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ORIGINAL RESEARCH ARTICLE

A Prospective Real-World Study of *Bacillus clausii* Evaluating Use, Treatment Habits and Patient Satisfaction in Italian Community Pharmacies: The PEGASO Study

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Abstract

Background Ailments such as diarrhoea and antibiotic-associated gut symptoms are generally self-managed using probiotics. Real-world data on reasons behind self-medication with over-the-counter (OTC) products and patient-reported outcomes can be investigated strategically by the pharmacists.

Objective This study evaluates the use of *Bacillus clausii* (Enterogermina®) at the Italian community pharmacies among self-medicating patients, their treatment habits and perceived benefits.

Design This is a multicentre, prospective, non-interventional study which included two visits [at screening (T0) and end of the study (T1) when symptoms had subsided, ≤ 30 days from T0]. Patients who were already inclined to buy *B. clausii* were enrolled and instructed to complete a questionnaire at T0 and T1. The primary objective was to evaluate the reasons for taking *B. clausii*. Secondary objectives assessed treatment duration, perceived effectiveness, quality of life (QoL), treatment satisfaction and safety outcomes.

Results Overall, 268 patients were enrolled; 99.6% of them were evaluated at T0 and 97.4% at T1, and safety was evaluated in 97.8% who had ≥ 1 dose of *B. clausii*. At T0, mean age was 50.7 years and majority were females (62.2%). In the interview, main reason stated for using *B. clausii* at T0 was diarrhoea (56.93%), followed by other gastrointestinal symptoms. Treatment duration was shorter in those with diarrhoea or abdominal pain versus those with constipation or abdominal tension. More than 90% perceived their symptoms to have improved or improved very much. Overall QoL improved in all the aspects measured. Treatment satisfaction was reported by nearly 90% of patients as satisfied, very satisfied or extremely satisfied. No adverse events were reported.

Conclusion This is the first pharmacy-based study in Italy that evaluated the real-world usage of an OTC probiotic containing *B. clausii* among self-medicating adults. Diarrhoea was the most common reason for use, with high-level of perceived effectiveness and patient satisfaction with *B. clausii*.

1 Introduction

Human gastrointestinal (GI) tract hosts diverse microbial communities. The gut microbiota preserves intestinal homeostasis, prevents pathogenic invasion and maintains barrier functions which has been highlighted by many studies [1, 2]. Microbiota imbalance leads to dysbiosis or dysmicrobism making the GI tract vulnerable to local disease states and intestinal and extraintestinal systemic inflammations [2]. In recent years, use of probiotics has gained immense interest across the globe. The International Scientific Association for Probiotics and Prebiotics has redefined probiotics as "*live microorganisms that, when administered in adequate amounts, confer a health benefit on the host*" [3].

Bacillus clausii four-strain combination [Enterogermina® (EG), Sanofi] is a globally-marketed probiotic containing non-pathogenic, Gram-positive, acid-resistant bacterium with gut-colonizing properties despite the presence of antibiotics [4–6]. EG is indicated for the treatment and prevention of intestinal dysmicrobism, subsequent endogenous avitaminosis and restoration of intestinal microbial flora altered due to antibiotics or chemotherapy [7].

Findings from previous prospective clinical trials have demonstrated the safety and effectiveness of *B. clausii* in the treatment of acute diarrhoea and in reducing the incidences of nausea, diarrhoea and epigastric pain among patients taking antibiotic regimen [5, 8–10]. A large prospective,

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Key Points

Self-management of common gastrointestinal symptoms using over-the-counter (OTC) probiotics is common, but further data are lacking. Therefore, patient-reported data from Italian community pharmacies during self-management of dysbiosis-related symptoms were evaluated for the reasons leading to OTC use of *Bacillus clausii* probiotics.

Although used as a non-prescription medication, the majority of the patients adhered to the instructions on the package leaflet, reinforcing the affordable role of self-medication for the treatment of mild and short term symptoms.

This is the first pharmacy-level real-world study in Italy for probiotics that has given confidence to generate high quality evidence on non-prescription based self-medication.

observational study in children (age 1 month to 6 years) reported that diarrhoea resolved with *B. clausii* use, including a significant reduction in diarrhoeal episodes, number of stools and incidence of GI symptoms (nausea, vomiting, abdominal pain and bloating) [11]. Various studies over the decades have consistently proven the safety and tolerability of *B. clausii* as acceptable and consistent [5, 9–11]. The four commercially available strains of *B. clausii* (O/C, N/R, SIN and T) are resistant to various antibiotics at varying degrees. The presence of these antibiotic-resistance genes in the genome of the microorganism enables concomitant use of EG with other antibiotics to reduce GI side effects [12].

A huge percentage of over-the-counter (OTC) products, including EG, are purchased and used without a physician's prescription [13, 14]. However, literature pertaining to patients requesting OTC probiotic products in pharmacies for common GI symptoms is lacking.

A majority of the patients consider common GI disorders as minor diseases and prefer self-management with non-prescription medicines or seek pharmacists' advice without a specialists' intervention. Unlike the prescription driven clinical data, real-world usage of OTC drugs often by self-medication can be better assessed from pharmacy records. Community pharmacists being most accessible to the public, providing immediate and efficient guidance on the use of self-medication, are in a strategic position to interact with subjects unlikely to turn to other healthcare professionals while dealing with common GI symptoms [15]. Although EG has been commercialized since 1958, having obtained OTC status in Italy only in 1999, validated information concerning the reason behind self-medication, treatment outcomes and patient satisfaction is scarce. Furthermore, several formulations of EG have been introduced, and the different usage patterns and satisfaction with various formulations are yet to be described. Although it is quite common to collect real-world evidence on OTC drugs in community pharmacies in several countries, it is still unconventional in Italy. An editorial by Chaplin and Blenkinsopp emphasised the role of pharmacy-based clinical trials to observe the usage and collection of both efficacy and safety data of OTC drugs [16]. In Italy there is a wide network of community pharmacies that can be leveraged to understand the drivers, barriers and consumer preferences in managing digestive symptoms using probiotics such as *B. clausii*.

In this real-world study, patient-reported data during self-management of dysbiosis-related symptoms were collected from community pharmacies in Italy. Treatment duration, dosage, perceived effectiveness, quality of life (QoL), treatment satisfaction and safety with the use of EG were also assessed.

2 Methods

2.1 Study Design

PEGASO, a multicentre, prospective, non-interventional study was conducted at 18 Italian pharmacies that participated in the study from October 2019 to April 2021, representing different geographical zones of Italy: North, Center, South, Islands and included two visits within a 30-days time period. At screening and enrolment on T0 (day 0), subjects purchasing EG (*B. clausii)* products for self-use at the participating pharmacies without any pharmacist's advice or a physician's prescription were asked to participate in the study. Following written informed consent, the pharmacist interviewed the subjects to collect data on demographic features, lifestyle (eating habits and exercise), medical history related to common GI symptoms, frequency of symptoms, concomitant medications [particularly drugs affecting intestinal microflora such as proton pump inhibitors (PPIs) and antibiotics] and usage of probiotics in the last 12 months and related outcome. Using a sponsor-provided tablet, the subjects completed a self-administered web-based questionnaire enquiring about the choice of formulation, the reasons for purchasing EG (symptoms included were possibly related to gut dysbiosis: diarrhoea, bloating, meteorism, constipation, abdominal pain and abdominal tension) and intensity of these symptoms and their impact on QoL. Validation of questionnaire included two forward translations by qualified independent translators and reconciliation (Italian to English), one back-translation (English to

Italian) by a quality controller, developer/client review, cognitive interviews on nine healthy subjects from the general population (age ≥ 18 years), proofreading and screenshot review.

Treatment was initiated within 24 h per the information leaflet. Subjects could purchase additional packages of EG later if needed to complete the treatment without exceeding a treatment period of 30 days.

At the end of the study (T1), subjects were asked to visit the pharmacy when symptoms had subsided, but no later than 30 days after day 0 (after the resolution of acute illness and at the end of therapy), and were again asked to complete the validated web-based questionnaire using a tablet. The questionnaire surveyed about the treatment duration, dosage, current symptomatology after treatment for the symptoms indicated at T0, time to onset of symptom improvement, impact of symptoms on QoL, perceived effectiveness of the treatment and treatment satisfaction. Data on any adverse events and concomitant use of PPIs and antibiotics occurring since T0 were also collected.

2.2 Key Eligibility Criteria

Subjects aged ≥ 18 years who were already inclined to buy EG before going to the pharmacy (influenced by neither the participation in this study nor the pharmacist's advice), buying EG for the ongoing symptoms (diarrhoea, abdominal pain, bloating, meteorism, constipation and abdominal tension) of GI discomfort and willing to start using EG within 24 h of purchase were eligible to participate in the study. Subjects who were unable to understand and complete the questionnaire, unable to return to the pharmacy at T1 for logistic reasons, purchased EG against the physician's prescription, participating in any interventional trial or were already using EG at the time of purchase were not eligible to participate in the study.

2.3 Study Objectives

The primary objective was to evaluate the reasons (symptoms) for using EG in a real-world setting. The secondary objectives were to evaluate treatment duration, choice of formulations, dosing regimen, intensity of symptoms, perceived effectiveness and onset of action, QoL, treatment satisfaction and safety associated with EG use.

2.4 Treatment

Subjects could choose any of the EG formulations available and the dosage was per the information leaflet:

- Vials containing 5 mL of oral suspension (*B. clausii*) taken orally as is or diluted in water or other liquids prior to intake
    - 2 billion colony forming units (CFU): 2–3 vials per day at regular intervals
    - 4 billion CFU: one vial per day
- Capsules (*B. clausii*—2 billion CFU): 2–3 capsules per day swallowed with water or other drinks
- Sachets containing powder for (*B. clausii*—6 billion CFU)
    - Oral suspension: one sachet/day dissolved in a glass of water
    - Oral powder: one sachet/day dispersed directly into the mouth without water

Participating pharmacies were chosen from a group of pharmacies selected in cooperation with the Italian Society of Clinical Pharmacy, which included pharmacists with a Master's degree in Clinical Pharmacy and were stratified by geographic region to respect geographic representativeness.

2.5 Statistical Analysis

Due to lack of published data on the incidence of common GI symptoms in subjects requesting an OTC treatment for probiotics, the estimated sample size for this study was based on market research performed by GfK Eurisko, 2015 and the registry by the Italian Society of General Medicine, 2010 [17].

The enrolled population composed of subjects who did not fail the screening criteria and provided informed consent to participate in the study. Evaluable population at T0 included the enrolled subjects fulfilling inclusion/exclusion criteria and performing the T0 evaluation. Evaluable population at T1 was a subset of the evaluable population at T0 including subjects with the T1 evaluation. Safety population was all subjects taking at least one dose of EG.

Descriptive statistics was performed on parameters such as usage (reason, treatment duration and posology), perceived effectiveness, symptomatology and QoL. Continuous data were summarized using descriptive statistics (number, mean and standard) and categorical data were summarized using frequency tables (frequencies and percentages).

3 Results

A total of 268 subjects were enrolled of which 267 (99.63%) were evaluated at T0 (evaluable population at T0), 262 (97.76%) took at least one dose of EG (safety population)

and 261 (97.39%) were evaluated at T1 (evaluable population at T1). At T0, the mean ± SD age of the subjects was 50.7 ± 17.72 years; a majority of them were women ($n = 166$, 62.17%): two of them were pregnant. The mean ± SD weight was 67.68 ± 13.20 kg, generating a mean ± SD body mass index (BMI) of 24.28 ± 3.91 kg/m^2: 150 (56.55%) subjects had normal BMI, 72 (26.97%) were overweight, 30 (11.24%) obese and 14 (5.24%) underweight (Table 1).

3.1 Primary Outcome

The main reason for using EG stated during the interview at T0 was diarrhoea (56.93%), followed by abdominal pain (13.11%), bloating (12.36%), constipation (9.36%), abdominal tension (4.49%) and meteorism [3.75%; Fig. 1, Supplementary Table 1, see electronic supplementary material (ESM)]. The same reasons were indicated in the questionnaires with varying percentages: diarrhoea—59.55%, abdominal pain—29.59%, bloating—22.47%, meteorism—10.11%, constipation—10.11% and abdominal tension—9.36%. Diarrhoea was the most common reason for using EG at T0 in subjects stratified by food intolerance (with and without), physical activity and previous use of probiotics (with and without).

3.2 Secondary Outcomes

3.2.1 Treatment Duration

The mean ± SD treatment duration was 7.1 ± 3.95 days and was below 1 week in 168 subjects (64.37%), between 8–14 days in 73 subjects (27.97%) and between 15–21 days in 20 subjects (7.66%). The mean ± SD treatment duration was shorter in subjects with diarrhoea (6.1 ± 3.34 days) or abdominal pain (7.5 ± 4.66 days), and longer in those with constipation (9.6 ± 4.55 days) or abdominal tension (8.5 ± 4.76 days).

3.2.2 Choice of Formulations

At T0, most subjects selected the 4 billion CFU vial formulation (50.57%) or the 2 billion CFU vials (39.08%; Supplementary Figure 1, see ESM). Sixty (22.99%) subjects purchased a new package of EG at T1, most of them were for constipation ($n = 17$; 70.83%) or abdominal tension ($n = 5$; 45.45%). The 2 and 4 billion CFU vials were the most popular at T1 and equally requested ($n = 25$ each, 41.67%).

The distribution of formulations purchased varied according to symptoms. At T0, the 4 billion CFU vials were preferred by subjects with diarrhoea (56.08%) and abdominal pain (57.14%). Subjects with bloating and meteorism opted similarly for the 2 and 4 billion CFU vials (bloating 30.30% and 39.39%, respectively; meteorism 40.00% for both formulations), while those with constipation or abdominal tension more often purchased the lower dosage in vials (62.50% and 54.55%, respectively).

At T1, the 4 billion CFU vials were preferred by subjects with diarrhoea (73.91%), while the 2 billion CFU vials were preferred by those with abdominal pain (50.00%), constipation (58.82%) or abdominal tension (80.00%). Subjects with bloating usually selected the 6 billion CFU sachets (57.14%) and 2 billion CFU vials (42.86%).

At T1, EG was repurchased by 70.83% of subjects for constipation, followed by 45.45% for abdominal tension, 21.21% for bloating, 20.00% for meteorism, 17.14% for abdominal pain and 15.54% for diarrhoea.

3.2.3 Dosing Regimen

Most subjects took EG once a day (63.22%) followed by twice a day (33.33%). Only seven subjects with diarrhoea ($n = 7/148$; 4.73% and one with meteorism ($n = 1/10$; 10.00%) took EG thrice a day.

3.2.4 Intensity of Symptoms

At T0, most subjects with diarrhoea had moderate (37.74%) or strong symptoms (36.48%) that completely resolved (81.17%) or were mild (12.34%) at T1. Similar outcomes were reported for other GI symptoms (Fig. 2, Supplementary Figure 2, see ESM). Subjects with constipation reported mostly strong (44.44%) or moderate (25.93%) symptoms, which at T1 became mild (42.31%) or were absent (38.46%).

There was a substantial improvement in the intensity of all symptoms. Most of the subjects (72.00%) who had very strong diarrhoea at T0 no longer had symptoms at T1. Similar findings were noted for subjects with strong (74.14%), moderate (91.38%) or mild (76.92%) diarrhoea (Supplementary Table 2, see ESM). Among the subjects with very strong abdominal pain at T0, 75.00% no longer had symptoms at T1, and same was the case with subjects having strong (74.07%), moderate (64.71%) or mild (88.89%) symptoms. Most of the subjects (61.54%) with very strong bloating at T0 had mild symptoms at T1, while 50.00% of those with strong symptoms, 47.06% of those with moderate symptoms and 66.67% of those with mild symptoms no longer had symptoms at T1. Most subjects with moderate (63.64%) or strong meteorism (44.44%) at T0 had mild symptoms at T1. The intensity of symptoms in subjects with constipation also tended to reduce and those with very strong symptoms at T0 had mild (50.00%), absent (33.33%) or moderate (16.67%) symptoms at T1, while those with strong symptoms at T0 had moderate (33.33%), mild (33.33%) or absent (33.33%) symptoms at T1. Similarly, in subjects

Table 1. Demographic characteristics, evaluable population at T0 and T1

	T0 ($N=267$)	T1 ($N=261$)
Demographic characteristics		
Age, years (mean ± SD)	50.7 ± 17.72	50.8 (17.82)
Sex, *n* (%)		
Female	166 (62.17)	164 (62.84)
Pregnancy status[a], *n* (%)		
Yes	2 (1.20)	2 (1.22)
Body mass index, kg/m^2 (mean ± SD)	24.28 ± 3.91	24.27 (3.90)
Body mass index (class), *n* (%)		
Underweight	14 (5.24)	14 (5.36)
Normal	151 (56.55)	148 (56.70)
Overweight	72 (26.97)	70 (26.82)
Obesity	30 (11.24)	29 (11.11)
Lifestyle and eating habits, *n* (%)		
Subjects who follow a specific diet	9 (3.37)	9 (3.45)
Specific diet		
Vegetarian diet	2 (0.75)	2 (0.77)
Vegan diet	2 (0.75)	2 (0.77)
Specific diet for intolerances	4 (1.50)	4 (1.53)
Other	1 (0.37)	1 (0.38)
Subjects allergic/intolerant to any food/food component	32 (11.99)	30 (11.49)
Intolerance		
Lactose intolerance	19 (7.12)	18 (6.90)
Gluten intolerance	4 (1.50)	4 (1.53)
Other	9 (3.37)	8 (3.07)
Frequency of sports/physical activity[b]		
Everyday	20 (7.49)	20 (7.66)
Every 2 days	23 (8.61)	23 (8.81)
Two times per week	47 (17.60)	45 (17.24)
Once a week	21 (7.87)	21 (8.05)
One time every 15 days	2 (0.75)	2 (0.77)
One time per month	2 (0.75)	2 (0.77)
Occasionally	73 (27.34)	69 (26.44)
Never	79 (29.59)	79 (30.27)
Frequency of sports/physical activity (class)		
More than one time per week	90 (33.71)	88 (33.72)
Once a week	21 (7.87)	21 (8.05)
Occasionally	77 (28.84)	73 (27.97)
Never	79 (29.59)	79 (30.27)
Medical history related to common GI symptoms, *n* (%)		
Subjects with at least one common GI symptom in the last 12 months[c]	267 (100.00)	261 (100.00)
Symptom/frequency		
Diarrhoea	157 (58.80)	153 (58.62)
Abdominal pain	62 (23.22)	61 (23.37)
Bloating	43 (16.10)	43 (16.48)
Meteorism	17 (6.37)	17(6.51)
Constipation	30 (11.24)	29 (11.11)
Abdominal tension	17 (6.37)	16 (6.13)
Irritable bowel syndrome	3 (1.12)	3 (1.15)
Previous usage of probiotics, *n* (%)		
Subjects who took probiotics in the last 12 months[d]	82 (30.71)	81 (31.03)

Table 1. (continued)

	T0 ($N=267$)	T1 ($N=261$)
Therapeutic main group (2nd level of ATC)/preferred term		
Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents	60 (22.47)	60 (22.99)
Bacillus clausii	34 (12.73)	34 (13.03)
Lactobacillus jensenii	1 (0.37)	1 (0.38)
Dietary supplement	5 (1.87)	5 (1.92)
Unknown	20 (7.49)	19 (7.28)

Percentages were computed on subjects belonging to the evaluable population at T0 and T1

Terms are coded using the WHO dictionary, version B3 Q1 2019

'Unknown' refers to probiotics for which subjects did not remember the brand name

Evaluable population at T0 consisted of all enrolled subjects fulfilling inclusion/exclusion criteria and performing the T0 evaluation. Evaluable population at T1 consisted of a subset of the evaluable population at T0 including subjects with the T1 evaluation

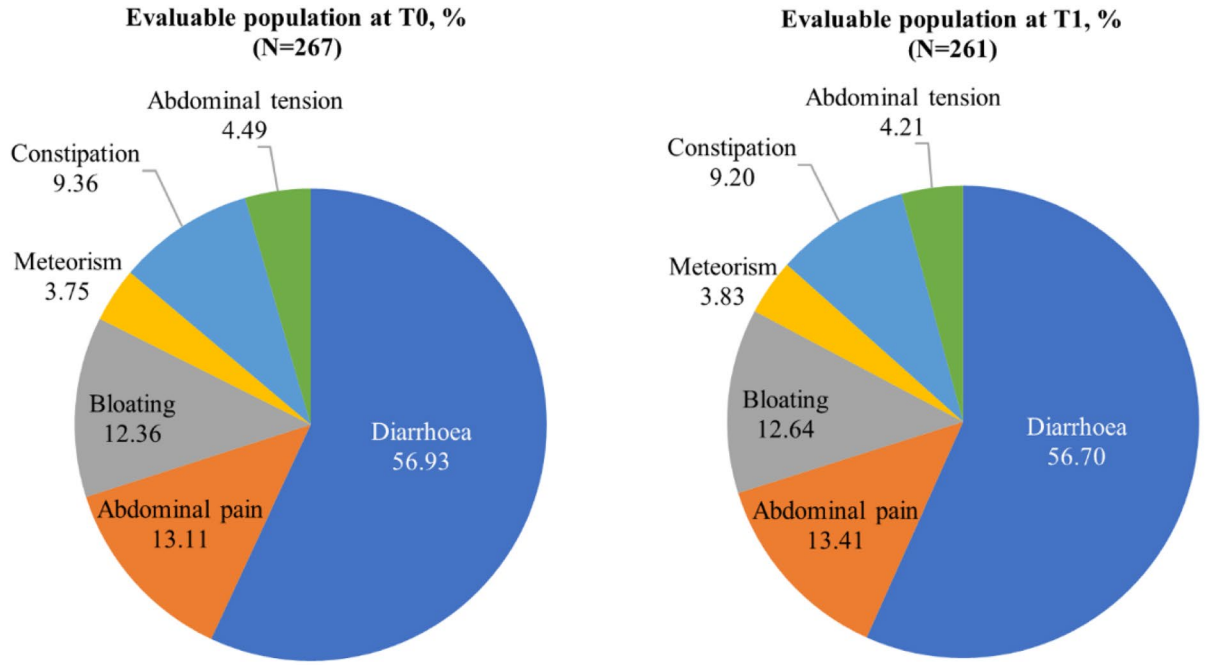
ATC anatomical therapeutic class, *GI* gastrointestinal, *Q1* 1st quartile, *Q3* 3rd quartile, *SD* standard deviation, *T0* start of the study, *T1* end of the study, *WHO* World Health Organization

[a]Percentages were computed on female subjects belonging to the evaluable population at T0 and T1.

[b]Sports/physical activity in class is defined as follows: "more than 1 time per week"—every day, every 2 days, two times per week; "once a week"—once a week; "Occasionally"—one time every 15 days, one time per month and occasionally; and "never"—never

[c]Subjects who reported more than one symptom in the last 12 months

[d]Subjects who reported more than one probiotics were counted only once for each probiotic/row



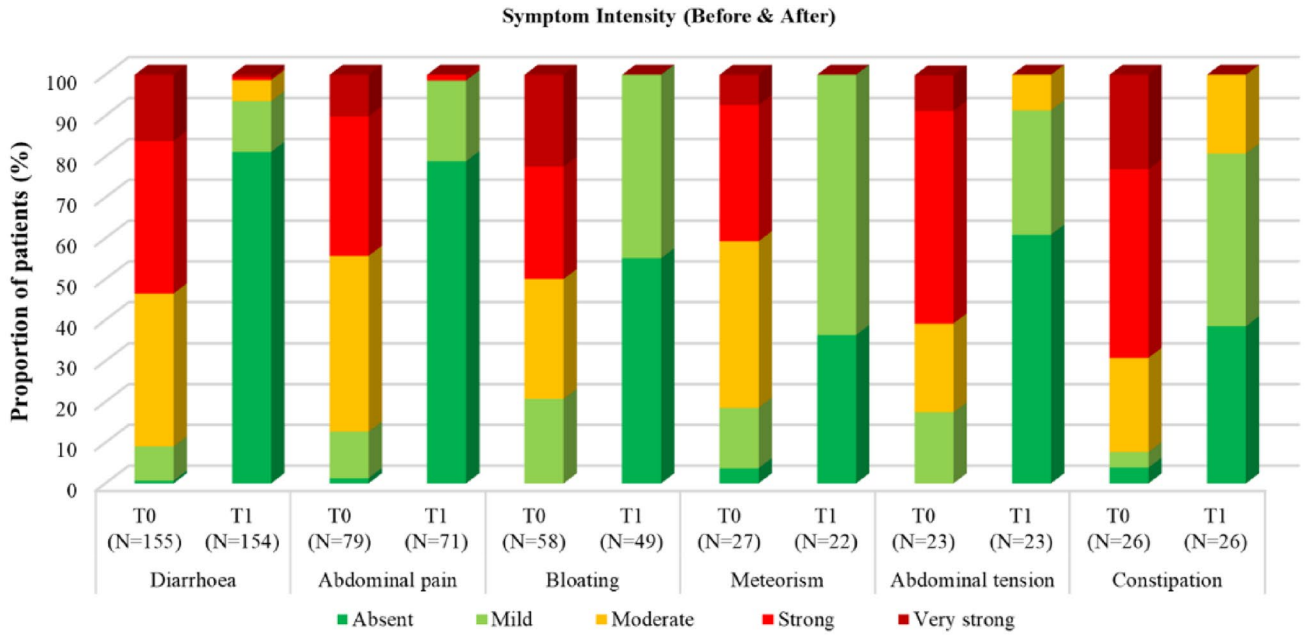
EG, Enterogermina®; T0, start of the study; T1, end of the study

Fig. 1 Summary of main reasons for using *B. clausii* (EG)

with abdominal tension, symptoms were absent at T1 in 50.00%, 66.67%, 40.00% and 75.00% of subjects with very strong, strong, moderate, or mild symptoms, respectively, at T0.

3.2.5 Perceived Effectiveness

At T1, subjects stated that their symptoms had improved very much (26.82%), improved (68.97%), remained



T0 start of the study, T1 end of the study. Percentages were computed on subjects belonging to the evaluable population at T0 and T1. Evaluable population at T0 consisted of all enrolled subjects who fulfilled inclusion/exclusion criteria and performing the T0 evaluation. Evaluable population at T1 consisted of a subset of the evaluable population at T0 including subjects with the T1 evaluation

Fig. 2. Summary of intensity of symptoms; evaluable population at T1

unchanged (2.68%), worsened or worsened very much (0.77% each). Two subjects who perceived their symptoms as having worsened had diarrhoea, whereas one subject each with diarrhoea and meteorism indicated that their symptoms worsened very much. Most subjects with diarrhoea or abdominal pain stated that their symptoms had improved (diarrhoea 60.14%, abdominal pain 65.71%) or improved very much (diarrhoea 35.14%, abdominal pain 31.43%). All subjects with constipation or abdominal tension stated that their symptoms improved (constipation 91.67%, abdominal tension 90.91%) or improved very much (constipation 8.33% and abdominal tension 9.09%), while most of those with bloating perceived their symptoms as having improved (87.88%).

3.2.6 Perceived Onset of Action

Mean ± SD time to onset of symptom improvement was 3.04 ± 1.94 days, with most subjects (69.36%) improving within 3 days. Mean ± SD time to onset of symptom improvement ranged from 2.61 ± 1.53 days for subjects with diarrhoea to 4.17 ± 2.22 days for those with constipation. Among the six subjects who perceived no effectiveness, three had diarrhoea (2.03%), one had abdominal pain (2.86%), and two had bloating (6.06%). Perceived onset of action was achieved within 1 day in 18.01%, within 2 days in 29.89%, within 3 days in 21.46%, within 4 days in 12.64%, within 5 days in 4.98%, after a week in 8.43% and after 10 days in 1.92% of subjects. There was no effectiveness in 2.3% of subjects.

3.2.7 Quality of Life

At T0, symptoms influenced mood 'a lot' (35.21%) or 'moderately' (29.59%), while at T1 mood was mostly 'not at all' (66.67%) or 'lightly' (22.61%) influenced. Daily activities were affected 'a lot' (30.34%), 'moderately' (28.09%) or 'lightly' (23.22%) at T0, but 'not at all' (70.88%) or 'lightly' (20.31%) at T1 (Fig. 3, Supplementary Table 3, see ESM).

Jobs were influenced 'a lot' (22.85%), 'lightly' (20.22%) or 'moderately' (17.23%) at T0, while at T1 most subjects reported that symptoms no longer affected their jobs (59.39%). Quality of sleep was affected 'not at all' (33.71%) or 'lightly' (22.85%) at T0, and 'not at all' in most subjects (83.14%) at T1. Symptoms influenced eating habits 'a lot' (29.96%) or 'moderately' (26.97%) at T0, and 'not at all' for 53.26% of subjects at T1. Results were similar for the evaluable population at T1.

3.2.8 Treatment Satisfaction

Overall, subjects were very satisfied (47.51%), satisfied (41.00%) or extremely satisfied (8.05%) with EG. Only few were dissatisfied, one subject with diarrhoea was extremely dissatisfied, two with bloating and one with diarrhoea were very dissatisfied and two subjects with bloating and one with abdominal pain were dissatisfied.

Subjects were stated to be satisfied (44.06%) or very satisfied (41.76%) with the ability of EG to treat symptoms, with its ease of use (very satisfied 47.51%; satisfied 29.12%) and with time to perceived efficacy (satisfied 52.87%; very satisfied 33.33%; Fig. 4).

3.3 Safety

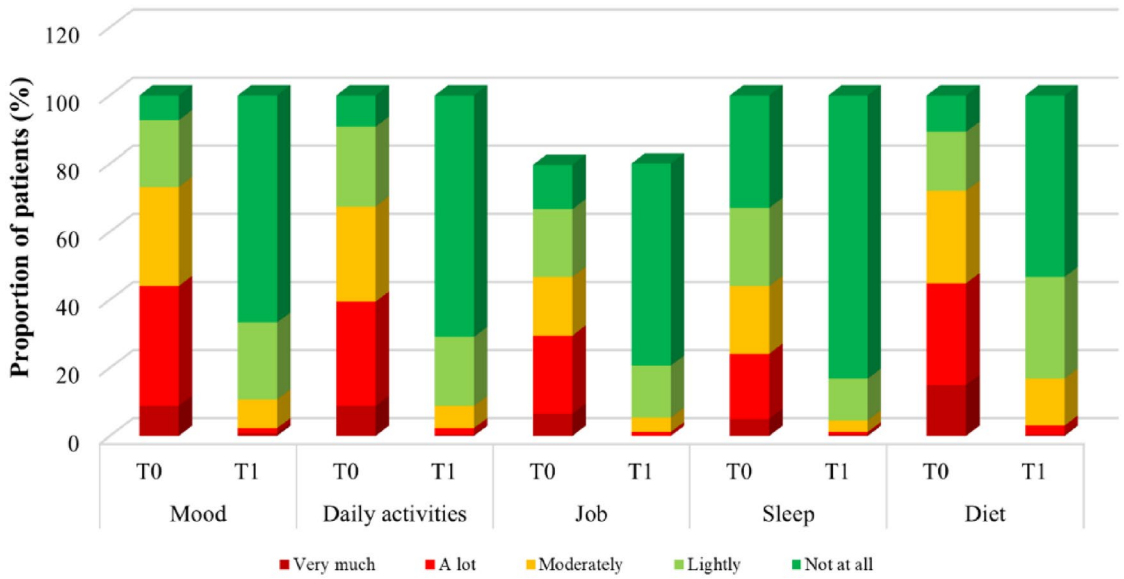
No adverse events were reported. One asymptomatic, intentional overdose was reported in a 30-year-old female subject. Five subjects (1.91%) reported the use of at least one concomitant antibiotic and 12 (4.58%) the use of at least one concomitant PPI.

4 Discussion

Probiotics usage for various GI disorders has widened in the recent years. However, patient data on self-medication practices with probiotics are very limited. This is the first pharmacy-level real-world clinical study approved in Italy for an OTC product that investigated the drug usage and reasons for probiotics use in subjects with GI disorders.

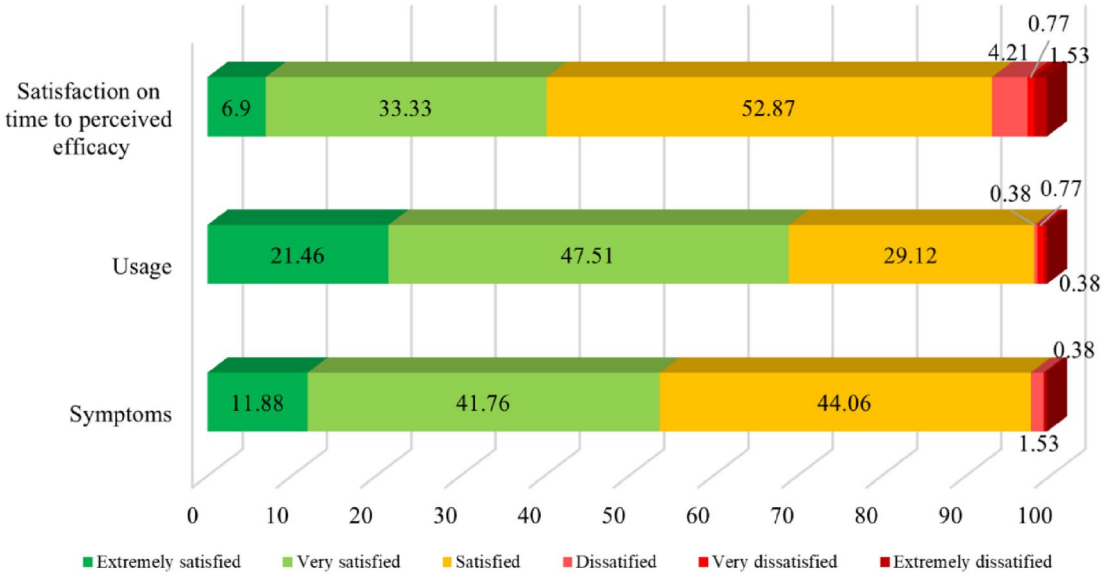
Reportedly, diarrhoea was the most common symptom (57%) prompting the use of EG despite no expert advice or physician's prescription and regardless of food intolerance, physical activity or the previous use of probiotics. Given the study design with a specific setting and inclusion criteria, drawing comparisons with other studies is challenging. Nevertheless, an explorative survey in Hungary found that the most common reasons for using probiotics were to alleviate the side effects of previous antibiotic treatment (87.6%) and the symptoms of diarrhoea (24.5%) [18]. Similarly, another study by Chin-Lee et al., reported the most common reasons for probiotic use as maintenance of gut health and immune status [19]. In contrary, a cross-sectional study found bloating as the main GI symptom associated with the use of probiotics, and patients preferred probiotics equally for both diarrhoea and constipation [20]. These variations may be associated with recommendation of experts (physicians and pharmacists), self-assessment with the aid of information leaflet and previous personal experience and the influence of commercial factors (brand, price and promotion and availability) [21].

Existing literature reported a decrease in diarrhoea with *B. clausii* use [5, 22]. Similarly, our study demonstrated a shorter average treatment duration and time to onset of symptom improvement in subjects with diarrhoea compared to those with constipation. In addition, repurchase of EG at T1 (70.83%) and twice daily intake (58.33%) were reported only in those with constipation.



T0 start of the study, T1 end of the study. Percentages were computed on subjects belonging to the evaluable population at T1

Fig. 3. Summary of quality of life; evaluable population at T1



T0 start of the study, T1, end of the study. Percentages were computed on subjects belonging to the evaluable population at T1. Evaluable population at T1 consisted of a subset of the evaluable population at T0 including subjects with the T1 evaluation

Fig. 4. Summary of treatment satisfaction

The 2 and 4 billion CFU vial formulations were preferred by majority of the subjects with diarrhoea and constipation or abdominal tension, respectively. The 6 billion CFU sachets were the least preferred in those with diarrhoea (6% at T0) but were preferred in subjects with bloating (21% at T0 and 57% at T1). The 6 billion CFU formulation had only been recently introduced to the Italian market, a few years prior to this study, which could explain the lower usage preference considering the lack of familiarity among the general population and possible consumer preference of ready-to-take liquid formulation (vials) over powder format which usually requires preparation prior to intake.

At T1, there were large improvements in symptom intensity with most subjects experiencing no (diarrhoea, abdominal pain, bloating and abdominal tension) or only mild (meteorism and constipation) symptoms. A prospective, randomized study by Nista et al., reported similar responses in symptom improvement [8]. Symptoms were perceived to be improved or improved very much in more than nine of ten subjects. Improvement in QoL with no further impact of the symptoms on mood, daily activities, work, quality of sleep and eating habits was achieved.

Finally, treatment satisfaction was good regardless of the reason for using EG. Approximately nine out of ten subjects were satisfied, very satisfied or extremely satisfied.

Unlike the prescription medicines, patients and consumers are the primary decision-makers for OTC medication use. Thus, data from prospective real-world studies focusing on the appropriate self-selection and safety of non-prescription medicine usage when used without medical supervision are extremely essential. Electronic health records (EHRs), claims databases and patient registries remain the conventional sources of real-world data, which are generally unavailable for non-prescription medicines. Moreover, detailed records on consumers, conditions, products and health outcomes are not always maintained. Consequently, data relating to non-prescription medicine exposure or information on outcomes associated with their use is missing from the patients' EHRs [21].

Strengths This study was able to observe the choice and use of an OTC probiotic medication directly in a real-world setting (community pharmacy), without any healthcare professional influence. The subjects included were already inclined to buy EG before visiting the pharmacy, manifesting the actual use of this OTC product in the general population. *Limitations* Similar to any observational research, there were risks of bias including site representativity which were minimised by selecting well-distributed sites within the country, patient representativity and attrition bias. However, loss to follow-up was limited in this study since 261 of the 267 subjects evaluable at T0 were also evaluable at T1. Another limitation was the reduced sample size than the number planned originally, leading to reduced precision of estimates of the population parameters. This may be attributed to the limited patients accessing pharmacies due to lockdown restrictions brought about by COVID-19.

Addition of a control group and stratification of first-time versus long-time probiotic users will enable us to further evaluate the difference of using probiotic in terms of outcome. Conducting similar studies in other geographies may unlock new knowledge on how people from other culture utilise probiotics in health management.

5 Conclusions

In summary, EG (*B. clausii*) was used most commonly for diarrhoea treatment which was resolved mostly within 3 days and majorly with 4 billion CFU formulation. However, constipation required a longer treatment duration and mostly 2 billion CFU was preferred. About 90% of the patients perceived positive outcome in terms of symptom resolution and treatment satisfaction. Use of EG remained safe and tolerable with no adverse events reported in this study. Findings from this study showed a high level of patients adherence to package leaflet instructions although used as a non-prescription medication. This indicates that the manufacturer provided package instructions are adequate for consumers in choosing the appropriate treatment options.

Most likely, consumers are the decision-makers for OTC medication usage and generation of evidence on non-prescription medicines from such prospective real-world studies is required to ensure safe use and appropriate self-selection of these medications when used under no medical supervision. In addition, this study witnessed the ability of trained pharmacists in Italy to conduct clinical observational studies at pharmacy and collect the high quality data to improve the knowledge on the usage of OTC drugs, possibly aiming at improving their indications, safety profile and rationale usage.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-023-00402-1.

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Author Contributions All authors contributed to the conception and design of the study. CG, FR EK, PP, MCU initiated the project. MP contributed to data analysis or interpretation. The SGCP Group consists of all local investigators who are responsible for participant recruitment. All authors have reviewed and approved the final manuscript.

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Data Availability Statement Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

Declarations

Conflict of interest C.G, E.K, F.R declare no conflict of interest. P.P., M.C. and M.P. are currently employees of Sanofi and may hold shares and/or stock options in the company. SGCP: None declared.

Ethical approval This study was conducted according to the guidelines of the Declaration of Helsinki, and the protocol was approved by the Ethics Committees of the local health authorities [Azienda Sanitaria Locale (ASL)] overseeing the participating pharmacies. List of approvals with the relevant protocol numbers: Comitato Etico Regione Toscana Area Vasta Nord Ovest prot n 52552, Comitato Etico ATS Sardegna prot. no. 172/2019/CE, Comitato Etico ATS Sardegna prot. no. 189/2019/CE, Comitato Etico Lazio 2 prot. no. 0201651, Comitato Etico di Area Vasta Sud Est, prot. no. 159, Comitato Etico Lazio 2 prot. no. 0027005/2020, Comitato Etico di Bergamo prot no. 180/19, Comitato Etico Campania Nord registro CECN/1177, Comitato Etico Regionale della Liguria registro CER Liguria 232/2020 and Comitato Etico ATS Sardegna prot. no. 261/2020/CE.

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