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Alimentary Tract

Impact of oral butyrate on clinical and biochemical parameters in IBD: A randomized placebo-controlled study targeting gut microbiota

Sonia Facchin[a,b,1], Matteo Calgaro[c,1], Mattia Pandolfo[c], Andrea Buda[d], Brigida Barberio[a,b], Fabiana Zingone[a,b], Nicola Vitulo[c,*], Edoardo Vincenzo Savarino[a,b,**]

[a] Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy
[b] Gastroenterology Unit, Azienda Ospedale Università di Padova, Padova, Italy
[c] Department of Biotechnology, University of Verona, Verona, Italy
[d] Gastroenterology Unit, Department of Oncological Gastrointestinal Surgery, S. Maria del Prato Hospital, Feltre, Italy

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ABSTRACT

Background and Aims: We performed a randomized, double-blind, placebo-controlled, trial to investigate the changes in microbiome composition induced by Butyrate-Lsc-Microincapsulated (BLM) supplementation in IBD patients and its impact on disease activity.
Methods: 140 IBD patients (n=60 Crohn's disease, CD and n=80 Ulcerative Colitis, UC) were randomized to oral administration of BLM, plus conventional therapy. Stool samples were assessed by 16S sequencing and fecal calprotectin (fCal) analysis. For the microbiota analysis, the Firmicutes/Bacteroidota (F/B) ratio was used. Clinical disease activity was assessed by using the Harvey-Bradshaw-Index (HBI) for CD and partial-Mayo-Score for UC, Quality-of-life (QoL) by using Inflammatory-Bowel-Disease-Questionnaire-32 (IBDQ) and adherence-dietary-recommendation was evaluated before and after supplementation
Results: microbiota analysis revealed two principal enterotypes, defined by the F/B ratio, in both CD and UC patients. BLM exerted a more pronounced effect on Enterotype 1 (low F/B ratio), resulting in greater clinical and biochemical improvements and potentially identifying a target population. After supplementation, clinical disease activity ($p=0.013$) and fCal ($p=0.047$) improved significantly in CD, while fCal showed a marginal reduction in UC ($p=0.09$). QoL increased significantly in both CD ($p<0.001$) and UC ($p=0.003$).
Conclusions: Supplementation with BLM, by modulating the gut microbiota, significantly improved disease outcomes and QoL in patients with IBD.
ClinicalTrial.gov registration: NCT04879914
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1. Introduction

Butyrate is usually found in the lumen of the human colon at a concentration of 10–25 mmol, higher in the proximal colon where most dietary fiber fermentation occurs [1–5]. Butyrate production depends on the amount and type of dietary fibers consumed, the presence of butyrate-producing bacteria, and the cross-feeding interactions with the gut microbiome, creating a network of microbial fermentation [6,7]. Butyrate serves as the primary energy source for colonocytes, resulting in the utilization of 95% colonic butyrate [8], while SCFA deficiency has been associated with mucosal hypoplasia and inflammatory colitis. Indeed, SCFA and, in particular, butyrate play a crucial role in the intestinal immune system through several mechanisms that include inhibiting the growth of luminal pathogens, enhancing mucosal integrity, and decreasing oxygen availability in the gut lumen, which can inhibit gut pathogen growth [9,10]. To date, different studies have evaluated the effect of supplementation of SCFA (mainly with enema) in patients with Ulcerative Colitis (UC) and Crohn's Disease (CD), providing evidence of SCFA utility in clinical practice with, however, conflicting results in terms of clinical outcome [1].

Some authors attributed butyrate to a paradoxical effect, indicating a differential effect of butyrate according to cell differentiation [11]. It has been shown that butyrate may stimulate the

* Corresponding authors. Department of Biotechnology, University of Verona, Cà Vignal, 1, Strada Le Grazie 15, 37134, Verona, Italy.
** Department of Surgery, Oncology and Gastroenterology (DISCOG), University Hospital of Padua, Padua, Italy.
E-mail addresses: nicola.vitulo@univir.it (N. Vitulo), edoardo.savarino@unipd.it (E.V. Savarino).
[1] These authors contributed equally to the article.

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growth of healthy, differentiated colonocytes' growth while inhibiting undifferentiated cells' growth. This concept is extremely interesting and could explain how the results obtained from various studies on chronic intestinal inflammation have given conflicting results [12]. Moreover, any investigations were carried out using only the enema, resulting in a partial effect in patients with more proximal inflammation. Other studies reported the use of mixtures of SCFA, and others were carried out with limited duration, volume, and concentration of butyrate or SCFA irrigation, and, finally, many investigations included a small number of patients [13,14].

On the other hand, in our first pilot study [14], we demonstrated that an oral formulation of exogenous microencapsulated sodium butyrate, contained in a lipophilic microcapsule, was able to provide extensive capacity for intestinal diffusion and to facilitate slow release of the active ingredient to avoid its overload (*i.e.,* potentially harmful to stem cells in cases of chronic intestinal inflammation), was able to modulate the gut bacteria, stimulating the growth of butyrogenic and SCFA genera in IBD [11]. However, it was not clear which IBD patients could particularly benefit from butyrate supplementation and the effect of this treatment on different clinical outcomes.

For this reason, we performed a monocentric, prospective, and randomized, double-blind, placebo-controlled trial aimed at investigating the changes in microbiome composition induced by BLM supplementation in IBD patients and determining the impact of the butyrate on the variation of clinical and biochemical disease activity.

2. Materials and methods

This study is a monocentric, prospective, double-blind, randomized, placebo-controlled trial conducted at Azienda Ospedale Università of Padua (Italy) between September 2020 and June 2022. I and my co-authors had access to the study data and have reviewed and approved the final manuscript.

Subjects, intervention compound, outcomes, clinical measures, ethical statement, library construction, detailed bioinformatic analyses, sample size calculation, and statistical analysis are described in the *Supplementary Materials*.

Breefly:

2.1. Subjects

Consecutive symptomatic patients (aged 18-80) with a histologically confirmed diagnosis of IBD within the last 6 months, undergoing follow-up colonoscopy, and agreeing to participate, were randomized. Exclusion criteria included prior extensive proctocolectomy (no patients with a J-pouch were enrolled), extraintestinal manifestations, recent antibiotic/probiotic use (excluded treatments for dental procedures within the first month of therapy and patients on stable probiotic treatment), colon extensive surgery, stoma presence, and recent COVID-19 infection. No therapy changes occurred during the 90-day study, except those associated with short antibiotic courses within the first month of therapy. Randomization was 1:1 for BLM (sodium butyrate) or placebo (PBO), with blind allocation and analysis.

2.2. Intervention

BLM (1,200 mg/day of microencapsulated sodium butyrate, corresponding to 600 mg of active compound) or placebo (starch capsules) was administered for 90 days, during main meals. The dose was consistent with previous studies and tailored for enhanced colonic absorption.

2.3. Outcomes

Primary Outcome: Changes in microbiome composition (diversity, enterotypes, abundance, F/B ratio).

Secondary Outcomes: Impact on disease activity (calprotectin, pMayo score, HBI, IBDQ, WCRF questionnaire).

2.4. Clinical measures

Disease activity was assessed via endoscopy, clinical scores (pMayo for UC, HBI for CD), and fecal calprotectin (ELISA). Fecal calprotectin data were logarithmically transformed to normalize distribution. Disease localization was scored according to the Montreal classification.

2.5. Additional assessments

Demographic and clinical data, IBDQ-32 questionnaire, and WCRF eating habits questionnaire were completed at baseline and after 3 months. Stool samples were collected at baseline and post-supplementation to analyze microbiota and calprotectin levels. Participants maintained their current therapy and diet.

2.6. Ethical statement

The study was approved by the Regional Ethical Committee for Clinical Trials (n. 4049/AO/17, updated 2019). Before participation, written informed consent was obtained from all eligible participants. The study was also registered at Clinicatrial.gov (NCT04879914).

2.7. 16S rRNA gene sequencing and bioinformatics analysis

Stool samples were stabilized in Xpedition Buffer (Zymo Research) and stored at −20°C. The V3–V4 regions of the 16S rRNA gene were amplified using primers Pro341F/Pro805R with Illumina overhang adapters, following the Illumina 16S Metagenomic Sequencing protocol. Libraries were normalized, pooled, and sequenced on an Illumina MiSeq platform (2 × 300 bp).

Raw FASTQ files were processed with DADA2, applying error correction and generating amplicon sequence variants (ASVs). Sequencing runs (n = 5) were processed independently and merged with mergeSequenceTables. Primers were trimmed using Cutadapt, and reads were filtered (truncLen = 280/220). Taxonomic assignment was performed with the naïve Bayesian classifier against the SILVA v138.1 database. ASVs unassigned at the phylum level were removed. Multiple sequence alignment was obtained with DECIPHER, and phylogenetic trees were built using phangorn.

3. Results

3.1. Patients' enrollment and randomization

One hundred sixty consecutive patients were assessed for eligibility. Two patients did not meet the inclusion criteria, five declined to participate (due to travel complications related to the COVID-19 pandemic or the inability to modify the therapy in the following 90 days), and one did not provide a sufficient stool sample. A total of 152 patients were randomized to receive either microencapsulated butyrate (BLM) or placebo (PBO), as shown in the flow diagram in **Figure S1**. Overall, in accordance with the minimum required sample size of 132, a total of 140 patients completed the study and were included in the analyses, as summarized in Table 1.

Table 1
Overall distribution of demographic variables, clinical variables, drug usage, and smoking habits across supplementation groups.

Randomisation table				
	Overall, N = 140[1]	**BLM**, N = 70[1]	**PBO**, N = 70[1]	**p-value**[2]
Demographic variables				
Sex				0.6
F	57 (41%)	27 (39%)	30 (43%)	
M	83 (59%)	43 (61%)	40 (57%)	
Age	50 (39, 61)	50 (36, 58)	50 (40, 64)	0.4
BMI	24.0 (22.2, 26.7)	24.0 (22.2, 25.2)	24.0 (22.0, 27.7)	0.6
Clinical variables				
Pathology				0.5
Crohn's Disease	60 (43%)	32 (46%)	28 (40%)	
Ulcerative Colitis	80 (57%)	38 (54%)	42 (60%)	
CD Behaviour (Crohn's Disease)				0.6
B1	39 (65%)	19 (59%)	20 (71%)	
B2	11 (18%)	7 (22%)	4 (14%)	
B3	10 (17%)	6 (19%)	4 (14%)	
CD Location (Crohn's Disease)				0.5
L1	10 (17%)	7 (22%)	3 (11%)	
L2	13 (22%)	6 (19%)	7 (25%)	
L3	37 (62%)	19 (59%)	18 (64%)	
SES Score (Crohn's Disease)				0.8
0-2 = Remission	26 (43%)	13 (41%)	13 (46%)	
3-6 = Mild	19 (32%)	11 (34%)	8 (29%)	
7-15 = Moderate	11 (18%)	5 (16%)	6 (21%)	
>15 = Severe	4 (6.7%)	3 (9.4%)	1 (3.6%)	
HBI Score (Crohn's Disease)				0.7
Mild	15 (25%)	9 (28%)	6 (21%)	
Mod-Severe	1 (1.7%)	1 (3.1%)	0 (0%)	
Remission	44 (73%)	22 (69%)	22 (79%)	
Montreal (Ulcerative Colitis)				>0.9
E1	16 (20%)	8 (21%)	8 (19%)	
E2	31 (39%)	15 (39%)	16 (38%)	
E3	33 (41%)	15 (39%)	18 (43%)	
MAYO Score (Ulcerative Colitis)				0.6
0 = Normal	42 (52%)	20 (53%)	22 (52%)	
1 = Mild	17 (21%)	6 (16%)	11 (26%)	
2 = Moderate	16 (20%)	9 (24%)	7 (17%)	
3 = Severe	5 (6.2%)	3 (7.9%)	2 (4.8%)	
partial MAYO Score (Ulcerative Colitis)				0.3
Remission	61 (76%)	29 (76%)	32 (76%)	
Mild	12 (15%)	4 (11%)	8 (19%)	
Mod-Severe	7 (8.8%)	5 (13%)	2 (4.8%)	
Endoscopic Disease Activity				0.7
Active	72 (51%)	37 (53%)	35 (50%)	
Inactive	68 (49%)	33 (47%)	35 (50%)	
Clinical Disease Activity				0.6
Active	35 (25%)	19 (27%)	16 (23%)	
Inactive	105 (75%)	51 (73%)	54 (77%)	
Previous surgery				
Crohn's Disease	25 (42%)	13 (41%)	12 (43%)	0.9
Ulcerative Colitis[3]	3 (3.8%)	3 (7.9%)	0 (0%)	0.10
Smoking habits and drug usage				
Smoker	16 (11%)	10 (14%)	6 (8.6%)	0.3
Probiotics	20 (14%)	8 (11%)	12 (17%)	0.3
Antibiotics	2 (1.4%)	1 (1.4%)	1 (1.4%)	>0.9
Biologicals	53 (38%)	28 (41%)	25 (36%)	0.6
Unknown	1	1	0	
Steroids	12 (8.6%)	4 (5.7%)	8 (11%)	0.2
PPI	17 (12%)	9 (13%)	8 (11%)	0.8
Unknown	1	1	0	
5-aminosalicylates	33 (24%)	15 (21%)	18 (26%)	0.6
Immunosuppressants	10 (7.2%)	4 (5.8%)	6 (8.6%)	0.5
Unknown	1	1	0	

[1] n (%); Median (IQR)
[2] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test
[3] subtotal colectomy and/or had rectal fistulas

3.2. Primary endpoint

3.2.1. Ecological analysis: Alpha and beta diversity at the baseline

Alpha diversity analysis was performed to assess the within-sample diversity. At baseline (T0), Shannon indexes were similar between treatment groups for both CD and UC patients ($p > 0.05$; Fig. 1**A-B**). Following the 90-day intervention (T1), a modest increase in Shannon diversity was observed in CD patients receiving placebo, whereas no consistent changes were detected in the other groups.

A beta diversity analysis was conducted to assess dissimilarities between samples. At baseline (T0), the treatment groups were

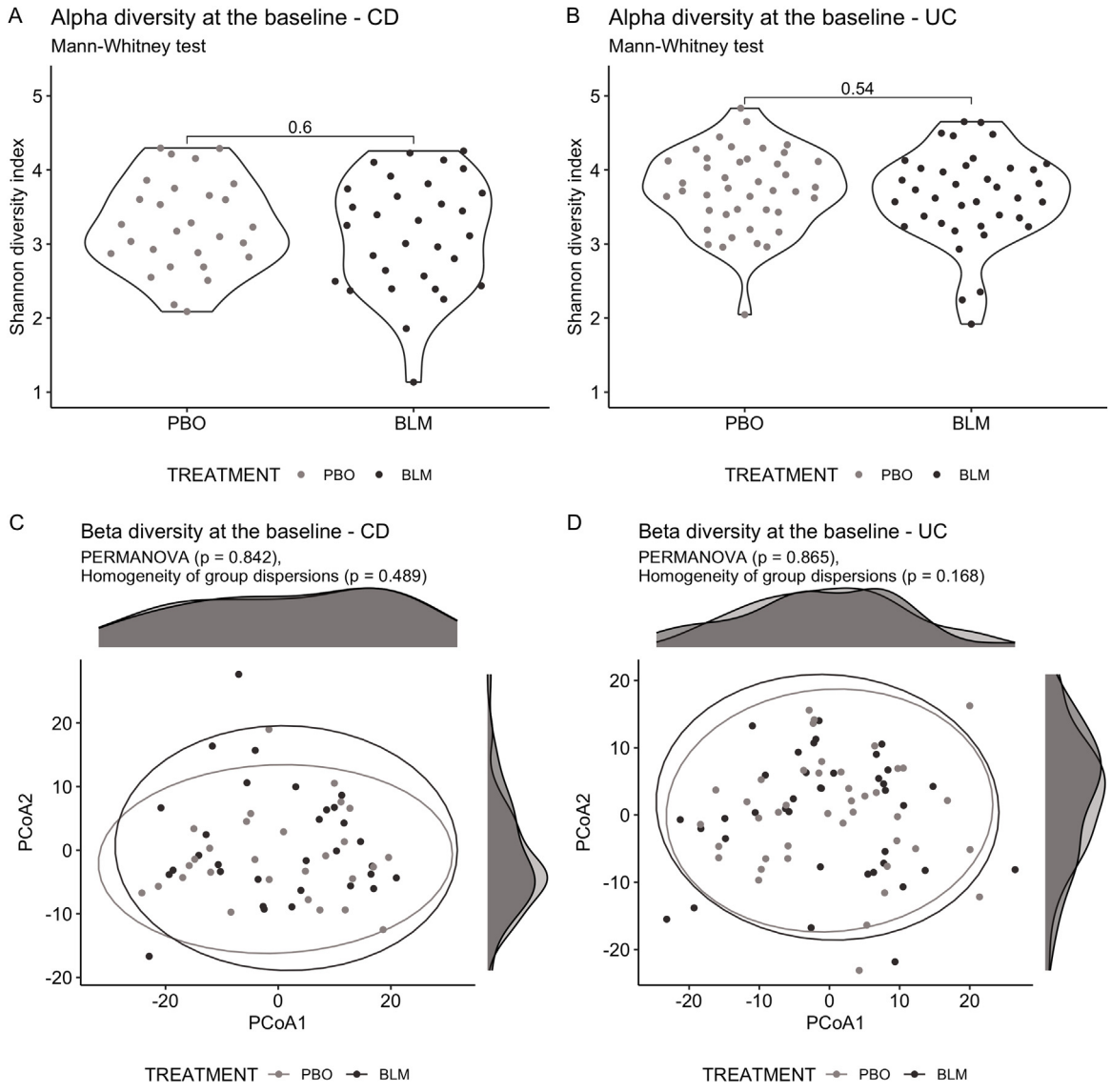


Fig. 1. A. CD patients' alpha diversities (Shannon diversity indexes) at the baseline. BLM (light gray) and PBO (dark gray) groups have comparable alpha diversities. **B.** UC patients' alpha diversities (Shannon diversity indexes) at the baseline. BLM (light gray) and PBO (dark gray) groups have comparable alpha diversities. **C.** CD patients' beta diversities at the baseline (PCoA of Aitchison distances between samples). BLM (light grey) and PBO (dark gray) groups are comparable. **D.** UC patients' beta diversities at the baseline (PCoA of Aitchison distances between samples). BLM (light grey) and PBO (dark gray) groups are comparable.

found to be comparable in both CD ($p = 0.842$ for PERMANOVA, $p = 0.489$ for homogeneity of dispersions; Fig. 1**C**) and UC samples ($p = 0.865$ for PERMANOVA, $p = 0.168$ for homogeneity of dispersions; Fig. 1**D**). Furthermore, the impact of various metadata variables (e.g., sex, age, BMI, endoscopic disease activity, drugs) on the microbial composition of the samples at T0 was investigated using PERMANOVA analysis. Significant changes and dispersion differences were observed related to previous surgical events ($p < 0.001$, dispersions $p = 0.002$; **Figure S2A**) in CD subjects, while significant changes were observed for gender ($p = 0.038$; **Figure S2B**), 5-aminosalicylates usage ($p = 0.036$; **Figure S2C**), and endoscopic disease activity ($p = 0.017$; **Figure S2D**) in UC subjects. When comparing samples longitudinally (T0 vs T1), temporal changes in beta diversity were observed in CD patients, particularly in the BLM group, where the effect of time explained a greater proportion of the overall microbial variance compared to placebo (1.3% vs 0.8%). No relevant shifts were detected in UC patients. However, due to the high inter-individual variability and the clinical heterogeneity of the cohort, we adopted a stratification approach based on baseline microbial community structure (enterotypes), allowing a more nuanced evaluation of microbiome dynamics and treatment effects.

3.2.2. Enterotype analysis

To facilitate the identification of common characteristics among patients within CD and UC groups, enabling further studies on their response to therapy, patients with a similar microbial composition (enterotype) at baseline were grouped together using a Dirichlet-Multinomial Mixture model. As observed in preliminary analyses of data collected for a previous pilot study [14], two main enterotypes were found for both CD and UC patients. From a phylum-level perspective, they were characterized by significantly different (Wilcox test $p < 0.05$) F/B ratios. For both pathologies, the first enterotype group was characterized by patients with a lower F/B ratio (median [IQR], 0.31 [0.18, 0.45] in CD, 0.74 [0.47, 1.02] in UC). On the contrary, the second enterotype group was characterized by patients with a higher F/B ratio (0.85 [0.58, 1.32] in CD, 1.36 [1.08, 2.02] in UC); (Fig. 2**A-B**).

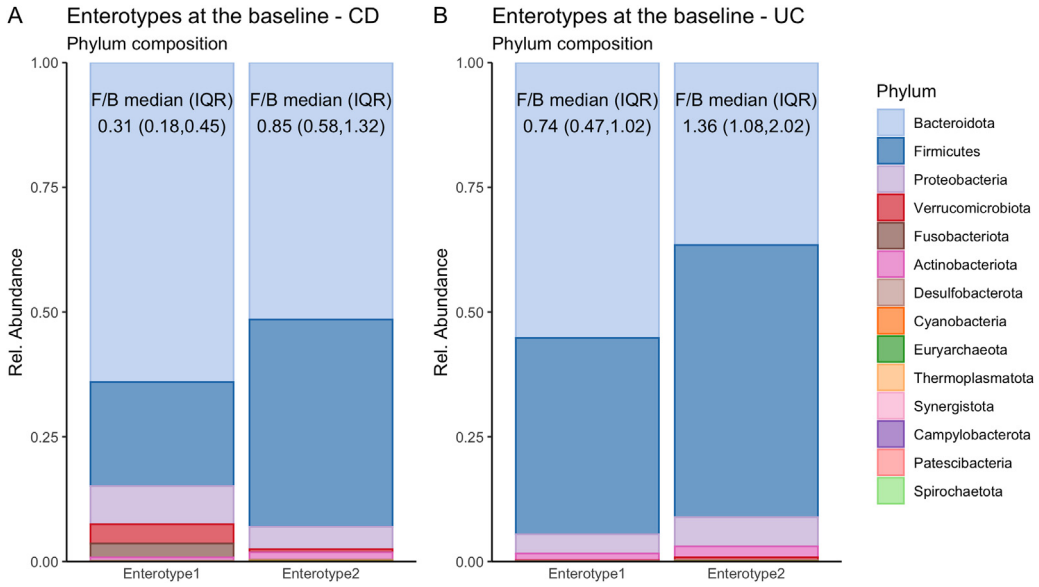


Fig. 2. A. Average phylum level relative abundances by enterotype group for CD patients at the baseline. For each enterotype group the median, the first, and the third quartiles are computed for the F/B ratio. **B.** Average phylum level relative abundances by enterotype group for UC patients at the baseline. For each enterotype group the median, the first, and the third quartiles are computed for the F/B ratio.

3.2.3. Association between enterotypes and covariates

From a microbiological perspective, patients within the same enterotype group exhibit comparable microbial compositions but distinct clinical and demographic characteristics. In UC patients, we observed significant age differences between the two enterotypes: the second enterotype had a median age of 62, while the first had a median age of 48 ($p < 0.001$; Table S1). In CD patients, enterotypes were significantly associated with previous surgeries: 62% of the first enterotype had surgeries compared to 24% of the second enterotype ($p < 0.004$; Table S1). The first enterotype also had slightly higher BMIs and a higher prevalence of clinically active disease.

We examined the associations between enterotypes and dietary and physical activity habits using the WCRF questionnaire (Table S2). No significant association was found between CD enterotypes and WCRF habits. However, in UC patients, the second enterotype showed a slight increase in neutral or detrimental habits, particularly regarding beer and wine consumption ($p = 0.077$) and refined flour products ($p = 0.06$).

3.2.4. Microbial variations associated with the supplementations

Although absolute shifts in the F/B ratio were observed in all patients, we did not find significant changes in the BLM group as compared to the placebo group (Table 2A). However, dividing the whole population according to disease type, BLM supplementation showed a more pronounced effect ($p = 0.02$; Table 2B) in CD patients, particularly when the first enterotype was present ($p = 0.01$; Table 2C).

Differential abundance analysis identified genera with significant abundance changes between time points. Baseline abundances were compared to those at the end of the supplementation for BLM and PBO groups, separately for CD and UC enterotypes. Beta diversity and PERMANOVA analysis showed significant changes for BLM-treated CD patients in Enterotype 1 ($p = 0.001$, dispersions $p = 0.05$; Figure S4A) and nearly significant in Enterotype 2 ($p = 0.071$; Figure S4B). Unexpectedly, significant changes were also observed for PBO-treated UC patients in the second enterotype ($p = 0.016$; Figure S5D).

In the BLM-treated CD group of Enterotype 1, significant reductions were observed in *Escherichia-Shigella, Klebsiella, Morganella* (Proteobacteria), *Bacteroides, Prevotella_9* (Bacteroidota), *Bilophila* (Desulfobacterota), and *Fusobacterium* (Fusobacteriota). Firmicutes genera showed mixed results: reductions in *Lachnoclostridium, Veillonella, [Ruminococcus] gnavus group, Anaeroglobus*, and Hydrogenoanaerobacterium family, but increases in *UCG-002*, Clostridia UCG-014 order, *Ruminococcus, Lachnospiraceae NK4A136 group, [Eubacterium] siraeum*, and *eligens* groups (Figure S6 and Table S3). No significant differences were found in BLM-treated CD patients of Enterotype 2 (Figure S5B), while *Terrisporobacter* (Firmicutes) increased in PBO-treated UC patients of Enterotype 2.

3.3. Secondary endpoints

3.3.1. Clinical variations associated with the supplementations

Analyzing the clinical data in the entire IBD cohort, we found no substantial variations associated with BLM or PBO supplementation. Hence, we investigated the impact of these treatments on CD and UC patients separately (Table 3). Quality of life as assessed by IBDQ significantly improved in the BLM-treated CD group ($p = 0.029$) and was found numerically greater in the BLM-treated UC group ($p = 0.086$). Specifically, in BLM-treated CD patients, the median score increased from 170 to 184 ($p < 0.001$), and in PBO-treated CD patients, from 188 to 197 ($p = 0.021$). For BLM-treated UC patients, the score raised from 185 to 195 ($p = 0.003$), while it remained stable in the PBO-treated UC patients ($p = 0.2$).

As to the fecal calprotectin levels (Table 4A), they markedly improved in BLM-treated CD patients as compared to placebo-treated CD patients ($p = 0.047$ vs. $p = 0.7$). A similar trend was observed in UC patients, though not statistically significant (BLM: $p = 0.09$ vs. PBO: $p = 0.14$). Clinical disease activity improved significantly in BLM-treated CD patients ($p = 0.013$), but not in UC patients, although a trend favoring BLM was noted (BLM: $p = 0.13$ vs. PBO: $p = 0.72$).

We then examined the impact of supplementations on UC and CD patients divided according to the two different enterotypes (Tables 4B-C). No major differences in calprotectin levels were detected, likely due to smaller sample sizes. However, a more pronounced effect of BLM supplementation was observed in CD patients presenting the Enterotype-1 ($p = 0.074$) compared to those presenting Enterotype-2 ($p = 0.2$), resulting in clinical improve-

Table 2
Mann-Whitney tests between F/B ratio absolute changes between T0 and T1. **A.** Comparison between BLM and PBO groups considering the entire cohort. **B.** Comparison between BLM and PBO groups separately by IBD pathologies. **C.** Comparison between BLM and PBO groups separately by IBD pathologies and enterotypes.

A. F/B ratio absolute change (whole cohort)

IBD		
BLM, N = 69[1]	PBO, N = 70[1]	p-value[2]
0.39 (0.21, 0.75)	0.34 (0.15, 0.75)	0.2

[1] Median (IQR) [2] Mann-Whitney test

B. F/B ratio absolute change by pathology

CD			**UC**		
BLM, N = 31[1]	**PBO**, N = 28[1]	**p-value**[2]	**BLM**, N = 38[1]	**PBO**, N = 42[1]	**p-value**[2]
0.42 (0.31, 0.71)	0.26 (0.11, 0.48)	0.020	0.38 (0.13, 0.78)	0.41 (0.23, 0.92)	0.7

[1] Median (IQR) [2] Mann-Whitney test

C. F/B ratio absolute change by pathology and enterotype

CD					
Enterotype 1			**Enterotype 2**		
BLM, N = 14[1]	**PBO**, N = 12[1]	**p-value**[2]	**BLM**, N = 17[1]	**PBO**, N = 16[1]	**p-value**[2]
0.53 (0.34, 0.69)	0.16 (0.06, 0.39)	0.010	0.38 (0.31, 0.71)	0.31 (0.17, 0.58)	0.2
UC					
Enterotype 1			**Enterotype 2**		
BLM, N = 22[1]	**PBO**, N = 26[1]	**p-value**[2]	**BLM**, N = 16[1]	**PBO**, N = 16[1]	**p-value**[2]
0.21 (0.08, 0.46)	0.33 (0.22, 0.67)	>0.9	0.68 (0.37, 1.56)	0.69 (0.35, 2.01)	0.4

[1] Median (IQR)
[2] Mann-Whitney test

Table 3
IBDQ average differences and their standard deviations (T1-T0) for each supplementation group (BLM and PBO). Mann-Whitney non-parametric unilateral tests have been used to determine BLM efficacy compared to PBO.

IBDQ average difference (T1-T0)					
CD, N = 60			**UC**, N = 80		
BLM, N = 31[1]	PBO, N = 28[1]	p-value[2]	BLM, N = 38[1]	PBO, N = 42[1]	p-value[2]
12.41 (23.06)	5.43 (11.15)	0.029	11.71 (21.91)	2.10 (15.61)	0.086

[1] Mean (SD);
[2] Mann-Whitney test

ment. Quality of life improved significantly in both CD and UC patients presenting the Enterotype-1 (CD: p = 0.001, UC: p = 0.019) and Enterotype-2 (CD: p = 0.026, UC: p = 0.045). BLM-treated CD-Enterotype-1 patients also showed a significant increase in the F/B ratio (p = 0.039; Table 4B).

Lastly, physical and dietary habits assessed using the WCRF questionnaire showed no significant differences, indicating similar behavioral patterns throughout the study (**Tables S5-S6**).

4. Discussion

Recent reviews [1,15] of clinical and animal studies confirm that butyrate, at appropriate concentrations, helps to maintain intestinal barrier function and regulate the immune response in the gut [16]. Thus, the concentration at which exogenous butyrate reaches the colon is crucial [17]. A small amount of butyrate would probably be irrelevant. In contrast, a high butyrate amount could suppress stem cell proliferation, as demonstrated in a zebrafish model [18], whose intestine physiologically does not contain crypts and lacks butyrate producers.

We conducted a double-blind, randomized, placebo-controlled trial to evaluate the clinical and microbiological effects of BLM in a large sample of IBD patients. We confirmed that BLM modifies the characteristics of microbiota in IBD patients, further overserving that BLM supplementation improves quality of life and clinical disease activity in both CD and UC patients. These findings suggest that BLM supplementation demonstrates potential to improve clinical activity, particularly in Crohn's disease patients with Enterotype 1 (CD-E1), who exhibit a lower F/B ratio and a more dysbiotic microbiota, indicating a phenotype more responsive to SCFA-based interventions.

Additionally, we confirmed the hypothesis [19] that, due to differences in UC and CD presentation [20], there might be a different response to SCFA administration between these two clinical phenotypes.

We evaluated IBD subjects' alpha and beta diversity before and after using BLM and PBO. The beta diversity analysis revealed associations between certain variables at the baseline (previous surgery, age, gender, drugs) and variations in the microbial composition of the samples (**Figure S2**). For instance, we observed that previous surgical interventions were found to have a marked impact on the microbial composition in CD patients, (**Figure S2A**). Likewise, previous studies have shown that bowel-altering surgeries can have a marked effect on the microbiome in the GI tract, creating an environment for IBD remission or flare [21,22]. Due to these observations, we stratified the patients' samples of both IBD pathologies according to their predominant enterotypes. This de-

Table 4
IBDQ questionnaire total score, Calprotectin, Clinical Disease Activity (Inactive when HBI or pMayo scores 0-2 [Remission], Active when HBI or pMAYO scores 3-4 [Mild] and 5-9 [Mod-Severe]), and F/B ratio comparisons between time points. **A.** Comparisons separately by BLM and PBO groups and IBD pathologies (CD and UC). **B.** Comparison separately by BLM and PBO groups and enterotypes in CD patients. **C.** Comparison separately by BLM and PBO groups and enterotypes in UC patients.

A. IBDQ and clinical variables comparisons by IBD pathology and supplementation group

	CD, N = 60					
	BLM, N = 32			**PBO**, N = 28		
	T0[1]	**T1**[1]	**p-value**[2]	**T0**[1]	**T1**[1]	**p-value**[2]
IBDQ	170 (148, 188)	184 (168, 207)	<0.001	188 (156, 200)	197 (162, 206)	0.021
Calprotectin (μg/g)	205 (53, 615)	111 (49, 367)		108 (53, 303)	120 (43, 298)	
log_{10}Calprotectin	2.31 (1.73, 2.79)	2.04 (1.69, 2.56)	0.047	2.03 (1.72, 2.48)	2.08 (1.63, 2.46)	0.7
Clinical Disease Activity			0.013			>0.9
Active	10 (31%)	2 (6.3%)		6 (21%)	6 (21%)	
Inactive	22 (69%)	30 (94%)		22 (79%)	22 (79%)	
	UC, N = 80					
	BLM, N = 38			**PBO**, N = 42		
	T0[1]	**T1**[1]	**p-value**[2]	**T0**[1]	**T1**[1]	**p-value**[2]
IBDQ	185(161,203)	195 (181, 204)	0.003	188 (159, 197)	188 (159, 201)	0.4
Calprotectin (μg/g)	107 (39, 271)	79 (24, 226)		63 (31, 220)	52 (24, 181)	
log_{10}Calprotectin	2.03(1.59, 2.43)	1.90 (1.38, 2.35)	0.090	1.80 (1.48, 2.34)	1.72 (1.38, 2.25)	0.14
Clinical Disease Activity			0.13			0.7
Active	9 (24%)	4 (11%)		10 (24%)	12 (29%)	
Inactive	29 (76%)	34 (89%)		32 (76%)	30 (71%)	

[1] Median (IQR); n (%);
[2] Wilcoxon signed rank test with continuity correction; McNemar's Chi-squared test with continuity correction

B. IBDQ, clinical variables, and F/B ratio comparisons in CD patients by enterotype and treatment group

	Enterotype1, N = 26					
	BLM, N = 14			**PBO**, N = 12		
	T0[1]	**T1**[1]	**p-value**[2]	**T0**[1]	**T1**[1]	**p-value**[2]
IBDQ	164 (150, 197)	200 (181, 208)	0.001	166 (142, 198)	176 (141, 199)	0.1
Calprotectin (μg/g)	174 (52, 551)	134 (63, 317)		111 (37, 269)	132 (32, 298)	
log_{10}Calprotectin	2.24 (1.72, 2.73)	2.13 (1.79, 2.49)	0.2	2.02 (1.54, 2.42)	2.03 (1.48, 2.46)	0.7
Clinical Disease Activity			0.074			0.5
Active	5 (36%)	0 (0%)		5 (42%)	3 (25%)	
Inactive	9 (64%)	14 (100%)		7 (58%)	9 (75%)	
F/B ratio	0.31 (0.11, 0.43)	0.69 (0.51, 0.85)	0.039	0.31 (0.24, 0.46)	0.42 (0.31, 0.65)	0.12
	Enterotype2, N = 33					
	BLM, N = 17			**PBO**, N = 16		
	T0[1]	**T1**[1]	**p-value**[2]	**T0**[1]	**T1**[1]	**p-value**[2]
IBDQ	170 (153, 187)	174 (157, 198)	0.026	192 (180, 203)	198 (190, 208)	0.062
Calprotectin (μg/g)	258 (54, 634)	103 (47, 459)		108 (81, 303)	120 (60, 291)	
log_{10}Calprotectin	2.41 (1.73, 2.80)	2.01 (1.67, 2.66)	0.10	2.03 (1.91, 2.48)	2.08 (1.77, 2.44)	0.6
Clinical Disease Activity			0.2			0.6
Active	5 (29%)	2 (12%)		1 (6.2%)	3 (19%)	
Inactive	12 (71%)	15 (88%)		15 (94%)	13 (81%)	
F/B ratio	0.85 (0.65, 1.23)	0.82 (0.41, 0.97)	0.9	0.84 (0.48, 1.37)	0.96 (0.55, 1.17)	0.4

[1] Median (IQR); n (%);
[2] Wilcoxon signed rank test with continuity correction; McNemar's Chi-squared test with continuity correction

C. IBDQ, clinical variables, and F/B ratio comparisons in UC patients by enterotype and supplementation group

	Enterotype1, N = 48					
	BLM, N = 22			**PBO**, N = 26		
	T0[1]	**T1**[1]	**p-value**[2]	**T0**[1]	**T1**[1]	**p-value**[2]
IBDQ	194 (165, 209)	194 (182, 208)	0.019	180 (159, 199)	182 (150, 195)	0.4
Calprotectin (μg/g)	78 (42, 226)	98 (32, 213)		69 (42, 277)	53 (24, 130)	
log_{10}Calprotectin	1.88 (1.62, 2.35)	1.99 (1.50, 2.32)	0.2	1.84 (1.62, 2.44)	1.72 (1.38, 2.11)	0.063
Clinical Disease Activity			0.2			>0.9
Active	5 (23%)	2 (9.1%)		8 (31%)	7 (27%)	
Inactive	17 (77%)	20 (91%)		18 (69%)	19 (73%)	
F/B ratio	0.77 (0.50, 1.15)	0.86 (0.59, 1.30)	0.2	0.73 (0.44, 0.87)	0.89 (0.57, 1.27)	0.087

(*continued on next page*)

Table 4 (*continued*)

A. IBDQ and clinical variables comparisons by IBD pathology and supplementation group						
	CD, N = 60					
	BLM, N = 32			**PBO**, N = 28		
	T0[1]	**T1**[1]	**p-value**[2]	**T0**[1]	**T1**[1]	**p-value**[2]
	Enterotype2, N = 32					
	BLM, N = 16			**PBO**, N = 16		
	T0[1]	**T1**[1]	**p-value**[2]	**T0**[1]	**T1**[1]	**p-value**[2]
IBDQ	179 (160, 199)	195 (182, 201)	0.045	190 (168, 196)	196 (170, 202)	0.1
Calprotectin (μg/g)	149 (36, 304)	42 (24, 373)		48 (24, 167)	41 (24, 296)	
log_{10}Calprotectin	2.16 (1.56, 2.48)	1.61 (1.37, 2.49)	0.2	1.67 (1.38, 2.22)	1.61 (1.38, 2.47)	0.6
Clinical Disease Activity			0.6			0.2
Active	4 (25%)	2 (12%)		2 (12%)	5 (31%)	
Inactive	12 (75%)	14 (88%)		14 (88%)	11 (69%)	
F/B ratio	1.23 (0.82, 2.02)	1.24 (0.79, 1.64)	0.8	1.53 (1.24, 2.02)	1.33 (0.89, 1.57)	0.9

[1] Median (IQR); n (%);
[2] Wilcoxon signed rank test with continuity correction; McNemar's Chi-squared test with continuity correction

cision was supported by earlier investigations, which showed that the partition into enterotypes was a valid strategy for the study of the role of microbiota in different diseases such as IBS and IBD as well as in various settings (*i.e.*, after FMT in UC, CD, and *Clostridioides difficile* infection) [23–25]. This approach allowed us to assess the effect of butyrate supplementation on groups of patients with similar microbial compositions, enhancing the reliability of our findings. Moreover, by grouping patients on similar microbial profiles, we explored the specific effects of butyrate supplementation within these subsets, potentially uncovering more targeted supplementation strategies and allowing a personalized approach.

We identified two enterotypes in each disease, characterized by varying levels of Firmicutes and Bacteroidota phyla (Fig. 2). It is important to emphasize that the F/B ratio is considered a marker of the well-being of the intestinal microbiota [26]. Some authors claim that values between 0.8 and 1.2 can be considered possible reference values [26]. Patients with CD having an Enterotype-1 (CD-E1) showed a very low F/B ratio (median F/B = 0.31), whereas patients with CD having an Enterotype-2 (CD-E2) had a relatively higher ratio (median F/B = 0.85) compatible with an optimal range (F/B = 0.8-1.2). Instead, UC patients showed a higher F/B ratio, especially those belonging to Enterotype-2 (median F/B = 1.36). In this case, the F/B ratio can be seen as a bacterial consortium capable, or not, of losing calories with stool [26] and therefore a patient population with very low F/B can be considered reasonably weaker. We hypothesized that for this reason, a significantly greater reaction to BLM supplementation was detected in the CD-E1 population, markedly improving the F/B ratio (0.31 vs. 0.69; p = 0.039) and QoL (median IBDQ from 164 to 200, p = 0.001)

In CD patients, the two enterotypes were associated with differences in BMI, previous colon-preserving surgical procedures, and clinical disease activity. In contrast, in UC patients, the two enterotypes were associated with differences in age only (**Table S1**). Further, neither BMI nor the age-associated variable were influenced by the supplementation with BLM. As we hypothesized that CD-E1 represented the population with the weakest gut microbiota due to a lower F/B ratio, our findings were corroborated by the fact that we observed that CD-E1 was more frequently associated with previous surgical interventions and was more subjected to changes after supplementation with BLM. A similar effect was not observed in the other groups of patients (**Figure S3A)**. In CD-E1, after supplementation with BLM, microbiota showed a reduction of potentially pathogenic bacteria such as *Escherichia-Shigella, Klebsiella*, and *Morganella* and an increase of SCFA producers such as *Ruminococcus, Lachnospiraceae NK4A136 group* (**Figure S5**). This result is consistent with our previous observations in the same study [14]. By carefully controlling for multiple potential confounders, our study design ensured increased reliability and validity. Using the WCRF questionnaire, we controlled for physical activity and dietary habits, key drivers of microbiota changes. Despite minor variations in associations between certain foods (Beer and Wine, Multicereal, Table 2) and UC enterotypes, overall dietary patterns remained consistent across enterotypes in both diseases, showing remarkable stability before and after supplementation. (**Table S3-S4**).

Differential abundance analysis identified significantly different taxa before and after treatment only in the CD group treated with butyrate and belonging to the first enterotype (**Figure S5)**. However, from a clinical perspective, we observed improvements in overall well-being (QoL) in all treated groups (CD and UC; Table 4). We hypothesized that several factors contributed to this phenomenon. First, butyrate, as a microbial metabolite, has shown various physiological effects beyond its direct influence on the gut microbiota. It serves as an energy source for colonic epithelial cells [27], regulates intestinal barrier function [28], and exhibits anti-inflammatory properties [29]. These broad effects of butyrate may have contributed to the overall well-being improvements observed across all BLM-treated groups, irrespective of enterotype and disease. In particular, the first enterotype groups, having a specific microbiota composition, particularly responded to butyrate treatment. Expanding on this idea, the presence of specific phyla, such as Verrucomicrobiota and Fusobacteriota, is worth mentioning in the first enterotype of CD patients at baseline. Verrucomicrobiota is a phylum of bacteria that includes several important members, such as *Akkermansia muciniphila*, known for its association with gut health and mucin degradation [30]. The presence and abundance of Verrucomicrobiota in the first enterotype group might have contributed to their responsiveness to butyrate treatment. Similarly, the phylum Fusobacteriota may have played a role in the responsiveness of the first enterotype group to butyrate treatment. Fusobacteriota has been linked to inflammation and disease. Moreover, the severity of clinical conditions, expressed by the history of previous surgeries and clinical indexes, suggests that CD-E1 patients were experiencing more significant symptoms and challenges related to their condition and, therefore, were more subjected to the effects of BLM. It is plausible to speculate that the specific microbial composition within the first enterotype group, coupled with the heightened disease activity, created an environment in which the therapeutic effects of butyrate were more noticeable. The altered microbial composition and the presence of

certain taxa within this enterotype might have interacted synergistically with the butyrate supplementation, resulting in detectable microbial changes and greater improvements in overall well-being.

However, it should be noted that PBO treatment also significantly improved the QoL of CD population (Table 4A: p = 0.021). This aspect has already been observed in the IBD population [31], concluding that the PBO effect on quality of life could be meaningful in IBD. This result could moderate the meaningfulness observed with the verum product.

In the BLM supplementation group of CD-E1 patients, our analysis revealed several significant changes in microbial composition (**Figure S5, Table S3**). Notably, we observed a significant reduction in various taxa within the Proteobacteria phylum, including *Escherichia-Shigella, Klebsiella*, and *Morganella*. This reduction suggests a potential modulation of the Proteobacteria population associated with inflammation and disease severity in CD [32]. Additionally, taxa within the Bacteroidota phylum, specifically *Bacteroides* and *Prevotella_9* genera, were significantly reduced. These findings are intriguing, as *Bacteroides* and *Prevotella* have been implicated in the pathogenesis of CD [33]. Furthermore, we observed a significant decrease in *Bilophila*, a bile-tolerant genus within the Desulfobacterota phylum, known for its potential pro-inflammatory properties [34]. Another noteworthy finding was the reduction of *Fusobacterium*, a genus within the Fusobacteriota phylum, associated with inflammation and colorectal cancer [35].

Regarding the Firmicutes phylum, our results demonstrated mixed changes in various genera. Within CD-E1 patients, we observed a reduction in *Lachnoclostridium, Veillonella, [Ruminococcus] gnavus group, Anaeroglobus*, and Hydrogenoanaerobacterium family. These reductions might reflect alterations in specific functional groups or metabolic activities associated with these taxa. On the other hand, we observed an increase in several Firmicutes genera, including *UCG-002*, Clostridia UCG-014 order, *Ruminococcus, Lachnospiraceae NK4A136 group, [Eubacterium] siraeum*, and *eligens* groups. These increases suggest potential shifts in the microbial community towards taxa that might contribute to improved gut health and immune modulation. Overall, our findings highlight the significant changes in microbial composition within the BLM supplementation group of CD-E1 patients. These changes involved inflammation-associated taxa, disease severity, and potential pathogenicity.

4.1. Study limitations

Our study has some limitations. First it was not possible to include the analysis of fecal short-chain fatty acid (SCFA) concentrations due to local restrictions imposed by the COVID-19 pandemic, which prevented the collection and storage of untreated whole stool samples (i.e., not processed using eNat kits); the study was not designed as a crossover trial, which may have strengthened the value of our results. We did not evaluate the metabolic pathways associated with the different enterotypes, limiting our findings' understanding. Additionally, we did not check for endoscopic improvement or remission of our patients. However, the treatment duration of our study was probably too short to document the presence of mucosal healing. Finally, we included patients with active and inactive disease (defined by HBI and partial Mayo score), indeed, our study population consisted of a consecutive cohort, thus limiting the generalizability of our findings, although our results revealed a greater reactivity to treatment in patients with active diseases.

In conclusion, BLM supplementation demonstrates potential to improve clinical activity and quality of life in patients with IBD. Patients characterized by Enterotype-1 may show a tendency towards greater benefits and improvements in quality of life compared to those with Enterotype-2, across both UC and CD populations

Author contributions

S.F., M.C., M.P., and E.V.S. contributed to the study design and manuscript drafting. S.F., E.V.S., and A.B. contributed to the experiments; M.C., M.P., and N.V. contributed to the data analysis; E.V.S. and N.V. supervised the study; B.B., F.Z., and A.B. contributed to the critical revision of the manuscripts and provided important intellectual content. All authors read and approved the final manuscript.

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Data availability

For sensitivity reasons, the data supporting this study's findings are not openly available, but they are available from the corresponding author upon reasonable request.

Some of the data supporting the findings of this study are available within the document and its Supplementary Information.

URL for the public repository (for the exclusive use of the reviewers)

https://dataview.ncbi.nlm.nih.gov/object/PRJNA1076133?reviewer=hpui0slmne67217vcu5bgbhv10

Declaration of competing interest

Sonia Facchin has received lecture or consultancy fees from SILA and Unifarco; Edoardo Vincenzo Savarino has served as speaker for Abbvie, Aboca, Abivax, Agave, AGPharma, Alfasigma, Apoteca, Biosline, CaDiGroup, Celltrion, Dr Falk, EG Stada Group, Eli Lilly, Fenix Pharma, Galapagos, Giuliani, Johnson&Johnson, JB Pharmaceuticals, Innovamedica/Adacyte, Lionhealth, Malesci, Mayoly Biohealth, Montefarco, Novartis, Omega Pharma, Pfizer, Rafa, Reckitt Benckiser, Sandoz, Sanofi/Regeneron, SILA, Takeda, Tillots, Unifarco; has served as consultant for Abbvie, Alfasigma, Apogee, AstraZeneca, Biogen, Bristol-Myers Squibb, Celltrion, Dr. Falk, Eli Lilly, Fenix Pharma, Ferring, Giuliani, Grunenthal, Johnson&Johnson, JB Pharmaceuticals, Merck & Co, Nestlè, Pfizer, PRO.MED.CS Praha a.s., Reckitt Benckiser, Sanofi/Regeneron, SILA, Takeda, Unifarco; he received research support from Bonollo, Difass, Pfizer, Reckitt Benckiser, Sanofi/Regeneron, SILA, Unifarco, Zeta Farmaceutici. All other authors: none declared.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2025.11.014.

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