Pathogenetic approach to the treatment of functional disorders of the gastrointestinal tract and their intersection: Results of the Russian Observation Retrospective Program COMFORT

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Abstract

Background

The aim of this study was to investigate the efficacy and safety of the novel complex drug, consisting of released-active form of antibodies to S-100 protein, tumor necrosis factor-α and histamine, (Kolofort) under outpatient conditions in patients with functional dyspepsia (FD), irritable bowel syndrome (IBS), and their combination.

Methods

The subject of the observational noninterventional retrospective program was the data of 14,362 outpatient records of patients with diagnosed FD, IBS, and/or their combination who received the drug Kolofort in monotherapy for 12 weeks, 2 tablets twice a day. To assess the presence and severity of symptoms of functional disorders of the gastrointestinal tract (FD GIT), a questionnaire “7*7” developed by a working group from the Russian Gastroenterological Association was used. The evaluated parameters included the proportion of patients: who had a reduction in the number of points by 50% or more; who have decreased the severity category of the condition; who have switched to the “healthy” and “borderline ill” severity categories;and the change in the number of points in domains 1–7.

Results

The final efficacy analysis included data from 9,254 patients. A decrease in the number of points by 50% or more was observed in 80.45% of patients with FD, 79.02% of patients with IBS, and in 83% of patients with both IBS and FD. A decrease in the severity category of the condition at the end of therapy was noted in 93.35% of patients with FD, in 93.80% of cases in patients with IBS, and in 96.17% of cases in patients with a combination of IBS and FD.A total of 94 adverse events (AEs) were reported in 80 patients (0.65%).

Conclusion

The COMFORT program has demonstrated the positive effect of treatment in the majority of patients with IBS and FD and their combination in real clinical practice.

Background
A variety of clinical forms and the heterogeneity of the pathogenetic mechanisms of functional disorders of the gastrointestinal tract (FD GIT) complicate the diagnosis and choice of an effective treatment regimen.\(^1\) Irrational pharmacotherapy, the prescription of symptomatic drugs that do not have indications for treatment of the FD GIT, leads to polypharmacy, low patient adherence to treatment, and an increased risk of developing adverse events.\(^2,3,4,5\)

Particular difficulties in the treatment of functional disorders arise from the combination of various forms of the disorder.\(^3\) The combination of irritable bowel syndrome (IBS) and functional dyspepsia (FD) is most commonly observed.\(^6\) Such patients have elevated visceral hypersensitivity, greater severity of gastrointestinal symptoms, and lower quality of life than patients with a single FD GIT.\(^7,8\)

In the FD, dysfunction of the digestive tract organs is often combined with pathology of the mental sphere.\(^9,10\) According to literary data, up to 90% of patients with FD GIT have concomitant psychiatric disorders.\(^11,12\) This neuropsychic component also serves as a key link in the pathogenesis of the combination of FD and IBS.\(^13,14\)

Real importance in the development and progression of FD GIT is given to the presence of chronic inflammation in the gastrointestinal tract caused by imbalances of pro-inflammatory and anti-inflammatory factors (tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)); interleukins (IL), IL-2, IL-6, IL-10, and histamine).\(^15,16\)

Due to the general pathogenetic mechanisms associated with impaired motor function of the GIT and a reduced threshold for the perception of stimuli, abdominal pain appears to be the main symptom of most of FD GIT.\(^17,18\)

To date, various symptomatic and pathogenetic means are used for the treatment of FD GIT: antispasmodics, proton pump inhibitors, drugs that relieve diarrhea/constipation, prokinetics, probiotics, antidepressants, antagonists of 5HT3 and 5HT4 receptors, opioid receptor agonists, and selective activators of C-2 chloride channels.\(^19,20,21\) Most of these drugs are not always able to effectively solve the problems of patients. In this regard, in the routine practice of
gastroenterologists, therapists, and general practitioners, there is a need for a multi-targeted drug affecting the main pathogenesis of FD GIT.

For the treatment of FD GIT, the combination of released-active form of antibodies to S-100 protein, TNF-α and histamine (RAF of Abs to S 100, Abs to TNF-α and Abs to H), a drug of pathogenetic action, Kolofort, was developed in the Research and Production Company Materia Medica Holding (LLC NPF “MATERIA MEDICA HOLDING”) Moscow, Russia and introduced into practical medicine. The RAF of Abs in the drug provide an anti-inflammatory, spasmolytic, and anxiolytic effect. 22

It was established experimentally that the antispasmodic effect of combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H is due to the relaxation of smooth muscles and a decrease in the tone of the walls of the stomach and intestines. Anti-inflammatory properties are realized due to the effect of the drug on the production of TNF-α and its associated cytokines. The positive effect of the drug components on the nervous and humoral regulation of functions of the gastrointestinal tract has been confirmed. 22

In a randomized, placebo-controlled clinical study of the efficacy and safety of combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H for the treatment of IBS, the effect of the drug on the relief of abdominal pain has been proven. Along with a decrease in the intensity of abdominal pain, there was a normalization of the frequency and consistency of the stool, indicating a restoration of the motor-evacuation function of the GIT. 23

The combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H also showed efficacy in the treatment of the combination of IBS and FD: 12 weeks of therapy with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H reduced the incidence of abdominal distention and nausea by 1.5 and 3 times compared with placebo. 23

At the same time, there was no large-scale population-based research on the study of the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H under outpatient conditions in patients with FD, IBS, and their combination, which served as the basis for the Russian Observation Program COMFORT.
Methods

Study design: An observational nonintervention retrospective program to study the efficacy and safety of the use of the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H in patients with FD, IBS, and their combination in outpatient settings.

The subject of the study was the data of outpatient records of patients with FD, IBS, and a combination of IBS and FD, who were observed by gastroenterologists from November 01, 2017, through March 30, 2018, and were treated with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H for 12 weeks, 2 tablets twice a day in accordance with instruction for medical use. The COMFORT Observation Program has been approved by the Independent Interdisciplinary Committee for the Ethical Review of Clinical Studies.

The study design did not imply additional methods of laboratory or instrumental examination for the inclusion of patient data in the program. To assess the presence and severity of symptoms characteristic of FD GIT, the questionnaire “7*7” was used.

The “7*7” questionnaire was developed by the Russian Gastroenterological Association based on clinical symptoms described in the Rome III criteria and recommended for use by gastroenterologists in routine practice to assess the presence and severity of the seven main symptoms of FD GIT over the past seven days. The first four domains in the questionnaire “7*7” are considered as symptoms of FD; domains 5 through 7 characterize IBS symptoms.

Patients completed the questionnaire before the beginning of therapy with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H and three months after the end of the course of treatment. The severity of the patient’s condition was evaluated by the sum of points and ranked by category as follows: 0–1—healthy; 2–6—borderline ill; 7–12—mildly ill; 13–18—moderately ill; 19–24—markedly ill; 25 or more—severely ill.

The overall score of domains 1 and 2 allows us to judge the intensity of abdominal pain; a total score of domains 3 and 4 allows us to judge the severity of symptoms of early satiety. The dynamics of points of the 5th domain allow us to estimate the intensity of pain, decreasing after bowel emptying, the 6th domain allows us to estimate the intensity of abdominal distention, and the 7th domain allows...
us to estimate the characteristics of the stool.

*Evaluated parameters:*

1) The proportion of patients in whom there was a decrease in the number of points according to the questionnaire “7*7” by 50% or more after 12 weeks of therapy in the groups with FD, IBS, and their combination.

2) The proportion of patients who have decreased the severity category of the condition according to the questionnaire “7*7” after 12 weeks of therapy in the groups with FD, IBS, and a combination of IBS and FD.

3) The proportion of patients who have switched to the “healthy” and “borderline ill” severity categories according to the “7*7” questionnaire after 12 weeks of therapy in the groups with FD, IBS, and a combination of IBS and FD.

4) The change in the number of points in domains 1–7 according to the questionnaire “7*7” after 12 weeks of therapy in the groups with FD, IBS, and a combination of IBS and FD.

*Methods of statistical analysis.* Descriptive statistics methods were used for statistical analysis. Continuous variables are presented as estimates of mean, standard deviation, median, 1st and 3rd quartiles, and minimum and maximum values. Categorical variables are presented as a number and proportion of patients in the respective categories. Data from patients with missing values were not included in the statistical analysis.

**Results**

*Patient Characteristics* 14,362 patients participated in the study. The final efficacy analysis included data from 9,254 patients. The data of 5,108 patients were not used to assess the effectiveness of the therapy, since 1,645 patients had organic gastrointestinal diseases besides the presence of FD GIT, and 3,463 patients had missing data that did not allow for evaluating the dynamics of symptoms. The safety analysis took into account the data of all 14,362 patients.

Among the patients included in the efficacy analysis, 2,404 patients were diagnosed with FD, 5,909 patients had IBS, and 941 patients had a combination of IBS and FD.

The average age of patients with FD was 33.52 ± 11.16 years, with IBS—37.76 ± 12.73 years, and
with a combination of IBS and FD—36.3 ± 11.27 years.

Among the participants of the COMFORT program, women prevailed (5,898 patients). In the group of patients with FD, there were 1,437 (59.78%) women and 967 (40.22%) men, in the group of IBS—3,849 (65.14%) women and 2,060 (34.86%) men, and in the group of patients with a combination of IBS and FD, there were 612 (65.04%) women and 329 (34.96%) men.

By severity, patients were distributed as follows: 383 patients (4.13%) “borderline ill” (score 2–6), 2,822 patients (30.60%) “mildly ill” (score 7–12), 3,236 patients (34.96%) “moderately ill” (total score 13–18), 1,708 patients (18.45%) “markedly ill” (total score 19–24), 1,105 patients (11.94%) “severely ill” (total score 25 or more) (Table 1).

The distribution of patients by categories of severity with various nosological forms is presented in Table 2.

**Efficacy evaluation**

According to the questionnaire “7*7,” after 12 weeks of treatment with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H, a decrease in the number of points by 50% was observed in 80.45% of patients with FD, 79.02% of patients with IBS, and in 83% of patients in the group with IBS and FD (Table 3).

A decrease in the severity category of the condition at the end of therapy was noted in 93.34% of cases in patients with FD, in 93.81% of cases in patients with IBS, and in 96.17% of cases in patients with a combination of IBS and FD.

After 12 weeks of treatment with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H, the distribution of patients according to the categories of severity was as follows: 1,930 patients (20.85%) comprised the group “healthy,” 4,871 patients (52.63%) — “borderline ill,” 1,915 patients (20.69%) — “mildly ill,” 435 patients (4.70%) — “moderately ill,” 78 patients (0.84%) — “markedly ill,” and 25 patients (0.27%) — “severely ill” (Table 4, Figure 1).

The distribution of patients according to severity categories in the groups with FD, IBS, and the combination of IBS and FD after therapy with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H is presented in Table 5.
In 159 (6.61%) patients with FD, there was no change in the severity of symptoms; in 1 patient (0.04%), there was a worsening of the state of health. The degree of severity of symptoms remained unchanged against the background of therapy with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H in 365 patients (6.18%) with IBS; in 1 patient (0.02%), a transition to a more “severe” group was observed. Symptom intensity did not change in 36 patients (3.83%) with a combination of IBS and FD; there were no patients who switched to a more “severe” category.

In 2,127 (88.48%) patients with FD, there was a change in the number of points in domains 1 and 2, which characterize pain and a burning sensation in the upper middle part of the abdomen. The score of domains 1 and 2, on average, decreased by 4.47. In 2,115 patients with FD (87.97%), the number of domains 3 and 4, which characterize the syndrome of early satiety, also decreased. The average decrease in points in the group was 3.5 (Table 6, Figure 2).

In 5,017 (84.9%) patients with IBS, there was a decrease in the number of points in domain 5, which characterizes abdominal pain that decreases after a bowel movement. The average decrease in the score in the group was 2.41. In the IBS group, also in the majority of patients (87.31%), there was a decrease in the number of points in domain 6, indicating a decrease in complaints of bloating. The average decrease in the score in domain 6 was 2.07. After 12 weeks of treatment with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H, 5,123 (86.70%) patients reported a decrease in complaints about the consistency and frequency of the stool. There was an average decrease of 3.12 points in domain 7 (Table 6, Figure 2).

In patients with a combination of IBS and FD, a decrease in the mean score in each of the 7 domains was found. A decrease in pain and burning sensation was noted in 774 (82.25%) patients with a combination of IBS and FD: in these patients, the scores of domains 1 and 2 decreased by an average of 3.35. A total decrease in the number of points in domain 3 and 4 (characterizing the syndrome of early satiety) was found in 783 (83.21%) patients. For this category of patients, on average, the score decreased by 3.06. 725 (77.05%) patients noted a decrease in the severity of pain after bowel movement. The average score in domain 5 decreased by 1.92 points. After 12 weeks of treatment with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H, 772 (82.04%) patients had a
decrease in the number of points in domain 6, indicating a decrease in complaints of bloating. In this
group, the average reduction in points was 1.84 points. For 830 (88.20%) patients, there was a
decrease in scores in domain 7, which characterizes a change in the consistency and frequency of
stools. The average decrease in the score was 3.17 (Table 6, Figure 2).

Safety evaluation
A total of 94 adverse events (AEs) were recorded (Table 7) in 80 patients (0.65%); less than 1 case
per 100 patients. Most adverse events (55 cases, 58.51% in the structure of all AEs) were
associated with dysfunction of the digestive organs. Nausea was recorded most frequently, 22 cases
of AE, given AE are “infrequent” (0.15%—i.e., less than 1 case per 100 people), according to doctors,
due to the nature of the course of functional gastrointestinal diseases.
Less commonly recorded adverse events concern the nervous system: 17 cases, 18.09% in the
structure of all identified AEs, are “infrequent” (0.11%).
There were recorded 10 AEs associated with skin diseases and subcutaneous fat, 10.63% in the
structure of adverse events, which is “rare” (0.06%, less than 1 case per 1,000 people).
Also recorded were general disorders (4 AEs, 4.25% in the structure of AEs), nutritional and metabolic
disorders (2 adverse events, 2.12% in the structure of all AEs), mental disorders and behavioral
disorders (3 adverse events, 3.19% in the structure of all AEs)—all classified as “rare”.
2 AEs associated with the musculoskeletal system and connective tissue (2.12% in the structure of all
AEs) and 1 AE associated with the circulatory system (1.06% in the structure of all AEs) were
recorded.
During the study period, no major AEs were identified. Cases of drug withdrawal of the combination of
RAF of Abs to S 100, Abs to TNF-α and Abs to H were not registered.
Discussion
In Russia, the observational program has been completed with the participation of 14,362 patients,
dedicated to the study of the efficacy and safety of the use of the combination of RAF of Abs to S 100,
Abs to TNF-α and Abs to H in patients with FD, IBS, and their combination.
The distribution of patients with the FD GiT by gender in the COMFORT program corresponded to the
According to the literature, the majority of patients with FD GIT have abdominal symptoms of mild to moderate severity.\textsuperscript{28} This tendency was also observed in the present study: the majority of patients at the stage of inclusion described the severity of symptoms as “moderately ill”.

The obtained results demonstrated that the combination of RAF of Abs to S 100, Abs to TNF-\(\alpha\) and Abs to H has a pronounced therapeutic effect, reducing the intensity of symptoms of functional diseases by more than half in 80.6\% of patients, which is consistent with previously obtained data in a multicenter, double-blind, placebo-controlled, randomized clinical trial of the efficacy and safety of using the combination of RAF of Abs to S 100, Abs to TNF-\(\alpha\) and Abs to H for treating patients with IBS.\textsuperscript{23}

According to Chen et al., the presence of a combination of FD GIT worsens their prognosis.\textsuperscript{29} Long-term, prospective observation of patients with a combination of FD and IBS showed that only 12\% of patients are able to achieve stable remission.\textsuperscript{30} Therapy with the combination of RAF of Abs to S 100, Abs to TNF-\(\alpha\) and Abs to H led to a greater increase in the number of patients in the “healthy” and “borderline ill” categories. The proportion of patients classified as “healthy” was 22.33\% (537) of patients with FD; 20.93\% (1237) of patients with IBS, and 16.57\% (156) of patients with a combination of IBS and FD. A cohort of patients with “borderline ill” consists of 1,339 patients (55.69\%) with FD, 3,044 patients (51.51\%) with IBS, and 488 (51.85\%) patients with a combination of IBS and FD (Table 5).

Thus, the proportion of patients with no clinical manifestations of FD GIT consists of 77.99\% with FD, 72.41\% with IBS, and 68.42\% with a combination of IBS and FD.

A systematic review of 22 studies evaluating the effectiveness of 12 antispasmodics in relieving symptoms of IBS in 1,778 patients revealed that 39\% of patients have persistent symptoms after therapy.\textsuperscript{31}

The observational program COMFORT showed a positive effect of the combination of RAF of Abs to S 100, Abs to TNF-\(\alpha\) and Abs to H in the majority of patients with a combination of IBS and FD: in 83\% of
cases, there was a decrease in the total score of the questionnaire “7*7” by 50% or more. These results confirm the previously obtained data that treatment with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H has a corrective effect on the manifestation of visceral sensitivity and nociceptive dysfunction.  

Used as a tool for assessing the severity of symptoms of FD, the questionnaire “7*7” is convenient for the doctor and does not take much time from the patient.  

According to the experience of practicing physicians, a detailed interview of a patient with functional diseases of the GIT cannot take less than 45–60 minutes. The questionnaire "7*7" used in this observational program is able to significantly minimize the time spent by a doctor when there is insufficient time allotted for the examination of the patient. 

Similar foreign scales are often difficult to understand, take a long time to fill out the questionnaire, and are cluttered with terminology. 

The questionnaire "7*7" meets the requirements of the European Medical Agency, which recommends separately monitored stool frequency, bowel movement consistency, the severity of abdominal pain, and abdominal distention. 

In the COMFORT program, patients with IBS were not subdivided into subtypes of IBS. The observational nature of the program did not suggest the presence of a comparison group. However, the value of this study is the maximum proximity to actual clinical practice and the possibility of obtaining additional data on the effectiveness of the drug in various FD GIT, including when they are combined.

Conclusions

The results of the COMFORT observational program demonstrated the effectiveness of the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H in treating patients with FD, IBS, and the combination of IBS and FD. In the absence of clear recommendations on overlap syndrome pharmacotherapy, an important conclusion of the study was the evidence of effective treatment of such patients.
The combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H demonstrated good tolerability and the absence of a negative effect on the patient’s condition, which is important for long-term therapy of functional diseases of the GIT.

Disclosure
Prof. Glazunov and Dr Putilovskiy authored this publication as employee of LLC NPF “MATERIA MEDICA HOLDING”. Prof. Epstein is the founder of LLC NPF “MATERIA MEDICA HOLDING”. Kolofort is a preparation manufactured and marketed by LLC NPF “MATERIA MEDICA HOLDING”. The authors report no other conflict of interest in this work.

Declarations

Ethics approval and consent to participate
The study was approved by the local clinical research ethics committees (the independent multidisciplinary Committee on ethical review of clinical research. Extract from the Protocol № 19 from 01.12.2017). All study participants provided informed written consent prior to study enrollment.

Consent for publication
Not applicable

Availability of data and materials
The conducted postmarketing surveillance study included data of 14362 outpatient patients’ records. Due to the vast data it is technically problematic. We are ready to provide the data at the request of the reviewer after the evaluation of this article. In such case we would kindly ask to provide us a non-disclosure agreement.

Competing interests
The authors declare that they have no competing interests.

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Author’s contributions
VTI, EAP contributed to the study concept and design. ABG, MAP, OIE contributed to the data
acquisition. EAP, VTI contributed to the data analysis and interpretation. EAP, VTI contributed to the drafting of the manuscript. All authors have read and approved the final draft of this manuscript.

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Abbreviations
Abs—antibodies
AEs—adverse events
FD—functional dyspepsia
FD GIT—functional disorders of the gastrointestinal tract
GIT—gastrointestinal tract
IBS—irritable bowel syndrome
IL—interleukins
LLC NPF “MATERIA MEDICA HOLDING”—Limited Liability Company Research and Production Company
Materia Medica Holding
RAF—released-active form
RAF of Abs to S–100—RAF of antibodies to S 100 protein
RAF of Abs to TNF-α—RAF of antibodies to tumor necrosis factor-α
RAF of Abs to H—RAF of Abs to histamine
TNF-α tumor necrosis factor-α

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Tables

Table 1 The distribution of patients according to severity categories according to the questionnaire “7*7” before treatment with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H.

| Severity category | Before treatment, n (%) |
|-------------------|-------------------------|
| Healthy           | 0                       |
| Borderline ill    | 383 (4.13%)             |
| Mildly ill        | 2822 (30.60%)           |
| Moderately ill    | 3236 (34.96%)           |
| Markedly ill      | 1708 (18.45%)           |
| Severely ill      | 1105 (11.94%)           |

Table 2. The categorization of severity among patients with FD, IBS, and a combination of IBS and FD before treatment with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H.
Table 3. The absolute number of patients with FD, IBS, and a combination of IBS and FD, in which there was a decrease in the number of points according to the questionnaire “7*7” by 50% or more after 12 weeks of therapy with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H.

| Group                        | Severity category       | Before therapy n (%) | After 12 weeks n (%) |
|------------------------------|-------------------------|----------------------|----------------------|
| FD                           | Healthy                 | 0 (0.0)              | 1934 (80.45%)        |
|                              | Borderline ill          | 161 (6.69%)          |                      |
|                              | Mildly ill              | 778 (32.36%)         |                      |
|                              | Moderately ill          | 740 (30.78%)         |                      |
|                              | Markedly ill            | 431 (17.92%)         |                      |
| IBS                          | Healthy                 | 0 (0.0)              | 4669 (79.02%)        |
|                              | Borderline ill          | 214 (3.62%)          |                      |
|                              | Mildly ill              | 1911 (32.34%)        |                      |
|                              | Moderately ill          | 2113 (35.75%)        |                      |
|                              | Markedly ill            | 1036 (17.53%)        |                      |
| Combination of IBS and FD    | Healthy                 | 0 (0.0)              | 781 (83%)            |
|                              | Borderline ill          | 8 (0.85%)            |                      |
|                              | Mildly ill              | 133 (14.13%)         |                      |
|                              | Moderately ill          | 383 (40.70%)         |                      |
|                              | Markedly ill            | 241 (25.61%)         |                      |

Table 4. The distribution of patients according to severity categories according to the questionnaire “7*7” before and after 12 weeks of therapy with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H.

| Severity category       | Before treatment, n (%) | After 12 weeks of therapy, n (%) |
|-------------------------|-------------------------|----------------------------------|
| Healthy                 | 0                       | 1930 (20.85%)                   |
| Borderline ill          | 383 (4.13%)             | 4871 (52.63%)                   |
| Mildly ill              | 2822 (30.60%)           | 1915 (20.69%)                   |
| Moderately ill          | 3236 (34.96%)           | 435 (4.70%)                     |
| Markedly ill            | 1708 (18.45%)           | 78 (0.84%)                      |
| Severely ill            | 1105 (11.94%)           | 25 (0.27%)                      |

Table 5. The categorization of severity among patients with FD, IBS, and a combination of IBS and FD before and after therapy with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H.
### Table 6. The number of points characterizing the severity of symptoms and their dynamics in domains 1–7 in patients with FD, IBS, and a combination of IBS and FD

| Domain | Symptom | FD Severity dynamics | IBS Severity dynamics | Combination of IBS and FD |
|--------|---------|----------------------|-----------------------|--------------------------|
| 1+2    | Before treatment, n (%) | After treatment, n (%) | Before treatment, n (%) | After treatment, n (%) |
| 1+2    | Intensity of abdominal pain | 6.16 | 1.69 | 4.47 | – | – | – | 4.73 | 1.38 |
| 3+4    | Early satiety | 4.67 | 1.52 | 1.92 | – | – | – | 10.08 | 3.14 |
| 5      | Intensity of abdominal pain after bowel movement | – | – | – | 3.37 | 0.96 | 2.41 | 2.76 | 0.84 |
| 6      | Bloating | – | – | – | 3.11 | 1.04 | 2.07 | 2.77 | 0.93 |
| 7      | The consistency and the frequency of stool | – | – | – | 4.78 | 1.66 | 3.12 | 4.55 | 1.37 |
### Table 7. Recorded Adverse Events

| Disease                                      | Number of AE | % from all patients | % in str |
|----------------------------------------------|--------------|---------------------|---------|
| **Total AE**                                 | 94           | 0.65                | 100.0000 |
| **N of patients who had at least 1 AE**      | 80           | 0.55                |         |
| **Skin and subcutaneous tissue disorders**   |              |                     |         |
| Erythema                                     | 1            | 0.007               |         |
| Pruritus                                     | 6            | 0.04                |         |
| Rash                                         | 1            | 0.007               |         |
| Urticaria                                    | 2            | 0.01                |         |
| **N of AE in this group**                    | 10           | 0.06                |         |
| **N of patients who had at least 1 AE in this group** | 8           | 0.05                |         |
| Myalgia                                      | 2            | 0.0139              |         |
| **N of AE in this group**                    | 2            | 0.0139              |         |
| **N of patients who had at least 1 AE in this group** | 2           | 0.0139              |         |
| Dizziness                                    | 3            | 0.02                |         |
| Dysgeusia                                    | 2            | 0.01                |         |
| Head discomfort                              | 1            | 0.007               |         |
| Headache                                     | 11           | 0.07                |         |
| **N of AE in this group**                    | 17           | 0.11                |         |
| **N of patients who had at least 1 AE in this group** | 15           | 0.10                |         |
| Abdominal distension                         | 2            | 0.01                |         |
| Abdominal pain                               | 14           | 0.09                |         |
| Abdominal pain upper                         | 1            | 0.007               |         |
| Anal pruritus                                | 1            | 0.007               |         |
| Constipation                                 | 4            | 0.02                |         |
| Diarrhoea                                    | 2            | 0.01                |         |
| Dyschezia                                    | 1            | 0.007               |         |
| Dyspepsia                                    | 1            | 0.007               |         |
| Epigastric discomfort                        | 3            | 0.0209              |         |
| Flatulence                                   | 1            | 0.007               |         |
| Nausea                                       | 22           | 0.15                |         |
| Tongue discomfort                            | 3            | 0.02                |         |
| **N of AE in this group**                    | 55           | 0.38                |         |
| **N of patients who had at least 1 AE in this group** | 51           | 0.35                |         |
| Cardiac disorders       | Palpitations |     |      |
|------------------------|--------------|-----|------|
|                        | N of AE in this group | 1   | 0.007|
|                        | N of patients who had at least 1 AE in this group | 1   | 0.007|
| Asthenia               | 2            | 0.01|
| Drug ineffective       | 1            | 0.007|
| Feeling jittery        | 1            | 0.007|
|                        | N of AE in this group | 4   | 0.02 |
|                        | N of patients who had at least 1 AE in this group | 3   | 0.02 |
| Agitation              | 2            | 0.01|
| Sleep disorder         | 1            | 0.007|
|                        | N of AE in this group | 3   | 0.02 |
|                        | N of patients who had at least 1 AE in this group | 2   | 0.01 |
| Decreased appetite     | 1            | 0.007|
| Increased appetite     | 1            | 0.007|
|                        | N of AE in this group | 2   | 0.01 |
|                        | N of patients who had at least 1 AE in this group | 2   | 0.01 |

Figures
The proportion of patients with FD, IBS, and a combination of IBS and FD, categorized according to severity according to the questionnaire “7*7”, before and after 12 weeks of treatment with the combination of RAF of Abs to S 100, Abs to TNF-α and Abs to H

The change in the number of points characterizing the severity of symptoms