (FD) in outpatient clinical practice.

Methods: Outpatients (*N* = 309) at the age of 18–45 in whom FD was diagnosed according to the Rome IV criteria were enrolled in a multicenter, double-blind, placebo-controlled, randomized clinical trial. Patients were randomized in two groups receiving Kolofort® or placebo 2 tablets tid for 8 weeks. The primary endpoint of the study was a change in the FD symptoms severity score according to the Gastrointestinal symptom score (GIS) at week 8. ITT and [PP] analysis were performed.

Results: at week 8 the reduction in GIS sum score was observed in Kolofort® group and placebo group (by 7.2 ± 3.3 [7.2 ± 3.4] and 6.3 ± 4.6 [6.2 ± 4.5], respectively, $p = 0.041$ [0.039]). The proportion of cases with GIS score reduction by ≥4 was 88,1 % [88.6 %] and 79.1 % [79.6 %] in Kolofort® group and placebo group, respectively ($p = 0.046$ [$p = 0.051$]). None of the patients in Kolofort® group had progression of FD symptoms or required additional therapy. There were 29 adverse events (AEs) recorded in 25 patients including 16 cases in 13 (8.6 %) patients in Kolofort® group and 13 AEs in 12 (7.6 %) patients in placebo group.

Conclusion: the clinical trial demonstrates the positive effect of Kolofort® in FD with a favorable safety profile.

Keywords: functional dyspepsia, placebo-controlled trial, technologically-treated polyclonal affinity-purified antibodies to the tumor necrosis factor-α, brain specific S-100 protein and histamine, efficacy assessment, safety profile Study protocol can be found on ClinicalTrials.gov. Identifier: NCT03119766.

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Availability of data and materials. The datasets obtained during this study will be available upon request to the corresponding author.

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Технологически обработанные поликлональные аффинно-очищенные антитела к ФНО-α, мозгоспецифическому белку S-100 и гистамину в лечении функциональной диспепсии: результаты многоцентрового рандомизированного двойного слепого плацебо-контролируемого клинического исследования

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Цель исследования: оценить эффективность и безопасность комплексного препарата, содержащего технологически обработанные антитела к белку S-100, фактору некроза опухоли альфа и гистамину (Колофорт®), у амбулаторных пациентов с функциональной диспепсией.

Методы: в многоцентровое двойное слепое плацебо-контролируемое рандомизированное клиническое исследование в параллельных группах были включены 309 амбулаторных пациентов в возрасте от 18 до 45 лет с установленным диагнозом «функциональная диспепсия» (ФД) согласно критериям IV Римского консенсуса и отрицательным тестом на *H. pylori*. Пациенты были рандомизированы в 2 группы: первая группа получала препарат Колофорт® по 2 таблетки 2 раза в день в течение 8 недель, вторая группа — плацебо по такой же схеме. Первичная конечная точка исследования — изменение выраженности симптомов ФД по шкале GIS через 8 недель от начала приема исследуемой терапии. Представлены результаты анализа эффективности intention-to-treat (ITT) и per protocol (PP).

Результаты: К 8-й неделе терапии в группе препарата Колофорт® наблюдалось уменьшение выраженности симптомов ФД в виде снижения суммарного балла по шкале GIS на 7,2 ± 3,3 (ITT) [7,2 ± 3,4 (PP)] балла, в группе плацебо — на 6,3 ± 4,6 [6,2 ± 4,5] балла соответственно, $p = 0,041$ [0,039]. Доля пациентов, у которых произошло снижение среднего суммарного показателя шкалы GIS на 4 балла и более, составила 88,1 % [88,6 %] и 79,1 % [79,6 %] в группе Колофорт® и плацебо соответственно ($p = 0,046$ [$p = 0,051$]). За время терапии не было отмечено ухудшения состояния ни у кого из пациентов, не потребовалось назначения дополнительной терапии. Всего в течение периода лечения и наблюдения было зарегистрировано 29 нежелательных явлений (НЯ) у 25 пациентов, в том числе 16 НЯ у 13 (8,6 %) пациентов группы препарата Колофорт® и 13 НЯ у 12 (7,6 %) участников группы плацебо.

Заключение: клиническое исследование продемонстрировало терапевтическую эффективность и безопасность применения препарата Колофорт® в лечении пациентов с ФД.

Ключевые слова: функциональная диспепсия, плацебо-контролируемое исследование, технологически обработанные поликлональные аффинно-очищенные антитела к ФНО-α, мозгоспецифическому белку S-100 и гистамину, эффективность, безопасность.

Протокол исследования опубликован на сайте ClinicalTrials.gov. Identifier: NCT03119766

Финансирование / Конфликт интересов. Клиническое исследование финансировалось за счет гранта ООО «НПФ «Материа Медика Холдинг». И.В. Маев, В.Б. Гриневич, И.Б. Хлынов и Ю.Г. Шварц получили грант от ООО «НПФ «Материа Медика Холдинг». Колофорт® — лекарственный препарат, производимый ООО «НПФ «Материа Медика Холдинг». Все авторы прочитали рукопись и согласились с тем, что работа готова к подаче в журнал, и принимают на себя ответственность за ее содержание. Авторы не заявляют о каком-либо другом конфликте интересов в связи с данной публикацией.

Доступность данных и материалов: данные клинического исследования можно запросить у автора, ответственного за переписку.

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Background

The prevalence of functional dyspepsia (FD) in adults is about 10 % [1]. FD, along with other functional gastrointestinal disorders (FGID), is considered to be a gut-brain axis disorder with the development of visceral hypersensitivity and impaired gastroduodenal motility, and it has multifactorial pathogenesis [2]. Pathogenetic association between FD and chronic gastritis remains to be studied more profoundly. Chronic gastritis can be found in a large proportion of patients with dyspeptic symptoms [3]. Moreover, the role of Helicobacter pylori *(H. pylori)* infection in dyspepsia is still unclear. Some authors indicate that dyspepsia may be a sign of acute or chronic *H. pylori* infection [4]. Whilst dyspepsia develops in *H. pylori*-associated chronic gastritis it should be categorized as "*H. pylori*-associated dyspepsia" but not as a primary FD [5–7].

Current algorithms for FD management include lifestyle modification, medications and psychotherapy in selected cases [8]. Drug therapy implies antisecretory agents, prokinetics and herbal preparations which normalize intestinal motility and visceral sensitivity. Antidepressants can be recommended in intractable cases [9, 10]. At the same time polypharmacy increases the risk of adverse events. The attempts to create complex acting medications for the treatment of FD is ongoing.

Kolofort® (Ltd. Research and Production Company "Materia Medica Holding") — a complex drug, consisting of technologically processed (highly diluted (HD)) affinity-purified antibodies (Abs) to TNF-α (anti-TNFα), to brain-specific protein S-100 (anti-S100), and to histamine (anti-H) can be considered as one of the approaches for the treatment of FD. The drug preparation (combination of HD Abs to S100, TNF-α and to H), trade name Kolofort®. The drug exerts a complex effect on the central and peripheral regulation of visceral hypersensitivity and hence can represent a complex approach for functional gastrointestinal disorders treatment [11–28].

Clinical and experimental studies demonstrate the reduction in colonic hypersensitivity to stretching, improvement in impaired gastrointestinal motility and stomach evacuation, relief of abdominal distention and pain in the course of treatment with the Kolofort®. It exerts antispasmodic action decreasing gastrointestinal tone and intraluminal pressure, normalizing defecation and stool consistency and relieving urgency, tenesmus, excessive straining and sensation of incomplete evacuation [29, 30].

It was shown recently that high dilutions of different substances obtained using a technological process that is a repeated dilution of the original substance in combination with external physical impact have the ability to modify the activity of the source substance or its target [12–14]. It has been established that the trigger mechanism of action of high dilutions is their ability to exert changes on conformation of the original substance/target molecule. Molecules of the initial substance are supposed to be observed in high dilutions [15–17]. The modifying effect has been repeatedly demonstrated in various experimental models, although its mechanisms need more fundamental study using special physico-chemical and immunochemical methods [17–23].

The technology of high dilutions has been gradually introduced into practice and several medications have been created based on high dilutions of antibodies [17-21]. Their efficacy and safety have been proven in numerous studies performed according to the principles of evidence-based medicine [24–28].

The aim of this study was to obtain additional data on the efficacy and safety of Kolofort® in the treatment of FD.

Materials and methods

The study was designed as a multicenter, double-blind, placebo-controlled, randomized clinical trial in parallel groups.

The study was conducted between June 2017 and January 2020 at 39 clinical centers in the Russian Federation according to the Federal Law of the Russian Federation dated 12.04.2010 № 61-FZ "On Circulation of Medicines" (with amendments), GOST R 52379-2005 "Good Clinical Practice", Guideline for Good Clinical Practice, E6 (R1, R2), the Rules of Good Clinical Practice approved by order of the Ministry of Health of the Russian Federation № 200n from April 01, 2016, and the Helsinki Declaration of the World Medical Association. The study was approved by the Ethics Council at the Ministry of Health of the Russian Federation (protocol № 141 from February 14, 2017) and local ethical committees of medical centers participating in the clinical trial and conducted with the permission of the Ministry of Health of the Russian Federation № 161 from March 22, 2017.

Outpatients 18-45 years of age were enrolled in the study. In all cases FD was diagnosed according to the Rome IV criteria (dyspepsia is defined as a complex of gastrointestinal disorders:

epigastric pain, epigastric burning, postprandial fullness and early satiety that occur over the last 3 months with an onset of at least 6 months in advance) [31]. Due to the inclusion criteria with the severity of symptoms of FD was not less than 6 points based on the GIS (Gastrointestinal Symptom Score) and negative results of endoscopic express-test for *H. pylori* infection. All patients signed a patient information sheet and informed consent form to participate in the clinical trial and used reliable contraception methods [32].

During the screening visit (Visit 1, from -14 to -1 days), doctors collected the medical history and complaints, registered concomitant diseases, performed physical examination. The severity of FD symptoms was assessed on the GIS scale, concomitant therapy was registered. Abdominal ultrasound, gastroscopy, *H. pylori* test were performed to exclude other possible causes of symptoms. A pregnancy test was conducted for all women of reproductive age.

On Visit 2 patients who met all the inclusion criteria and none of the exclusion criteria were randomly assigned to one of two groups: patients in the Kolofort® group received Kolofort® 2 tablets 2 times a day for 8 weeks and patients in the placebo group received placebo according to the same regimen as the Kolofort® group for 8 weeks.

3 more visits were planned: Visit 3 (week 2), Visit 4 (week 4), and Visit 5 (week 8) during which doctors collected complaints, performed physical examination, registered concomitant therapy, and assessed patient compliance and safety of the treatment.

The GIS scale (assesses the severity of dyspepsia symptoms) and Nepean Dyspepsia Index (NDI), assesses the impairment of the dyspepsia-specific health-related quality of life) were filled on Visit 3, 4, and 5. The Short Form Health Survey (SF-36) was filled on Visit 2 and 5. The Clinical Global Impression-Efficacy Index (CGI-EI) was filled on Visit 5. The duration of the follow-up period was up to 10 weeks.

1 month prior to the inclusion and during the study the administration of the following drugs was prohibited: drugs for acid-related disorders, drugs for functional gastrointestinal disorders, antihistamines, steroids and non-steroidal anti-inflammatory drugs (except for topical/inhaled corticosteroids), anti-inflammatory and anti-rheumatic drugs, analgesics, antitumor drugs, immunostimulants, immunosuppressants, immune serums and immunoglobulins, vaccines, calcium supplements, iron supplements, zinc supplements, potassium supplements, antimicrobial drugs for systemic use and any other drug except Kolofort® produced by "NPF "Materia Medica Holding". The patient was allowed to take antispasmodic drug drotaverine in a total dose of no more than 640 mg during treatment (equivalent to 16 tablets of drotaverine 40 mg or 8 tablets of drotaverine 80 mg).

Patients were randomized into two groups using an automated interactive voice system (IVS) based on a number generator.

In this study, double-blind placebo control was used. Kolofort® tablets and placebo had the same appearance and organoleptic properties. The test drug was delivered in packages and blisters which lacked any labels indicating the presence of active substances. The batch number, package number, number of the study protocol, number of tablets in the package, and the drug route were indicated on the cardboard pack. Patients, researchers, research center staff, and the project sponsor team were not informed about the prescribed study therapy (Kolofort® or placebo) until the trial was completed and the database was closed.

The primary endpoint of the study was a change in FD symptoms severity according to the GIS at week 8. As **secondary endpoints** were assessed: the percentage of patients with reduced severity of FD symptoms according to the GIS sum score after 8 weeks of treatment, a change in the NDI index at week 8, a change in the quality of life according to SF-36 at week 8, the percentage of patients withdrawn from the study prematurely due to ineffectiveness of therapy, indicators of therapeutic and side effects, Clinical Global Impression efficacy index (CGI-EI) after 8 weeks of therapy.

During the study period adverse events were recordered. The dynamics of vital signs was used to assess the safety of the studied drug.

The following rules and assumptions were taken into account when calculating the sample size: the power of statistical criteria was set to 80 %, the probability of type I error "α" was less than 5 %, statistical criteria for intergroup comparisons were bilateral; the sample size was based on assumptions about expected the effect, declared in the main performance criteria of this protocol; the ratio between the sample sizes of the Kolofort® group and placebo group was 1:1; the difference between the average decrease of the total score on the GIS scale was less than 15 % from the baseline level in the Kolofort® and placebo groups (d = 0.15, the difference between the average decrease of the total score on the GIS scale in both groups, classified as the mean starting value on the scale). Based on these statistical assumptions, in order to assess the superiority of the study drug over placebo, the size of each group was 129. Given the possible

dropout of at least 30 % of patients during the study for various reasons, it was necessary to obtain a signed informed consent form from at least 370 patients, 185 patients in each group.

To compare the results in both groups, analysis of continuous variables was carried out using the Student's t-test, non-parametric Wilcoxon test, and median analysis. The normality test was carried out using visual analysis of the QQ plot of the model. Two-factor analysis of variance was used to compare changes in the indicators in both groups, where the factors were "Group" and "Visit". A single-factor analysis of variance was used with the "Group" factor. Frequency analysis with the comparison of shares (percentage) in the two groups was performed using Fisher's exact test. Data processing and all statistical calculations were performed using the statistical package SAS-9.4 Licensee: Ltd. Research and Production Company "Materia Medica Holding", №70100045.

For all the statistical analyses the results are reported for the intention to treat (ITT) group and for the per protocol group (PP) [in brackets].

Results

Patient flow

Patients who had signed the informed consent (N = 370) were assessed for eligibility criteria (Figure 1). Among them 61 patients were withdrawn at screening visit as they didn't completely meet the inclusion criteria or met the exclusion criteria, 309 patients were randomized into two groups (n = 151, Kolofort® group; n = 158, placebo group). Intention-to-treat (ITT) analysis was based on the data of these patients (n = 309).

There were 282 patients (n = 140, Kolofort® group; n = 142, placebo group) who completed therapy per protocol (PP), 27 cases (n = 11, Kolofort® group; n = 16, placebo group) were excluded from PP analysis due to some deviations from protocol requirements.

Patient demographics

The mean patients' age in Kolofort® group was 30.5 ± 7.7 [30.6 ± 7.7] years and in placebo group 29.7 ± 7.9 [29.9 ± 7.8] years (p = 0.3035 [p = 0.4033]). Females predominated in both groups (69.5 [69.3] % and 69.6 [67.6] %). There were 30.5 [30.7] % of men in Kolofort® group and 30.4 [32.4] % in the placebo group (p = 0.9872 [p = 0.7615]). There were no other significant differences in demographic characteristics between the two groups. At the screening visit all the patients had negative results of *H. pylori* test, The initial GIS score had no significant difference between the groups, reaching a total of 10.4 ± 3.5 [10.4 ± 3.4] points in Kolofort® group and 10.1 ± 4.0 [10.0 ± 4.0] points in placebo group (p = 0.1209 [p = 0.0763]).

Co-morbidities were registered among 47.7 % [47.1 %] of patients in Kolofort® group and 48.1 % [47.9 %] in placebo group (p = 0.164 [p = 0.400]). Diseases of digestive system or indirectly related to digestion (chronic gastritis, dental caries, umbilical hernia, diverticulum of the intestine, etc.) were registered in 23.2 % [22.9 %] cases in Kolofort® group and in 25.3 % [25.4 %] cases in placebo group. Respiratory system disorders (asthma, chronic bronchitis, vasomotor rhinitis, etc.) were noted in 2.6 % [2.9 %] and 3.8 % [3.5 %] cases, and previous surgery (appendectomy, cesarean section, cauterization of the cervix, rhinoplasty, phlebectomy, etc,) — in 3.3 % [3.6 %] and 4.4 % [4.2 %] cases, respectively. Other diseases were registered in a small percentage of patients in both groups.

The most common concomitant pathology was *H. pylori*-negative chronic gastritis which was detected in 21.2 % [20.7 %] of patients in Kolofort® group and in 23.4 % [23.2 %] of patients in placebo group.

Concomitant therapy was registered in 9.9 % [9.3 %] of cases in Kolofort® group and 13.3 % [10.6 %] of cases in placebo group (p = 0.665 [p = 0.949]) and included sex hormones and their modulators, mainly contraceptives (3.3 % [3.6 %] and 3.8 % [3.5 %] in both groups, respectively, p = 1.00 [p = 1.00]). Other concomitant medications were rare. Fisher's exact test showed no significant difference in co-morbidities and concomitant therapy in both ITT- and PP-analyses.

Three patients (1.98 % [2.1 %]) in Kolofort® group and 8 patients (5.06 % [4.4 %]) in placebo group received medication for FGID: drotaverine in allowed doses in 10 cases and mebeverine considered as a prohibited drug in 1 case (this patient was withdrawn from the study). Z-test showed no significant difference between groups in ITT-analysis (p = 0.05).

The patients' compliance was close to 100 % and did not have significant difference between groups on Visit 3, Visit 4 and Visit 5 (p = 0.9130 [p = 0.7537]; p = 0.4282 [p = 0.6852]; p = 0.3944 [p = 0.2412]).

Efficacy assessment

By the end of week 8 a reduced severity of FD symptoms was observed according to the GIS score in both groups (by 7.2 ± 3.3 [7.2 ± 3.4] in Kolofort® group and by 6.3 ± 4.6 [6.2 ± 4.5] in placebo group, respectively. The difference in the average score on the GIS scale was 0.94 [0.98] points. After 8 weeks of therapy, analysis of variance showed statistically significant differences

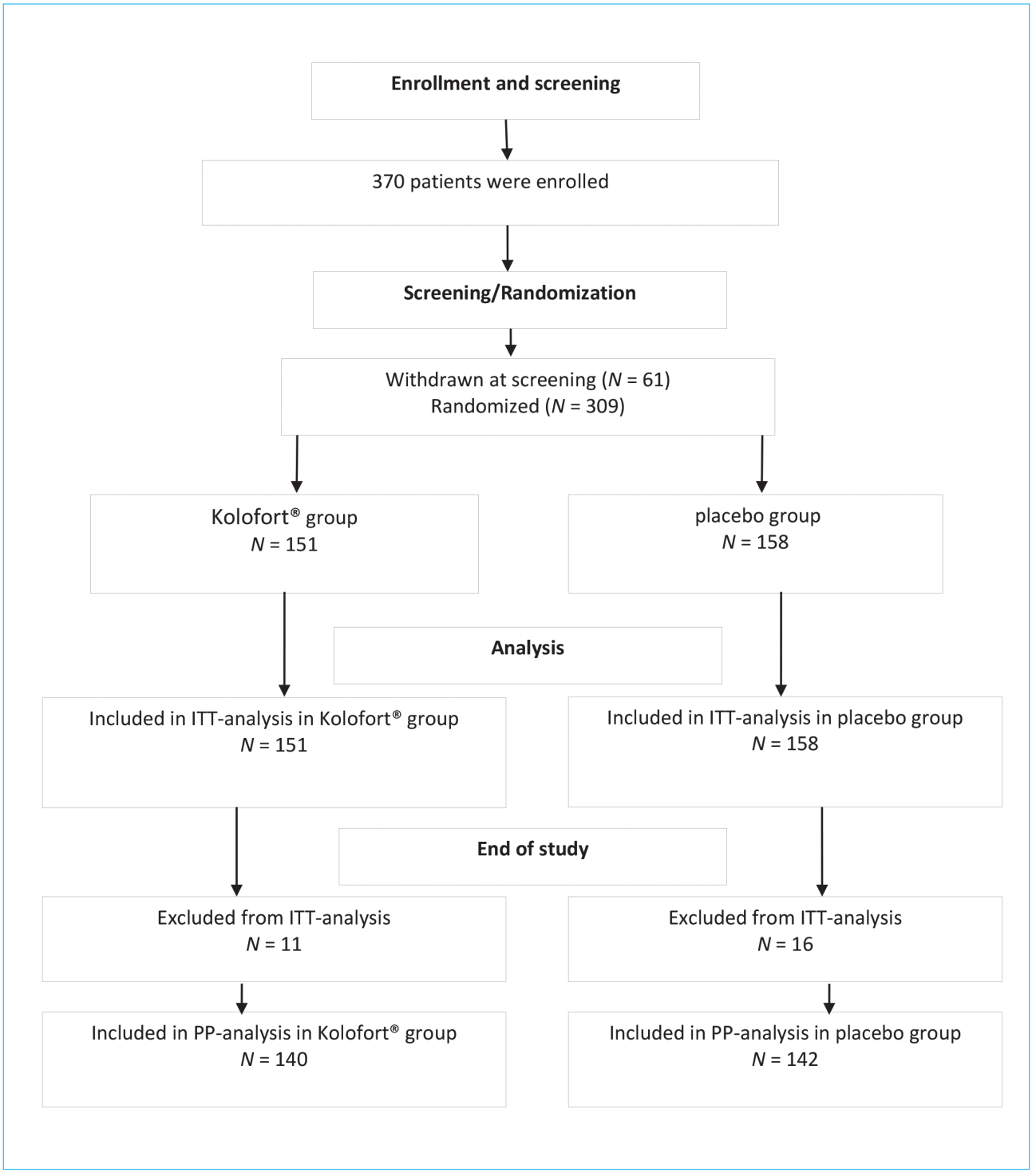

Fig. 1. Patient flow char

between the mean changes of the average score on the GIS scale between the Kolofort® and placebo group ($p = 0.041$ [0.039]) (Table 1).

The regression of FD symptoms according to the GIS scale at week 8 was analyzed by its degree ("category", with decrease by 1, 2, 3, 4 or more points). In Kolofort® group the proportion of patients with reduced severity of FD symptoms by ≥ 1 points was 99.3 % [100.0 %] at week 8, in placebo group — 95.6 % ($p = 0.067$ [$p = 0.122$]).

In the ITT-sample the median GIS sum score decreased by 2 points in 96 % of patients in Kolofort® group and 89.2 % of patients in placebo group ($p = 0.029$); by ≥ 3 points in 91.4 % of patients in Kolofort® group and 84.8 % of patients in placebo group ($p = 0.082$); by ≥4 points in 88.1 %

Table. Change in the severity of FD symptoms according to the GIS sum score after 8 weeks of treatment

Index	ITT-analysis		PP-analysis	
	Kolofort® group $N = 151$	placebo group $N = 158$	Kolofort® group $N = 140$	placebo group $N = 142$
Mean ± SD	7.2 ± 3.3	6.3 ± 4.6	7.2 ± 3.4	6.2 ± 4.5
Median	7	6	7	6
Min and Max	1–18	-12–33	1–18	-12–33
Lowest and highest quartile (Q1-Q3)	5–9	4–8	5–9	4–8
95 % CI	[6.4; 8.0]	[5.5; 7.1]	[6.4; 8.0]	[5.5; 7.1]
Kolofort® group, difference in means 95 % CI	0.94 [0.04–1.85]		0.98 [0.05–1.92]	
P-value	"Group" factor $P = 0{,}041$		"Group" factor $P = 0{,}039$	

Notes. Comparison of the average GIS scores was carried out using analysis of variance with fixed "Group" factor. Yeo-Johnson ($\lambda = 0$) data transformation was used for the two-factor ("Group" and "Visit" factors) analysis of variance, leading to normalization of distribution of residuals. 95 % CI — 95 % confidence interval.

of patients in Kolofort® group and 79.1 % of patients in placebo group ($p = 0.046$).

The initial score of the average NDI index value was 23.5 ± 7.0 [23.6 ± 7.0] in Kolofort® group and 23.5 ± 6.9 [23.4 ± 7.1] points in placebo group. At week 8 a tendency to reduction in the FD symptom influence on daily activity was seen in the Kolofort® group: at weeks 4 and 8 NDI score corresponded to 17.1 ± 5.6 [17.1 ± 5.8] and 14.4 ± 5.1 [14.5 ± 5.2] in Kolofort® group versus 17.0 ± 6.0 [17.1 ± 6.4] and 14.9 ± 6.0 [15.0 ± 6.2] in placebo group, respectively. Thus, the total change in NDI score in the course of treatment was 9.1 ± 7.1 [9.1 ± 7.2] in Kolofort® group and 8.5 ± 6.6 [8.5 ± 6.7] in placebo group, $p = 0.435$ [$p = 0.450$] for the "Group" factor.

By the week 8, the median score of the SF-36, demonstrating the physical health component, increased from 49.9 ± 7.8 [49.7 ± 7.9] to 56.3 ± 6.5 [56.4 ± 6.6] in Kolofort® group, and from 49.4 ± 7.7 [49.4 ± 7.9] to 56.2 ± 6.3 [56.2 ± 6.5] in placebo group. According to analysis of variance with fixed "Group" factor, the median score increased by 6.4 ± 7.5 [6.7 ± 7.6] in Kolofort® group and by 6.8 ± 7.0 [6.8 ± 7.1] in placebo group ($p = 0.655$ [$p = 0.908$]).

The median score of the SF-36, demonstrating the mental health component, increased from 33.6 ± 5.7 [33.5 ± 5.8] to 37.1 ± 4.5 [37.0 ± 4.5] in Kolofort® group, and from 34.0 ± 6.1 [33.8 ± 6.1] to 36.9 ± 4.9 [36.9 ± 5.0] in placebo group. So the change of median score was 3.5 ± 6.3 [3.5 ± 6.3] in Kolofort® group and 2.9 ± 6.6 [3.1 ± 6.6] in placebo group ($p = 0.375$ [$p = 0.599$]).

None of the patients in Kolofort® group had experienced stable persistence or progression of FD symptoms or required additional prohibited therapy throughout 8 weeks of treatment. One patient in placebo group required additional prohibited therapy for progression of FD symptoms and therefore was withdrawn from the study.

The majority of investigators evaluated the therapeutic effect of Kolofort® group as "pronounced". The median therapeutic effect score was 2.67 ± 2.96 [2.71 ± 3.01] in Kolofort® group and 3.33 ± 3.49 [3.27 ± 3.49] in placebo group ($p = 0.139$ [$p = 0.258$]).

According to investigators' opinion, there were no adverse effects in the majority of patients throughout 8 weeks of therapy. According to the CGI-EI scale the median score of adverse effects in Kolofort® and placebo groups were 1.09 ± 0.31 [1.08 ± 0.27] and 1.04 ± 0.19 [1.04 ± 0.20], respectively ($p = 0.08$ [$p = 0.201$]).

According to investigators' estimation the final clinical efficacy index was 3.76 ± 2.98 [3.79 ± 3.04] points in Kolofort® group and 4.37 ± 3.51 [4.31 ± 3.52] points in placebo group ($p = 0.251$ [$p = 0.371$]).

In addition the dynamics of FD symptoms was analyzed among the group of patients with the signs of superficial gastritis without atrophy and *H.pylori* that were found out during gastroduodenoscopy. There were 32 patients in

Kolofort® group. Changes in the GIS sum score (the difference between the first and last visits) show the reduction in symptom severity in cases of FD associated with chronic gastritis (Figure 2). The most significant changes were seen for epigastric pain, bloating and early satiety.

Safety assessment

The safety and tolerability of therapy were evaluated in patients who received at least one dose of Kolofort® group or placebo (Safety population, $n = 309$). The safety of the drug was assessed in terms of adverse events (AEs), their severity and relation to the study drug, outcomes.

Statistical analysis with the Bonferroni correction method showed no influence of Kolofort® group and placebo on systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and respiration rate on Visits 1–5.

During the study period 29 AEs were recorded in 25 patients. In the study 16 AEs were recorded in 13 (8.6 %) patients in Kolofort® group and 13 AEs in 12 (7.6 %) patients in placebo group, Fisher's exact test showed no significant difference in AE rate in both groups ($p = 0.836$). There was no significant difference in the number of patients with AEs with particular MedDRA codes between the two groups.

Most AEs. $N = 7$ (4.6 %) cases in Kolofort® group and $N = 4$ (2.5 %) in placebo group were associated with digestive system dysfunction. Symptoms of gastrointestinal tract hyperkinesia ($n = 1$), diarrhea ($n = 1$), dyspepsia ($n = 1$), constipation (n = 1), mouth dryness ($n = 2$), and nausea ($n = 1$) were recorded in Kolofort® group. Diarrhea (n = 1), constipation ($n = 2$), and mouth dryness ($n = 1$) were recordered in placebo group.

In 4 (2.6 %) patients in Kolofort® group and in 3 (1.9 %) patients in placebo group infections and infestations were detected, Other AEs in Kolofort® group included nasopharyngitis ($n = 1$), rhinitis ($n = 1$), acute respiratory infection ($n = 2$). In placebo group acute respiratory infection ($n = 1$), nasopharyngitis ($n = 1$), tonsillitis ($n = 1$), and cystitis ($n = 1$) were detected.

According to investigators' opinion, the cause-effect relationship of AEs with the study drug (Kolofort®) was assessed as negative in 10 cases ($n = 10$; 62.5 %). possible in 2 cases ($n = 2$; 12,5 %) and probable in 4 cases ($n = 4$; 25.0 %), No AE with a reliable connection to the study drug was registered. The distribution of AEs according their severity ($p = 0.632$) and a causal relationship with the study drug ($p =$

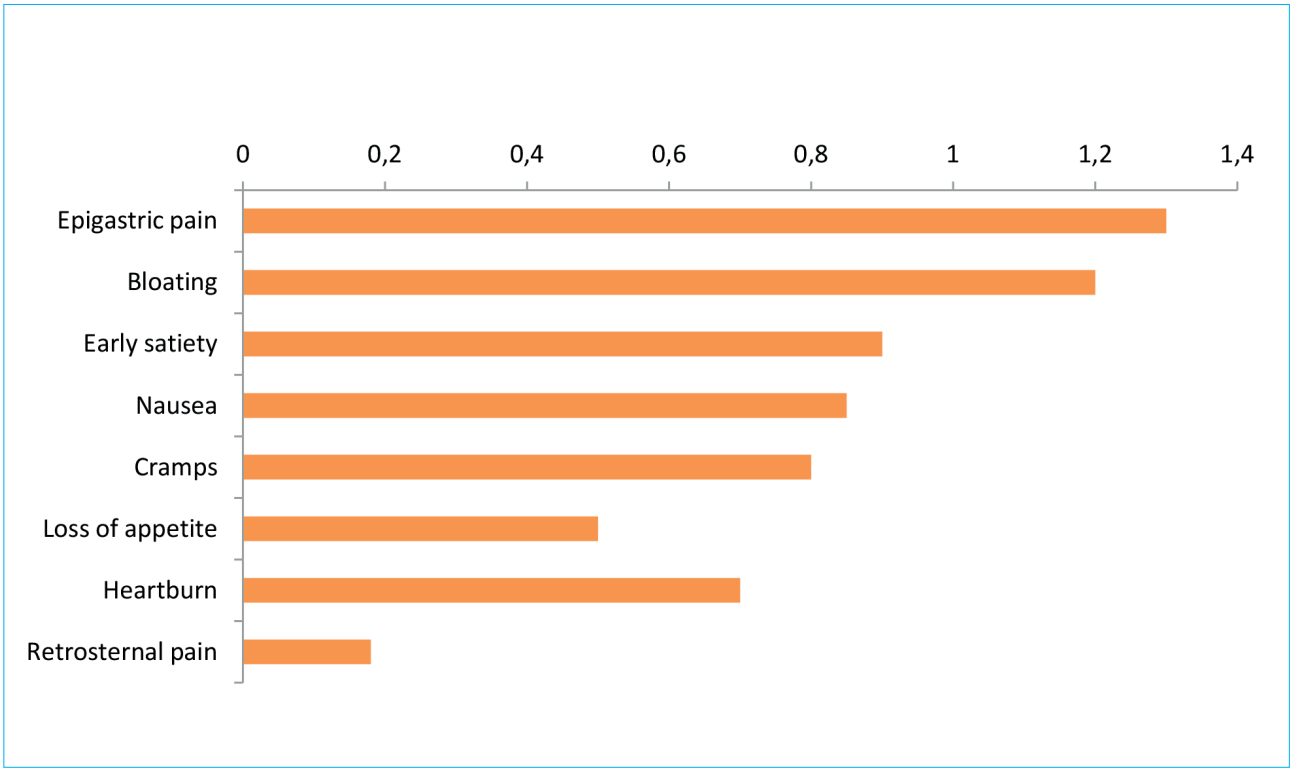

Fig. 2. Changes in the severity of FD symptoms according to the GIS sum score in patients (N = 32 in Kolofort® group) with signs of superficial *H. pylori*-negative chronic gastritis based on gastroduodenoscopy

0.785) did not differ between the groups. No severe AEs were reported throughout the study.

Discussion

The study demonstrates a significant improvement of FD symptoms (epigastric pain, early satiety, nausea, vomiting, bloating, heartburn/acid belching, feeling of weakness in combination with pain, nausea, and loss of appetite) in the course of 8-week therapy with Kolofort®. In the subgroup with *H. pylori*-negative chronic gastritis a distinct trend for FD symptom improvement although not statistically significant is shown.

Treatment with Kolofort® showed no statistically significant impact on the quality of life although a clear positive trend was demonstrated in terms of daily activities. The absence of statistic significance can be explained by the insufficient length of the study since a pronounced residual placebo effect may persist in 8 weeks. A longer study may be needed to assess the effect of the Kolofort® on daily activities and quality of life in FD more profoundly. It would be appropriate to accentuate that according to a Cochrane review prokinetics which represent a clear positive effect in many patients with postprandial distress syndrome do not demonstrate the significant impact on the quality of life [33].

In Kolofort® group there were no cases of early withdrawal from the study due to therapy ineffectiveness or to prescription of accessory medications for FD prohibited in the protocol. The rate of additional prescriptions for the treatment of functional gastrointestinal symptoms in Kolofort® group was 2.7 times lower than in placebo group that indirectly indicates its clear influence on the gastrointestinal function.

The study demonstrates the safety of Kolofort® in the treatment of FD. No AEs were registered having a clear causative relationship with the studied preparation. No cases of incompatibility with other medication were registered, including those used for functional gastrointestinal disorders, bronchial asthma, rhinitis, analgesics, medications affecting renin-angiotensin system, beta-blockers, sex hormones and modulators of the reproductive system. The treatment was well-tolerated, with high patients' compliance.

This multicenter, double-blind, placebo-controlled trial had demonstrated the efficacy and safety of Kolofort® in FD, including cases of FD in *H. pylori*-negative chronic gastritis. The therapeutic activity of Kolofort® in FD can be attributed to the influence on the mechanisms of inflammation, visceral hypersensitivity and gut-brain axis dysfunction [30]. In an 8-week period the effect of Kolofort® can be also implemented through anxiolytic, antispasmodic, anti-inflammatory action and normalization of gastrointestinal motility [29, 30]. Taking in account the frequent overlap of FD with other functional gastrointestinal disorders (e.g., irritable bowel syndrome) further investigations of Kolofort® efficacy seem to be rational [34, 35].

However, there are some limitations of the study. Given the significant heterogeneity inherent to the presentation and disease course of FD, in conjunction with the known high placebo response rate in patients with FGIDs, the design of this trial without a crossover period is concerning. Secondly, the 8 weeks period probably could limit the study. Furthermore, long-term follow-up period could show more beneficial results. Although it is worth noticing that while a number of therapeutic agents have been recommended for therapy in FD, none have shown complete efficacy [36].

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