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UNIVERSITÀ DEGLI STUDI DI BRESCIA

Nutritional support with TGF-β2 Food for Special Medical Purposes (TGF-β2 FSMP) in adult allogeneic hematopoietic Stem cell transplantation (allo-HSCT) for the prevention of malnutrition: a prospective, randomized, multicenter study - (TGF-NUTRIALLO study)

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Synopsis

Study Synopsis	
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Clinicaltrials.gov	
Study Design	Prospective, open-label, randomized, multicentric, interventional TGF-β2-enriched supplementation (Modulen IBD ®) in patients submitted to allogeneic hematopoietic stem cell transplantation (allo-HSCT) (***Figure 1***)
Primary Objectives	To identify if TGF-β2-enriched nutritional supplement (Modulen-IBD®) given from day -7 to day +28 is superior to best supportive therapy (BST) in preventing malnutrition in patients submitted to allo-HSCT. Patients not accomplishing oral Modulen-IBD® assumption, are proposed to be treated through naso-gastric tube (NGT).
Secondary Objectives	• To reduce cumulative incidence (CI) of acute-graft versus leukemia disease (aGVHD) at 100 days after alloHSCT in the experimental group; • To reduce cumulative incidence of severe (II-IV MAGIC) GVHD at 100 days after alloHSCT in the experimental group; • Feasibility of NGT enteral feeding at + 28 days; • Microbiome evaluation before alloHSCT and at + 28 days; • Malnutrition at +100 days; • Lean mass by Dual Energy X-ray Absorptiometry (DEXA)/ bioimpedentiometry (BIA) at baseline and day + 100; • Duration of hospitalization; • Transplant related mortality (TRM) at +30, +100, +180, +365 days; • GVHD Relapse Free Survival (GRFS) at 1 year; • Relapse Free Survival (RFS) at 1 year; • Overall survival (OS) at 1 year;
Primary End Points	• Patient generated-Subjective Global Assessment (PG-SGA) score C (severe malnutrition) at day +28 less than 50%
Secondary Endpoints	• CI of gastrointestinal aGVHD at day +100 <12.5%; • CI of MAGIC II-IV aGVHD at day +100; • Percentage and days of NGT enteral feeding; • Pre and Post-alloHSCT microbiome profiles; • Percentage of PG-SGA at 100 days;

	● Descriptive analysis of DEXA)/ BIA at 100 days; ● Days of hospitalization in the first 100 days; ● TRM at +30, +100, +180, +365 days; ● GVHD Relapse Free Survival (GRFS) at 1 year; ● Relapse Free Survival (RFS) at 1 year; ● OS at 1 year;
Patient Population	● Adults (≥ 18 yo) undergoing allo-HSCT
Inclusion Criteria	● Intact intestinal tract ● Myeloablative or non-myeloablative conditioning ● Matched related donor (MRD), or Mismatched unrelated donor (MUD) or Haploidentical allo-HSCT >18 years
Exclusion Criteria	● Active hematological disease at the beginning of conditioning ● Personal history of inflammatory bowel diseases ● Personal history of bowel resection ● Personal history of gastric bypass procedures ● Enrolment in a competitive prospective study (malnutrition or GVHD as primary outcome) ● Subjects with known hypersensitivity to milk proteins or components of Modulen-IBD
Enrollment Plan and statistical design	Two step sequential model will be applied to confirm superiority in the experimental arm for the two principal outcomes: malnutrition and acute gastrointestinal GVHD. **First Phase** In the first phase 214 patients will be enrolled in a prospective multicenter, randomized, interventional study, assuming a power of 80%, with a superiority target of severe malnutrition (PG-SGA C at +28 days) defined as a reduction from 70% (expected in the BST arm) to 50% (in the experimental arm), margin 0.05, with an expected drop-out due to dysgeusia or oral intolerance of 15%. **Second phase** In the second phase 136 more patients will be enrolled to define a superiority also in the second primary outcome (gastrointestinal aGVHD cumulative incidence reduction from 25 to 12.5% at 100 days in the experimental arm). An interim analysis will be performed after 100 patients to avoid futility if the percentage of malnutrition at +28 days of the whole population will be under 60% and the cumulative incidence of gastrointestinal aGVHD of the whole population will be under 20%. (https://clincalc.com/stats/samplesize.aspx). Ratio of patients undergoing myeloablative or non-myeloablative conditioning will be 1:1 in both arms to standardize the intervention. Analysis will be carried out in an intention to treat analysis and per protocol to explore adherence to treatment and percentage of patients requiring NGT enteral feeding. The high drop-out incidence is expected also due to critical patients' conditions after high dose chemotherapy or radiation which might implicate several side effects i.e: taste perception alteration, oral mucositis, GI tract intolerance, mood alteration and, consequently, increase patient's anorexia and reduce his

	willingness to eat.
Participating Centers	• University of Brescia/ASST Spedali Civili • 2 competitive Italian hematology Centers affiliated to the Italian Group for Bone Marrow Transplantation, Hematopoietic Stem Cells and Cell Therapy (GITMO)
Interventional Plan	Nutritional assessment will be carried out according to Table 1: At admission (enrollment) patients will be assessed through: • Anthropometric measures: Body weight (BW), height, Body mass index (BMI), bicipital and abdominal circumferences; • PG-SGA; • Biomarkers: microbiome analysis, butyrate, IGF-1, citrulline, fecal calprotectin.. Nutritional assessment with PG-SGA will be performed twice weekly until discharge, at + 28, and + 100 days. Biomarkers will be assessed at +14, +28, +100 days. **General recommendations** (EBMT Handbook 2019, adapted): 1. Early involvement of dietitians and nutritional services; 2. Consider placement of nasogastric tube in case of defective oral calories intake <75% for more than 3 days (or at admission in case of high risk of malnutrition); 3. Standardized monitoring of nutritional intake: calories intake should be defined twice weekly according to diet adherence (according to canteen calories tables and self-reporting food waste analysis - figure 2), amount of dextrose infusions per day; 4. Nutritional reassessment every 3 days using PG-SGA; Any additional nutritional support adjunctive to Modulen IBD® should be discontinued if oral intake is more than 50% of TDEE, for 3 consecutive days at any time, but in any case, after day +28. Estimation of caloric needs according to Table 2 **Definitions**: *ONS* (oral nutritional support): additional snacks rich in proteins and energy, protein or calories, additional protein and energy drinks, enrichment of main courses (superfood, potentiated food) *Enteral Nutrition*: special liquid food mixtures containing protein, carbohydrates, fats, vitamins and minerals given through NGT (ASPEN 2021). *Parenteral Nutrition*: intravenous administration of nutrition, which may include

	protein, carbohydrate, fat, minerals and electrolytes, vitamins and other trace elements for patients who cannot eat or absorb enough food through tube feeding formula or by mouth to maintain good nutrition status (ASPEN 2021).

Table 1

	At Enrollment	Daily	Twice weekly	+28	+100
PG-SGA	x		X	X	x
GLIM	x			x	x
BMI	x		X	X	x
SF36, SAT-P Predimed	x			x	x
Caloric intake (caloric value from canteen)			X		
BW	x	X		X	x
Waste analysis auto-evaluation		X			
Urine IN/OUT		X			
Hydric overload (amount of dextrose solutions/ day)		X			
Biomarkers*	x		x (only +14)	X	x
Ancillary studies	x			x	x
BIA	x			X	x
DEXA	x			X	x

Total Daily Energy Expenditure will be calculated as reported in the table 2 (or if available based on calorimetry or according Harris-Benedict formula):

Table 2

	PG-SGA A	PG-SGA B	PG-SGA C	Calories by Modulen IBD® of TDEE
if BMI < 20	40 kcal / kg	42 Kcal / Kg	44 kcal /kg	20%
if BMI 20-24.9	35 kcal / kg	39 kcal / kg	42 kcal / kg	15%
if BMI 25 - 29.9	30 kcal / kg	33 kcal / kg	36 kcal / kg	12%
if BMI > 30	25 kcal / kg	28 kcal / kg	30 kcal / kg	10%
	TDEE			

The experimental treatment is Modulen-IBD®, a food for special medical purpose, polymeric, enriched with TGF-beta. If the patient refuses the experimental supplementation, NGT will be proposed to ensure the correct intake of Modulen-IBD® supplementation.

If the patient refuses, not tolerates, or there are contraindications to NGT placement, best supportive therapy will be warranted as reported below (BST).

1) MODULEN-IBD SUPPLEMENTATION

From hospital admission to day +28 calories by Modulen-IBD® will integrate oral diet with 20% of calories by Modulen IBD® of TDEE, according to table 2 and to twice weekly monitoring

Oral administration:

Once reconstituted with bottled water according label instructions and at a caloric concentration of ≤1 kcal/ml, the supplement could be flavored according to the patient's tastes with barley coffee or decaffeinated coffee or cocoa. It is recommended to take in 2-3 portions to be taken throughout the day.

NGT route:

	Placement of a small NGT (max 8-10 fr.) is recommended. Food assumption is encouraged even when NGT is placed. In case of NGT placement, the amount of calories by tube is the difference between TDEE and the amount of calories assumed with food. Modulen IBD® will be prepared and administered in 100-250 ml boluses (every 4-6 hours) to ensure the stability of the product. If a patient refuses food, Enteral Nutrition as polymeric standard, isocaloric, isoproteic, +/- fibers, 280-320 mOsm/L formula should be used. In this case the amount of calories covered by Modulen-IBD® should be at least 20% of TDEE. **2) Best Supportive Treatment (BST)** Nutritional support in patients randomized to BST should be carried out according to EBMT-Handbook standards. If the patient's caloric intake is less than 75% for 3 days (instead 60% as proposed by EBMT manual) nutritional intervention is warranted and calculated according to BMI (see above). ONS: ONS should ensure the same amount of caloric intake of the experimental treatment in addition to usual food assumption. If patients could not assume the right amount of calories with ONS and refuse NGT parenteral nutrition is permitted. Parenteral Nutrition (PN): 3-1 formulations with a 1.1 Kal/ml content should be preferred (ex. Smofkabiven®, Olimel®) through a central line. The choice of PN type is according to the center's policy and used in combination with food or ONS assumption. **Complementary nutritional supports:** All the patients should receive complementary nutritional support as described below: Oral water (if possible): 1 L/mq Vitamins and oligo-elements: daily Cernevit® 1 fl from day +1 to +28 or to discharge, vit. K 1 fl weekly, vit. D 25000 IU weekly Use of probiotics without lactose is permitted (and should be registered) in case of diarrhea and intestinal GVHD.

Ancillary studies	If available data from BIA, DEXA or Indirect calorimetry could be performed to obtain support for anthropometric data. Patients reported outcome measures (PROMs) should be submitted at the entry and at the end of the study. ● QoL (SF36) questionnaires ● Mediterranean diet questionnaire
*Biological and biomarkers studies	● Microbiome analysis ● SCFA ● IGF-1 ● Citrulline ● Fecal Calprotectin ● Urine 3-indoxyl sulfate ● Amphiregulin ● Zonuline
	Special conditions *Acute gastrointestinal GVHD:* aGVHD is classified according to MAGIC/IBMTR scoring. In case of suspected aGVHD biopsy of the affected organ is recommended. In case of gastrointestinal aGVHD Modulen-IBD® should be continued, enteral nutrition should be preferred except in case of aGVHD grade III/B (more than 1000 ml/day of diarrhea). Enteral semi-elementary normocaloric normoproteic formula (without fibers) (Peptamen®), Modulen-IBD® boluses as prescribed *Non-invasive ventilation:* In case of non-invasive ventilation, the amount of lipids in the parenteral nutrition should not exceed 1 mg/kg/day.
End of study	After 28 days from the last patient enrolled (primary outcome). Study duration will be 3 years according to centers capacity of enrollment.
Ethical aspects	The study will be conducted according to good clinical practice (GCP) and privacy rules, Helsinki declaration and should be approved by local ethical committees.
Informed consent	Every local PI is responsible to enroll patients after signing informed consent according to GCP rules.

Data protection	Study data should be protected according to General Data Protection Regulation (GDPR)
Keywords	malnutrition, graft versus host disease, inflammatory bowel disease, TGF-β2, special foods for medical purposes, allogeneic hematopoietic stem cell transplantation

Protocol abstract

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) represents the only curative option for a wide spectrum of hematologic disorders, but its outcome is hampered by a high non-relapse mortality (NRM). The nutritional status and the graft-versus leukemia host disease (GVHD) are two relevant causes of NRM. Supplementation with special Foods for medical purposes (FSMP) may be an easy and valid alternative to enteral/parenteral nutrition to reduce malnutrition. Until today, there haven't been any randomized studies that explored the potential benefit of malnutrition prevention in the allo-SCT context. Transforming growth factor beta 2 (TGF-β2) enriched FSMP (MODULEN-IBD®) is approved for nutritional supplementation in patients with inflammatory bowel disease (IBD) and it has been successfully tested in our previous prospective, single center study on transplant patients. The nutritional TGF-β2 FSMP supplementation was significantly correlated with decrease in patients' malnutrition 28 days after allo-SCT and reduced incidence of severe acute GVHD improving overall survival.

Thus, based on these significant findings, we designed a prospective, randomized, multicenter study to confirm the potential benefits of TGF-β2 enriched FSMP. The primary objective is to evaluate the superiority of supplementing with TGF-β2 FSMP (experimental arm) compared to best supportive treatment (BST) in preventing malnutrition in patients submitted to allo-SCT. The secondary endpoints include the assessment of reduction of incidence of severe acute GVHD at day +100.

The study comprises two steps. In the first phase of the study, 214 patients will be enrolled and randomized 1:1 to receive TGF-β2 FSMP from day -7 to day +28 post allo-SCT or BST. The randomization will be stratified by type of conditioning, myeloablative conditioning (MAC) or reduced intensity conditioning (RIC) and by post-transplant cyclophosphamide intake. The primary endpoint is the reduction from 70% to 50% of the malnutrition defined as PG-SGA C at +28 in the experimental arm in comparison to the BTS one, with an expected drop-out due to dysgeusia or gastrointestinal intolerance of 15%. In the second phase,136 more patients will be enrolled to assess the aGVHD cumulative incidence reduction from 25 to 12.5% at 100 days in the experimental arm. Analysis will be carried out in an intention to treat analysis.

1. BACKGROUND AND RATIONALE

1.1 Background

Malnutrition is associated with poor outcome in patients submitted to allogeneic hematopoietic stem cell transplantation (allo-HSCT)[1,2]. Indeed, severe malnutrition extends engraftment time and augments the risk of infections resulting in prolonged hospitalization stays and increased mortality rates[3]. Consequently, nutritional assessment and support play a pivotal role in transplant patients management, thereby enhancing transplant outcomes[4]. The Patient-Generated Subjective Global Assessment (PG-SGA) questionnaire is recommended as the standard tool for nutritional screening, assessment, monitoring, and triaging for nutritional interventions in cancer patients[5]. Concerning nutritional support, enteral nutrition (EN) is generally considered the preferred approach to ensure adequate intake of proteins and calories[6,7]. Although EN is recommended in both ASPEN and ESPEN guidelines the nasogastric tube placement is not always accepted in the allo-SCT setting[8,9].
Transforming growth factor beta 2 (TGF-β2) enriched FSMP (MODULEN-IBD®) is approved for nutritional supplementation in IBD[10,11]. Due to its biological properties it was tested in our previous exploratory study on 55 patients submitted to allo-HSCT[12]. We observed in patients who took at least 50% of the prescribed dose, the reduction of malnutrition (p= 0.0001) and also the reduction in the incidence of gastrointestinal (GI) graft-versus leukemia host disease (GVHD) (p = 0.005). Given these encouraging results, we conducted a second prospective study on 133 patients consecutively allo-transplanted for hematological malignancies between April 2018 and February 2023 at our institution Spedali Civili di Brescia[13]. The nutritional status was assessed by PG-SGA at admission and on days 0, +7, +14, +21, and +28 post-transplant. Patients were categorized into three groups as follows: A) good nutritional status, B) moderate malnutrition and C) for severe malnutrition. The patients diet was supplemented with oral TGF-FSMP and the TGF-FSMP dosage was calculated based on body mass index (BMI) and total daily energy expenditure (TDEE). Patients who assumed ≥50% of the prescribed TGF-FSMP were classified in Group A, while those who received less than 50% were included in Group B according to personal compliance: the cut-off of 50% was defined per protocol as the sufficient dose to have an hypothetical effect on malnutrition and on secondary outcomes. The primary endpoint of the study was therefore the assessment of severe malnutrition 28 days after transplant (according to the PG-SGA C categorization) in patients assuming a sufficient amount of FSMP (Group A). On day +28 post-transplant the following outcomes were observed: i) Patients in Group A displayed significantly lower rates of severe malnutrition compared to those in Group B (28% versus 79%, respectively, OR 2.86 - CI 1.94-4.23 -, p=0.0001). ii) The incidence of severe (MAGIC II-IV) aGVHD and any grade of GI aGVHD was higher in Group B compared to Group A (43% versus 21%, p=0.003) and (34.5% versus 9.2%, p=0.001) iii) Pneumonia was more common in malnourished patients in Group B than in well/moderately nourished patients in Group A (52.7% versus 27.6%, p=0.002). The estimated median overall survival (OS) was 33 months in Group A and 25.1 months in Group B (p=0.03). Multivariate and artificial neural network (ANN) analyses indicated that TGF-FSMP treatment ratio (TR) < 50% intake was significantly associated with malnutrition, severe and GI aGVHD, pneumonia, and reduced OS. Considering the results of these two previous studies, we aim to conduct a randomized study to investigate whether the supplementation with MODULEN-IBD® reduces malnutrition in transplant patients, potentially leading to improved outcomes[13].

1.2 Rationale

The pathophysiology of gastrointestinal acute GVHD (GI aGVHD) is multifactorial and shares several similarities with chronic inflammatory bowel disease (IBD), including the loss of the intestinal epithelial barrier and the alteration in intestinal microbiota composition[14,15]. In the context of IBD, TGF-β2 is the most studied bioactive

peptide for nutritional support. TGF-β2 is an anti-inflammatory cytokine and a pivotal gut microbiota regulator[10]. It regulates the immune cell crosstalk and controls the differentiation, proliferation, and activation state of lymphocytes, macrophages, and dendritic cells[16] . Therefore it plays a critical role in the mechanisms of tolerance, prevention of autoimmunity, and in anti-inflammatory processes in the gut.In this context, we want to evaluate in a randomized prospective study whether the addition of TGF-β2 enriched FSMP (MODULEN-IBD®) to the oral diet determines a reduction in severe malnutrition in patients after allo-SCT and reduces the risk of GI aGVHD.

2. AIMS

The aim of this study is to assess the impact of TGF-β2-enriched Food for Special Medical Purposes (Modulen-IBD®) given from day -7 to day +28 following allo-HSCT in a superiority, independent, controlled trial, in preventing malnutrition in comparison to the best supportive nutritional treatment.

3. POTENTIAL RISKS AND BENEFIT FOR THE PATIENTS

Malnutrition is associated with poor outcome in patients submitted to allo-SCT[1,2] . Indeed, severe malnutrition extends engraftment time and augments the risk of infections resulting in prolonged hospitalization stays and increased mortality rates[3]. Consequently, nutritional assessment and support play a pivotal role in transplant patients management, thereby enhancing transplant outcomes[4]. The Patient-Generated Subjective Global Assessment (PG-SGA) questionnaire is recommended as the standard tool for nutritional screening, assessment, monitoring, and triaging for nutritional interventions in cancer patients[3]. Concerning nutritional support, EN is generally considered the preferred approach to ensure adequate intake of proteins and calories[5]. Although EN is recommended in both ASPEN and ESPEN guidelines the nasogastric tube placement is not always accepted in the allo-SCT setting[6,7]. Thus, the use of Food for Special Medical Purposes (FSMP) can be considered an alternative nutritional supportive approach for transplanted patients to avoid malnutrition. Another significant complication following allo-HSCT is GVHD, which represents the primary cause of non-relapse mortality (NRM)[17] .The pathophysiology GI a-GVHD is multifactorial and shares several similarities with chronic IBD, including the loss of the intestinal epithelial barrier and the alteration in intestinal microbiota composition[14,15]. TGF-β2 is an anti-inflammatory cytokine and a pivotal gut microbiota regulator[10]. It regulates the immune cell crosstalk and controls the differentiation, proliferation, and activation state of lymphocytes, macrophages, and dendritic cells[16]. Therefore it plays a critical role in the mechanisms of tolerance, prevention of autoimmunity, and in anti-inflammatory processes in the gut.In this context, we want to evaluate in a randomized prospective study whether the addition of TGF-β2 enriched FSMP (MODULEN-IBD®) to the oral diet determines a reduction in severe malnutrition in patients after allo-SCT and, exploratively, reduces the risk of GI a-GVHD.

TGF-β2 enriched FSMP (MODULEN-IBD®) is approved for nutritional supplementation in IBD[13]. Due to its biological properties it was tested in our previous exploratory study on 55 patients submitted to allo-HSCT[18]. We observed in patients who took at least 50% of the prescribed dose, the reduction of malnutrition (p= 0.0001) and also the reduction in the incidence of GI GVHD (p = 0.005). Given these encouraging results, the prospective study was extended on 133 patients consecutively allo-transplanted for hematological malignancies between April 2018 and February 2023 at our institution Spedali Civili di Brescia[13]. Nutritional status was assessed by PG-SGA at admission and on days 0, +7, +14, +21, and +28 post-transplant. Patients were categorized into three groups as follows: A) good nutritional status, B) moderate malnutrition and C) for severe malnutrition. The patients diet was supplemented with oral TGF-FSMP and the TGF-FSMP dosage was calculated based on body mass index (BMI) and total daily energy expenditure (TDEE). Patients who assumed ≥50% of the prescribed TGF-FSMP were classified in Group A, while those who received less than 50% were included in Group B according to

personal compliance: the cut-off of 50% was defined per protocol as the sufficient dose to have an hypothetical effect on malnutrition and on secondary outcomes. The primary endpoint of the study was therefore the assessment of severe malnutrition 28 days after transplant (according to the PG-SGA C categorization) in patients assuming a sufficient amount of FSMP (Group A). On day +28 post-transplant the following outcomes were observed: i) Patients in Group A displayed significantly lower rates of severe malnutrition compared to those in Group B (28% versus 79%, respectively, OR 2.86 - CI 1.94-4.23 -, p=0.0001). ii) The incidence of severe (MAGIC II-IV) aGVHD and any grade of GI aGVHD was higher in Group B compared to Group A (43% versus 21%, p=0.003) and (34.5% versus 9.2%, p=0.001) iii) Pneumonia was more common in malnourished patients in Group B than in well/moderately nourished patients in Group A (52.7% versus 27.6%, p=0.002). The estimated median overall survival (OS) was 33 months in Group A and 25.1 months in Group B (p=0.03). Multivariate and artificial neural network (ANN) analyses indicated that TGF-FSMP treatment ratio (TR) < 50% intake was significantly associated with malnutrition, severe and GI acute GVHD, pneumonia, and reduced OS. Considering the results of these two previous studies, we aim to conduct a randomized study to investigate whether the supplementation with MODULEN-IBD® reduces malnutrition in transplant patients, potentially leading to improved outcomes.

4. OBJECTIVES

The aim of this project is to carry out an independent, not company driven, prospective, open-label, randomized, multicentric, interventional study in which TGF-β2-enriched Food for Special Medical Purposes (Modulen IBD ®) will be tested in patients submitted to allogeneic hematopoietic stem cell transplantation (allo-HSCT) to reduce malnutrition in comparison to the best supportive treatment for malnutrition.

4.1 Study Plan

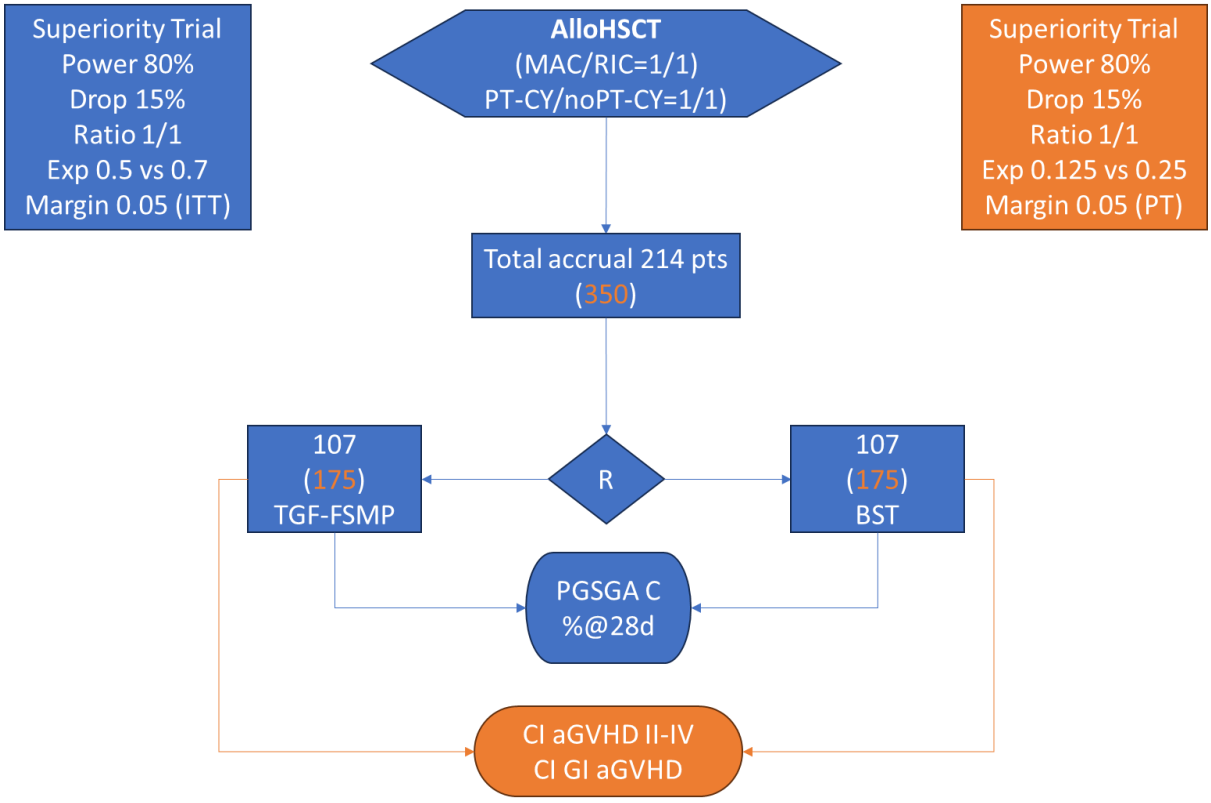

Figure 1 - Study plan: 214 patients will be enrolled and randomized 1:1 to receive TGF-β2 Food for Special Medical Purposes (FSMP) or the best supportive therapy (BST) from day -7 to day +28 post allo-SCT. The primary endpoint is the reduction from 70% to 50% of the malnutrition defined as PG-SGA C at +28. In the second phase, 68 more patients will be enrolled in each arm to assess the aGVHD cumulative incidence reduction from 25 to 12.5% at 100 days.

4.2 Primary Objective

To identify if a TGF-β2-enriched Food for Special Medical Purposes (Modulen-IBD®) given from day -7 to day +28 is superior to best supportive therapy (BST) in preventing malnutrition in patients submitted to allo-HSCT. Patients not accomplishing oral Modulen-IBD® assumption, are proposed to be treated through naso-gastric tube (NGT).

4.3 Secondary Objectives

- To reduce cumulative incidence of gastrointestinal aGVHD at 100 days after alloHSCT in the experimental group
- To reduce cumulative incidence of grade II-IV MAGIC acute GVHD
- Feasibility of NG enteral feeding at + 28 days
- Microbiome evaluation before alloHSCT and at + 28 days
- Malnutrition at +100 days
- Lean mass by Dual Energy X-ray Absorptiometry (DEXA)/ bioimpedentiometry (BIA) at baseline and day + 100
- Duration of hospitalization
- Transplant related mortality (TRM) at +30, +100, +180, +365 days
- GVHD Relapse Free Survival (GRFS) at 1 year
- Relapse Free Survival (RFS) at 1 year
- Overall survival (OS) at 1 year

4.4 Primary endpoint

- PG-SGA score C (severe malnutrition) at day +28 <50%

4.5 Secondary endpoints

- Cumulative incidence of gastrointestinal aGVHD at day +100 <12.5%
- Cumulative Incidence of aGVHD MAGIC II-IV at day +100 reduced by 15% from at least 35% in the control arm
- Percentage and days of NGT enteral feeding
- Pre- and Post-alloHSCT microbiome profiles
- Percentage of PG-SGA C at 100 days
- Descriptive analysis of DEXA/BIA at 100 days
- Days of hospitalization in the first 100 days
- TRM at +30, +100, +180, +365
- GVHD Relapse Free Survival (GRFS) at 1 year
- Relapse Free Survival (RFS) at 1 year
- Overall survival (OS) at 1 year

4.6 Ancillary studies

Biological sampling will be performed at each center and samples will be stored at -80°.
Analyses will be performed at the end of specimens' collection and after study end (after the second phase, enrolment of 350 patients).
Analyses for clinical management of malnutrition, infections, transplant monitoring and GVHD will be performed according to clinical practice. If GVHD is suspected, biopsy of the target organ is suggested for histological characterization and future studies.

4.6.1 Fecal sample collection and biomarker detection

Participants in the clinical study will receive instructions and a special kit for self-collection of feces. The feces will be placed in a dedicated stool-collector tube with a spoon, packed in a soft-film bag, and stored at - 20 °C until delivery to the collection point. Samples will be then stored at -80 °C until used for analysis.
A small amount of biological samples will be processed according to the manufacturer's instructions to test the level of Zonulin-1 (ZO-1) and Calprotectin in feces. ZO-1 is a protein involved in the regulation of tight junctions between intestinal cells, while Calprotectin is a neutrophilic protein released during inflammation. Their presence in stool is often used as a marker of intestinal permeability and inflammation. These markers will be evaluated by means of specific ELISA detection kits designed for stool samples and research use only.

4.6.2 Microbiome analysis

Microbiome analysis will be carried out through a metagenomic approach. Bacterial DNA will be extracted from samples by conventional methods and amplification of the region of interest (V3 to V4 region of bacterial 16S DNA) will be carried out using specific primers. Libraries obtained from the patient's sample through Illumina's 16S metagenomic protocol will be grouped together, so each sample will be equally represented in the pool. Sequencing will take place on a MiSeq device (Illumina). Bioinformatic analysis and AI-driven biostatistical analysis will provide us information as the taxonomic assignment and phylogenetic analysis of each sample and will allow us to fully evaluate microbiome composition.

4.6.3 Blood sample collection and biomarker detection

Participants will undergo fasting venous blood sampling by qualified medical personnel in disposable plastic vacuum tubes with anticoagulating agents. Blood samples will be then processed to obtain a plasmatic fraction by centrifugation.
Specific biomarkers related to intestinal permeability such as ZO-1 and LPS-Binding Proteins (LBP) will be measured in human plasma with specific human ELISA kits.
LBP is involved in the immune response to LPS and elevated levels of LBP in blood may indicate the presence of LPS outside the intestinal lumen, suggesting increased permeability. The measurement of zonulin-1 and LBP levels in plasma has shown promise in clinical settings as potential markers of leaky gut. Elevated levels of these biomarkers may be associated with various gastrointestinal disorders, autoimmune conditions, and systemic inflammation. Monitoring changes in zonulin-1 and LBP levels over time can offer valuable insights into the dynamics of intestinal barrier function and help guide therapeutic interventions aimed at restoring gut integrity.
In addition, a panel of pro-inflammatory cytokines will be tested by using a Magnetic Luminex High Performance Assay that simultaneously profiles Human cytokines expression in different plasma samples. This will allow us to use a limited amount of plasma and optimize this task.
Biomarkers analysis: IGF-1 (if available), Citrulline (if available), lymphocyte subpopulations, Vitamin D, will be collected according to clinical indications.

All samples will be centralized. The various samples collected (whole blood, plasma, faecal sample) will be stored at -80; at interim analysis or at the end of the study they will be sent to the Brescia centre, which will proceed with the biological analysis.
The cost of shipment will be borne entirely by the Promoter.

4.6.4 Body Impedance Assessment (BIA) e Dual Energy X-ray Absorptiometry (DEXA)

BIA (where available): "The Body Impedance Assessment is a method used to measure the body's composition, typically through the analysis of electrical impedance. This technique involves passing a low-level electrical current through the body and measuring the resistance and reactance encountered. The compartments measured include body cell mass, fat mass, extracellular tissue, and fat-free mass". Akern BIA 101 BIVA PRO will be used at our institution to perform BIA analysis.
Following parameters will be registered:

- PA: phase angle
- TBW: total body water composed by intracellular water (ICW) and extracellular water ECW.
- FFM: fat free mass
- BCM: body cell mass
- FM: fat mass
- BMR: basal metabolic rate
- MM: muscle mass

If BIA is not available, the body composition can be detected with DEXA.

DEXA: body composition will be performed by measuring bone mineral density, lean tissue mass, and fat mass using low-dose X-rays emitted from two energy sources (Not mandatory).

4.6.4 Patients' reported outcomes (PRO) questionnaire

Following questionnaires will be collected at enrollment, after 28 days and after 100 days from transplantation:

4.6.4.1 Predimed (Appendix VI)

4.6.4.2 SF-36 (Appendix VII)

4.6.4.3 SAT-P (not mandatory)

5. Sample size and Study Population

5.1 Sample Size

Two step sequential model will be applied to confirm superiority in the experimental arm for the principal outcome (malnutrition) and for the explorative secondary immunological effects on acute GVHD.
In the first phase 214 patients will be enrolled in a prospective multicenter, randomized, interventional study, assuming a power of 80%, with a superiority target of severe malnutrition (PG-SGA C at +28 days) defined as a reduction from 70% (expected in the BST arm) to 50% (in the experimental arm), margin 0.05, with an expected drop-out due to dysgeusia or oral intolerance of 15%.
In the second phase 136 more patients will be enrolled to define a superiority also in the secondary explorative

immunological outcome (GI aGVHD CI reduction from 25 to 12.5% at 100 days in the experimental arm). An interim analysis will be performed after 100 patients to avoid futility if % of malnutrition at +28 days of the whole population will be under 60% and the CI of GI aGVHD of the whole population will be under 20% (https://clincalc.com/stats/samplesize.aspx).
Ratio of patients undergoing myeloablative or non-myeloablative conditioning will be 1:1 in both arms to standardize the intervention (according to TCI score >2[19]). Even more, for the same reasons, post transplant Cyclophosphamide will be allocated in a 1:1 ratio in both arms.
The study is powered also for the secondary outcome "reduction of grade II-IV MAGIC aGVHD": a significant reduction of 15% (if the cumulative incidence of grade II-IV MAGIC in the control arm will be >35%) in CI of grade II-IV aGVHD is warranted by the second step of enrolment when at least 150 patients per arm are included.
Analysis will be carried out in an intention to treat analysis and per protocol to explore adherence to treatment and percentage of patients requiring NGT enteral feeding.
The high drop-out incidence is expected also due to critical patients' conditions after high dose chemotherapy or radiation which might implicate several side effects i.e: taste perception alteration, oral mucositis, GI tract intolerance, mood alteration and, consequently, increase patient's anorexia and reduce his willingness to eat.
Adverse events will be registered according to EU law for food for special medical needs.

5.2 Statistical analysis

The characteristics of the study arms and the endpoints will be reported through descriptive statistics, with categorical data presented with frequencies and percentages, while continuous data with means, standard deviations, median and range.
Associations between response to experimental treatment with nutritional and immunological outcomes will be assessed with the Fisher's exact test and/or the chi-square test. OS, GRFS and RFS will be evaluated with Kaplan-Meier estimator. Log-rank test will be used to assess differences among subgroups. A Gray model for competing risks will be utilized for cumulative incidence of aGVHD, cGVHD, NRM and RI calculation. Death without the event of interest will be considered as a competing event. For these endpoints, Gray test will be used to assess differences among subgroups. Uni and multivariate analysis will be carried out by Cox proportional hazard regression or Fine-Gray hazard regression for competing risks, as appropriate.

5.3 Study duration

Study duration will be 2 years and 1 month for the first phase (214 patients) and 4 years for the second phase (all 350 patients) according to the centers' capacity of enrollment. End of study will be programmed after 12 months from the last patient enrolled (primary and secondary outcomes).
The study will be performed in 4.5 years from the first patient enrolled according to the following times:

- 36 months for enrollment (from the first patient)
- 12 months of follow up
- 6 months for statistical analysis, drafting of the final report and paper.

5.4 Patient Population

Adults aged more than 18 years old, undergoing alloHSCT. Myeloablative or non Myeloablative conditioning, Matched Related, Matched Unrelated, Haploidentical allo-HSCT, peripheral blood, bone marrow or cord blood stem cells as source are all permitted.

5.4.1 Inclusion Criteria

- Intact intestinal tract

- Life expectancy more than 12 weeks
- Allogeneic stem cell transplantation
- Signed informed consent

5.4.2 Exclusion Criteria

- Active hematological disease at the beginning of conditioning
- Personal history of inflammatory bowel diseases
- Personal history of bowel resection
- Personal history of gastric bypass procedures
- Enrolment in a competitive prospective study (malnutrition or GVHD as primary outcome)
- Subjects with known hypersensitivity to milk proteins or components of Modulen-IBD

6. Treatment plan

6.1 Nutritional assessment at enrolment

Nutritional and biological assessment will be carried out according to *Table 1*:
At admission (enrollment) patients will be assessed through:

- Anthropometric measures (BW, height, BMI, bicipital and abdominal circumferences)
- PG-SGA and GLIM criteria
- Biomarkers (microbiome analysis, butyrate, IGF-1, citrulline, fecal calprotectin, zonuline, amphiregulin)

Nutritional assessment with PG-SGA will be performed twice weekly until discharge, at + 28 and +100. GLIM criteria will be performed only at + 28 and +100.
Biomarkers will be assessed at enrolment (before conditioning), at +14, at +28, at +100 (Flow Chart).

6.2 Interventional plan

6.2.1 General recommendations

All the patients will be evaluated according to EBMT handbook (2019, adapted)[20]:
1. Early involvement of dietitians and nutritional services
2. Consider placement of NGT in case of defective oral calories intake <75% for more than 3 days.
3. Standardized monitoring of nutritional intake: calories intake should be defined twice weekly according to diet adherence (according to canteen calories tables and self-reporting food waste analysis - ***Appendix I***), amount of dextrose infusions per day.
4. Nutritional reassessment twice weekly using anthropometric data and PG-SGA; GLIM criteria, instead, will be submitted at +28 and +100.
5. Discontinuation of nutritional support if oral intake is more than 50% of TDEE, for 3 consecutive days at any time, but in any case, after day +28.

6.2.3 PG-SGA

The Patient-Generated Subjective Global Assessment (PG-SGA) is a nutritional assessment composed by two components[5]:

- the patient-generated component that was designed to be completed by the patient and to reflect approximately 80–90% of the score
- professional component that was completed by the professionist (physician, dietitian, nurse...)

The patient generated component (**Appendix II**) consists of four boxes: box 1, questions regarding body weight (scored 0–5); box 2, food intake (score 0–4); box 3, symptoms affecting oral food intake (scored 0–23); and box 4, regarding activities and function.
The professional component (**Appendix III**) consists of four worksheets: scoring weight loss; disease and its relation to nutritional requirements; metabolic demand (fever, fever duration, corticosteroids) and physical exam (muscle status, fat stores, fluid status).
PG-SGA total numeric score provides professionals with clearer guidelines as to the level of medical nutrition therapy needed in a given case, while the A (well-nourished); B (moderately malnourished); or C (severely malnourished) rating provides an overall picture of a patient's current status.
A higher PG-SGA score indicates an increased risk of deterioration in nutrition status, and according to this tool, the cut off point of ≥9 indicates a critical need for nutrition intervention and/or symptom management.
Informations about PG-SGA and PG-SGA calculator are available at https://pt-global.org/pt-global/

6.2.4 GLIM criteria

Global Leadership Initiative on Malnutrition (GLIM) proposed diagnostic criteria for malnutrition[21]. The GLIM includes a combination of phenotypic (percentage weight loss, low body mass index, reduced muscle mass) and etiologic (reduced food intake or assimilation, acute or chronic inflammation) criteria for the diagnosis of malnutrition. The presence of at least one of these following criteria identifies malnutrition. The remaining participants were categorized as well-nourished (**Appendix IV**).

Phenotypic and etiologic criteria for the diagnosis of malnutrition.

Phenotypic Criteria[g]			Etiologic Criteria[g]	
Weight loss (%)	Low body mass index (kg/m^2)	Reduced muscle mass[a]	Reduced food intake or assimilation[b,c]	Inflammation[d–f]
>5% within past 6 months, or >10% beyond 6 months	<20 if < 70 years, or <22 if >70 years Asia: <18.5 if < 70 years, or <20 if >70 years	Reduced by validated body composition measuring techniques[a]	≤50% of ER > 1 week, or any reduction for >2 weeks, or any chronic GI condition that adversely impacts food assimilation or absorption[b,c]	Acute disease/injury[d,f] or chronic disease-related[e,f]

6.2.5 Total Daily Energy Expenditure (TDEE)

Total Daily Energy Expenditure will be calculated as reported in the table 2 (or if available based on calorimetry, BIA or according Harris-Benedict formula).

Table 2				
BMI (kg/mq)	PG-SGA A	PG-SGA B	PG-SGA C	Calories by Modulen IBD® of TDEE

if BMI < 20	40 kcal / kg	42 Kcal / Kg	44 kcal /kg	20%
if BMI 20-24.9	35 kcal / kg	39 kcal / kg	42 kcal / kg	15%
if BMI 25 -29.9	30 kcal / kg	33 kcal / kg	36 kcal / kg	12%
if BMI > 30	25 kcal / kg	28 kcal / kg	30 kcal / kg	10%
	TDEE			

According to TDEE calculation nutritional intervention will be added to food daily oral intake. Enteral route should be preferred[20].

6.2.6 Type of available nutritional interventions - definitions

Food for Special Medical Purposes: food specially processed or formulated and intended for the dietary management of patients, including infants, to be used under medical supervision; it is intended for the exclusive or partial feeding of patients with a limited, impaired or disturbed capacity to take, digest, absorb, metabolize or excrete ordinary food or certain nutrients contained therein, or metabolites, or with other medically-determined nutrient requirements, whose dietary management cannot be achieved by modification of the normal diet alone (Regulation UE 609/2013).
Oral nutritional support (ONS): additional snacks rich in proteins and energy, protein or calories, additional protein and energy drinks, enrichment of main courses (superfood, potentiated food)
Enteral Nutrition (EN): special liquid food mixtures containing protein, carbohydrates, fats, vitamins and minerals given through NGT (ASPEN 2021).
Parenteral Nutrition (PN): intravenous administration of nutrition, which may include protein, carbohydrate, fat, minerals and electrolytes, vitamins and other trace elements for patients who cannot eat or absorb enough food through tube feeding formula or by mouth to maintain good nutrition status (ASPEN 2021).
The experimental treatment is Modulen-IBD®, a food for special medical purpose, polymeric, enriched with TGF-beta. If the patient refuses the experimental supplementation, naso-gastric tube (NGT) will be proposed to ensure the correct intake of Modulen-IBD® supplementation.
If the patient refuses, not tolerates, or there are contraindications to NGT placement, best supportive therapy will be warranted as reported below (BST).

6.3 Experimental arm - MODULEN-IBD ® supplementation

In the experimental arm Modulen-IBD will be proposed to all randomized patients in order to prevent malnutrition. From hospital admission to day +28 calories by Modulen-IBD® will integrate oral diet according to BMI and PG-SGA (Table 2):

- 20% of calories by Modulen IBD® of TDEE if BMI is < 20 kg/mq
- 15% of calories by Modulen IBD® of TDEE if BMI is between 20 and 24,9 kg/mq
- 12% of calories by Modulen IBD® of TDEE if BMI is between 25 and 29,9 kg/mq
- 10% of calories by Modulen IBD® of TDEE if BMI is > 30 kg/mq

Then, according to table 2 and to twice weekly monitoring of PG-SGA and BMI. GLIM criteria will be assessed at +28 and +100
One scoop provides 8,3 grams, which corresponds to 41.08 kcal.

6.3.1 Oral administration

Once reconstituted with bottled water according label instructions and at a caloric concentration of ≤1 kcal/ml, the supplement could be flavored according to the patient's tastes with barley coffee or decaffeinated coffee or cocoa. It is recommended to take in 2-3 portions to be taken throughout the day.
Reconstitution will be performed according to technical specifications (Appendix V).
One 400g MODULEN® IBD tin provides 2000 kcal. The dosage of MODULEN® IBD is dependent on the age, weight and clinical condition of the patient. The recommended feed concentration is 1 kcal/ml (20%). As a guide, MODULEN® IBD can also be concentrated to provide 1.25 kcal/ml (25% concentration) or 1.5 kcal/ml (30% concentration) but additional fluid should be advised.
Shelf life of 24 months from date of manufacture when stored at room temperature. Consume the contents within 4 weeks of opening. Once reconstituted, use within 6 hours at room temperature or 24 hours if refrigerated.
PREPARATION INSTRUCTIONS (For healthcare professional use only)
1. Wash hands thoroughly. Follow the mixing table and select the volume required.
2. Measure cool boiled or bottled water (room temperature) and pour into a clean bowl or container.
3. Scoop and level the desired amount of powder using the scoop in the tin or weigh in grams.
4. Add the powder to the water and immediately stir until well mixed.
5. After use, store the scoop inside the can.

6.3.2 Nasogastric Tube (NGT) route

Placement of a small NGT (max 8-10 fr.) is recommended according to the EBMT handbook. Food assumption is encouraged even when NGT is placed. In case of NGT placement, the amount of calories by tube is the difference between TDEE and the amount of calories assumed with food.
Modulen IBD® will be prepared and administered in 100-250 ml boluses (every 4-6 hours) to ensure the stability of the product.
If a patient refuses food, EN as polymeric standard, isocaloric, isoproteic, +/- fibers, 280-320 mOsm/L formula should be used. **In this case the amount of calories covered by Modulen-IBD® should be at least 20% of TDEE.**

6.4 Control arm - Best Supportive Treatment (BST)

Nutritional support in patients randomized to BST should be carried out according to EBMT-Handbook standards. If the patient's caloric intake is less than 75% of TDEE for 3 days nutritional intervention is warranted and calculated according to BMI and PG-SGA: TDEE will be assessed at least twice weekly and daily calories amount will be calculated. If the patient could not reach the TDEE amount with food ONS or PN will be added according to clinical conditions.
ONS: ONS should ensure the same amount of caloric intake of the experimental treatment in addition to usual food assumption. If patients could not assume the right amount of calories with ONS and refuse NGT, parenteral nutrition is permitted. Daily caloric/protein intake with parenteral nutrition should be registered.
PN:: 3-1 formulations with a 1.1 Kal/ml content should be preferred (ex. Smofkabiven®, Olimel®) through a central line. The choice of PN type is according to the center's policy and used in combination with food or ONS assumption. Total Parenteral Nutrition should be discouraged[20] except for clinical indications.

6.5 Complementary nutritional supports

All the patients should receive complementary nutritional support as described below:

- Oral water (if possible): 1 L/mq
- Vitamins and oligo-elements: daily Cernevit® 1 fl from day +1 to +28 or to discharge, vit. K 1 fl weekly, vit. D 25000 IU weekly

Use of probiotics (without lactose) is permitted (and should be registered on CRFs) in case of diarrhea and/or intestinal GVHD. Other probiotics use should be specified.

7. Safety monitoring and ethical issues

7.1 Safety

Safety monitoring will be conducted according to clinical practice for FSMP, but toxicity will be classified according to *The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0*.
Document can be downloaded from the following website:
https://www.eortc.be/services/doc/ctc/CTCAE_v5_Quick_Reference_5x7.pdf"https://www.eortc.be/services/doc/ctc/CTCAE_v5_Quick_Reference_5x7.pdf

7.2 Safety monitoring

Safety monitoring will be conducted according to clinical practice by Safety Monitoring Board (DSMB). Any AE or SAE will report within 24h to Pharmacovigilance.

7.2.1 Definitions of Adverse Events

According to Regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 for definition of adverse events, adverse reactions and reporting including causality.
For the purpose of this protocol adverse events are classified into the following categories:

- Adverse Event (AE): Adverse event' means any untoward medical occurrence in subject to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this treatment;
- Adverse Drug Reaction (ADR): is "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man". In this description it is of importance that it concerns the response of a patient, in which individual factors may play an important role, and that the phenomenon is noxious (an unexpected therapeutic response, for example, may be a side effect but not an adverse reaction).
- Serious Adverse Event (SAE): Serious adverse event' means any untoward medical occurrence that at any dose requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in congenital anomaly or birth defect, is life-threatening, or results in death;
- Unexpected Serious Adverse Event (USAE): means a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information;
- Unexpected Adverse Event: An unexpected adverse event is an event, the nature or severity of which is not consistent with applicable product information.

7.2.2 Safety Reporting

7.2.2.1 Reporting of adverse events

Data from all subjects who receive study treatment will be included in the safety analyses. The severity of the toxicities will be graded according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) whenever possible. In the by-subject analysis, a subject having the same event more than once will be counted only once.

Adverse events will be summarized by worst NCI CTC grade and classified by System Organ Class (SOC) and preferred term (PT). Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTC Grade 3 or Grade 4, study-drug-related events, and serious adverse events will be summarized separately.

7.2.2.2 Exceptions from AEs reporting

The following events are expected following stem cell transplant and will be recorded if of grade≥ 3 (clinical) or ≥ 3 (laboratory):

- nausea and vomiting;
- stomatitis, mucositis and diarrhea;
- hair loss;
- fever of undetermined origin during neutropenia;
- anemia, leucopenia and thrombocytopenia:
- fatigue during hospitalization for transplantation or related to anemia;
- loss of appetite;
- cytopenia;
- minor bleeding diathesis during thrombocytopenia;
- headache;
- hypo-hypertension;
- vasomotor effects including flushing;
- dizziness;
- allergic reactions;
- electrolytes disturbances;
- liver and renal function disturbances;
- chills, tachycardia, fluid retention and pyrexia during the days of Anti-thrombocyte globulin administration.

7.2.2.3 Reporting of adverse events and serious adverse events by the investigator to the sponsor

- The investigator should record and document adverse events or laboratory abnormalities identified in the protocol as critical to the safety evaluation and report them to the sponsor in accordance with the reporting requirements and within the periods specified in the protocol.
- The investigator shall record and document all adverse events, unless the protocol provides differently. The investigator shall report serious adverse events to the sponsor without undue delay but not later than within 24 hours of obtaining knowledge of the events, unless, for certain serious adverse events, the protocol provides that no immediate reporting is required. Where relevant, the investigator shall send a follow-up report to the sponsor to allow the sponsor to assess whether the serious adverse event has an impact on the benefit-risk balance of the clinical trial.
- The sponsor shall keep detailed records of all adverse events reported to it by the investigator.

- If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational FSMP that occurs after the end of the clinical trial in subjects treated by him or her, the investigator shall, without undue delay, report the serious adverse event to the sponsor.

7.2.2.4 Adverse Events and Causality

- Medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the product, shall be subject to the same obligation to report as adverse reactions.
- In determining whether an adverse event is an adverse reaction, consideration shall be given to whether there is a reasonable possibility of establishing a causal relationship between the event and the investigational medicinal product based on an analysis of available evidence.
- In the absence of information on causality provided by the reporting investigator, the sponsor shall consult the reporting investigator and encourage him to express an opinion on this issue. The causality assessment given by the investigator shall not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor shall be provided with the report.

7.2.3 Information for the reporting of SUSARs

7.2.3.1 Responsibility of the Investigators

The investigator is responsible for reporting to the Trial Coordinator all serious adverse events in relation to subjects treated by him in the clinical trial. The investigator does not need to actively monitor subjects for adverse events once the trial has ended, unless provided otherwise in the protocol.
The investigator shall report all serious adverse events immediately to the sponsor. For reference safety information please contact the Safety Monitoring Board. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter.
The purpose of this obligation is to ensure that the Trial Coordinator has the necessary information to continuously assess the benefit-risk balance of the clinical trial.
Immediate reporting should allow the sponsor to take the appropriate measures to address potential new risks in a clinical trial. Therefore, the immediate report should be made by the investigator within a very short period and under no circumstances should this exceed 24 hours following knowledge of the serious adverse event.
The follow-up report should allow the sponsor to determine whether the serious adverse event requires a reassessment of the benefit-risk balance of the clinical trial, if the relevant information was not already available and provided in the initial report.
In the event of a notified death of a subject, the Investigator gives it communication to the Sponsor of the clinical trial and to the Ethics Committee providing any additional information required.

7.2.3.2 Responsibility of the Sponsor

The Trial Coordinator shall keep detailed records of all adverse events which are reported to him by the investigator or investigators.
The Trial Coordinator, through Pharmacovigilance, shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.
All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor.

Once a year during the clinical trial, the Trial Coordinator provides the competent authority and the Ethics Committee with a list of all the suspected serious adverse reactions that occurred during this period and a report on the safety of the subjects. "
The trial Sponsor guarantees that all relevant information relating to Suspected Adverse Reactions Unsuccessful Series (SUSAR), which they have lethal result for the subject of the experiment or put in danger of life, are registered and notified as soon as possible to the Ministry of Health, as well as to the Ethical Committee (s) concerned, and in any case within seven days of calendar (eg urgency procedure) since the Sponsor of the trial has become aware of the case, and that subsequent relevant information is communicated within eight days of the first report.
All other SUSARs are notified to the Ministry of Health and to the Committee (s) ethical / i interested, as soon as possible and in any case within fifteen days from the day on which the trial Sponsor learned about it for the first time.
The Trial Coordinator also informs all investigators by mail lists.
The Trial Coordinator records all the SUSARs of a medicine in the testing phase brought to his knowledge.
Once a year for the duration of the clinical trial, the Sponsor of the experiment provides to the Ministry of Health and Ethics Committees involved a list of all SAR suspects observed over the entire period and a report on the safety of the people subjected to clinical trials.

The contacts for Pharmacovigilance are:

ASST degli Spedali Civili di Brescia
farmacia.sperimentazioni@asst-spedalicivili.it
Dott.ssa Paola Rehmann
Tel +39 030 3998303

The information contained in the SUSARs shall at least include:
(a) a valid trial code;
(b) a sponsor study number;
(c) an identifiable coded subject;
(d) an identifiable reporter;
(e) a SUSAR;
(f) a suspect investigational medicinal product (including active substance name-code);
(g) a causality assessment.
In addition, in order to properly process the report electronically, the following administrative information shall be provided:
(a) the sender's (case) safety report unique identifier;
(b) the receive date of the initial information from the primary source;
(c) the receipt date of the most recent information;
(d) the worldwide unique case identification number;
(e) the sender identifier.

7.3 Ethical issues

The study will be conducted in accordance with the ethical principles derived from the Declaration of Helsinki, the CGP and regulations.

Before starting the study, the protocol will be sent to the Ethics Committee, in accordance with the current legislation on interventional study.

7.3.1 Informed consent

Each local Principal Investigator is responsible for ensuring that all patients enrolled in this study signed the Informed Consent to participate in the study before being enrolled in the study, compiled according to the GCP, which informs patients of their participation in the study, the type of study, data processing, their rights and how much they involve participation in clinical study.

7.3.2 Personal data and protection

Patient data will be processed, managed and stored in full compliance with the Regulation (EU) 2016/679 and in accordance with all applicable legislation. At any time and completely free of charge, every patient can have access to their data, request their modification or cancellation or oppose their use.
The owner of the processing of personal data is ASST Spedali Civili di Brescia as a Sponsor. As part of the study, the collected data will be processed anonymously. The Principal Investigator is responsible for data collection according to the GCP guidelines. Access to clinical data should be reserved exclusively for authorized personnel. The investigators will have to verify and ensure the strict confidentiality of documents that could identify patients in compliance with the regulations on privacy and the processing of personal data and must allow the monitoring of clinical data related to the study, IRB/IEC reviews and inspections by the regulatory authorities in compliance with the regulations in force in Italy, ensuring direct access to the patient's clinical documentation guaranteeing maximum collaboration.

8. Definitions and outcomes

8.1 Definitions

Food for Special Medical Purposes: food specially processed or formulated and intended for the dietary management of patients, including infants, to be used under medical supervision; it is intended for the exclusive or partial feeding of patients with a limited, impaired or disturbed capacity to take, digest, absorb, metabolize or excrete ordinary food or certain nutrients contained therein, or metabolites, or with other medically-determined nutrient requirements, whose dietary management cannot be achieved by modification of the normal diet alone (Regulation UE 609/2013).
ONS (oral nutritional support): additional snacks rich in proteins and energy, protein or calories, additional protein and energy drinks, enrichment of main courses (superfood, potentiated food)
Enteral Nutrition: special liquid food mixtures containing protein, carbohydrates, fats, vitamins and minerals given through NGT (ASPEN 2021).
Parenteral Nutrition: intravenous administration of nutrition, which may include protein, carbohydrate, fat, minerals and electrolytes, vitamins and other trace elements for patients who cannot eat or absorb enough food through tube feeding formula or by mouth to maintain good nutrition status (ASPEN 2021).

8.2 Outcomes:

Nutritional support will be reported twice weekly according to table 2 and TDEE.
Daily mandatory measures:

- *Amount of Modulen-IBD® expressed in Kal*
- *Amount of calories intake (food intake and percentage of food waste auto-evaluation)*
- *Amount of ONS/Enteral Nutrition/Parenteral Nutrition/intravenous fluids volume and calories*
- *Amount of oral water intake*
- *Body weight*

- *Fluid balance (IN/OUT)*

8.2.1 Malnutrition

Malnutrition will be evaluated according to GLIM criteria and PG-SGA at enrolment, together with anthropometric measures (weight and BMI), circumferences (arm, waist, waist-to-hip ratio), BIA o DEXA o calorimetry (if available).
PG-SGA will be assessed twice a week.
Body weight will be assessed daily.

8.2.2 GVHD

GVHD will be classified according to MAGIC Criteria and IBMTR for acute GVHD and NIH criteria for chronic GVHD. eGVHD app is recommended to classify GVHD and register events (https://www.uzleuven.be/egvhd)[22].
Date of onset will be registered.
Each GVHD episode should be registered on CRF according to the downloaded pdf from eGVHD app.

8.2.3 Feasibility of NG enteral feeding

Feasibility of nasogastric enteral feeding will be indagated:Date of placement and removal of NG enteral tube (NGT) will be registered. Side effects of NGT will be registered. Causes of NGT removal or displacement will be registered.

8.2.4 Microbiome evaluation

Fecal samples will be collected before alloHSCT and at + 28 days and at +100 days.
The gut microbiome will be assessed before alloHSCT and at +28 days and +100 days. Next-generation metagenomics sequencing will allow the assignment of bacterial sequences to different taxonomic levels. The microbiome will be analyzed in terms of diversity of commensal/pathogenic bacterial populations (dysbiosis) and in terms of relative abundance (%) of some bacterial genus associated with transplant complications and outcomes and which could serve as a predictive indicator.

8.2.5 Body composition by BIA/DEXA at baseline, +28 days and day + 100 days

If BIA is available following parameters will be registered at baseline, +28 days and +100 days:

- PA: phase angle
- TBW: total body water composed by intracellular water (ICW) and extracellular water ECW.
- FFM: fat free mass
- BCM: body cell mass
- FM: fat mass
- BMR: basal metabolic rate
- MM: muscle mass

If DEXA is available following parameters will be registered at baseline, +28 days and +100 days

- Total body fat percentage
- Total lean percentage
- Regional composition
- Bone Density

8.2.6 Duration of hospitalization

Days of hospitalization in the first 100 days will be registered.

8.2.7 Overall survival (OS) at 1 year post-transplant.

OS is defined as the time from transplant to the date of death due to any cause or to the last date the patient was known to be alive (censored observation) or to the date of the data cut-off for final analysis.

8.2.8 The cumulative incidence of Transplant Related Mortality (TRM)

TRM will encounter all deaths occurring due to one of the following: GVHD, graft failure, cardiac toxicity, infection, EBV proliferative disease, pulmonary toxicity, Veno-occlusive disease, other HSCT-related causes.

8.2.9 One year probability of GRFS (GvHD free, relapse free survival)

GRFS events are defined as occurrence of grade III-IV acute GvHD, chronic GvHD requiring systemic immunosuppressive treatment, disease relapse, or death from any cause during the first 12 months after HSCT.

8.2.10 Relapse free survival

Relapse and Residual Disease: testing for recurrent malignancy in the blood, marrow or other sites will be used to assess relapse after transplantation. Date of relapse will be registered.

8.2.11 Allo-SCT Engraftment

Neutrophil engraftment: the first of three days with neutrophil count > 0.5 x 10^9/L. Platelet engraftment: the first of three days Platelets (without transfusion) > 20 x 10^9/L.
Lost graft: neutrophils increase to >0.5x109/l and subsequently decrease to a lower level until additional treatment to obtain engraftment is given (secondary graft failure).
Poor graft function (PGF): PGF is diagnosed in patients with at least two between Hb<10 g/dL, neutrophil count <1.0x109/L, platelet count <30x109/L for at least 2 consecutive weeks beyond day +14 post-transplant, with transfusion requirement, associated with hypoplastic-aplastic bone marrow, in the presence of complete donor chimerism and in the absence of severe GVHD and relapse.
Graft failure: a) Primary graft failure is defined as < 5% donor chimerism. Secondary graft failure (graft rejection) is defined as initial recovery followed by neutropenia with <5% donor chimerism. b) Rate of graft rejection and graft failure by day +100, and 1 year after transplantation.

8.2.12 Biomarkers

Following biomarkers will be studied on stored fecal samples:

- Zonulin-1 (ZO-1)
- Calprotectin
- Short Chain Fatty Acids

Following biomarkers will be studied at the end of the study on stored blood/plasma:

- Butyrate
- IGF-1
- Citrulline
- Zonuline
- Amphiregulin
- Short Chain Fatty Acids

Lymphocyte subpopulations will be collected and performed at +28 and +100 days according to center capability.

8.2.13 Patients' reported outcomes

At enrolment and 100 days after transplantation SF36, ... and "Predimed" questionnaire will be administered to enrolled patients. Descriptive analysis will be performed. (**Appendix VI)**

9. Keywords

Malnutrition, Graft versus host disease, Intestinal bowel disease, TGF-β2, Food for Special Medical Purposes, allogeneic Hematopoietic Stem Cell Transplantation.

10. Medical Monitoring

It is the responsibility of the local institutional Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

11. Trial management

11.1 Registration of patients

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent.
The patients are screened for entry into the study. For those subjects who fail screening the reason(s) for exclusion must be recorded in the subject's source documents.
On the day of registration, the patient must meet all inclusion criteria and no exclusion criteria should be present (see section Eligibility Criteria).
The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.
Once signed written consents will be obtained from either patient, the patient is ready to be enrolled in the study and will be randomized according to protocol.
Registration data will be collected and managed using RedCap.
After entering the Registration in e-CRF an e-mail will be sent immediately by the electronic web-based system to the center notifying the unique patient number (UPN) assigned to the patient and the arm of randomization.

11.2 End of participation of the patient

The participation of the patient in the study is regularly terminated 1 year after transplantation or in case of death.

11.3 Subject Withdrawal or Discontinuation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care.
If the subject withdraws from the trial and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected.

Subjects who have been discontinued from study treatment but have not withdrawn consent should continue to be followed as "in-study, off treatment" patients.
Treatment with study FSMP is discontinued when any of the following occurs:

- adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of experimental treatment;
- general or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator;
- major violation of the study protocol;
- withdrawal of consent;
- lost to follow up;
- death;
- in the Investigator's opinion, it is in the subject's best interest;
- the study is terminated by Sponsor of study or Principal Investigator;
- lack of compliance with administration of study medication or with protocol procedures such that reliable safety and efficacy assessments are compromised.
- A discontinuation must be reported immediately to the Sponsor of study and in Case Report Form (CRFs). The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for such subjects, and document the course of the subject's condition.

11.4 Deaths occurring during the study

The death of any subject that occurs during the period of study must be reported immediately. The cause of death should be reported in e-CRFs.

11.5 End of enrollment

Enrollment may then terminate after the evaluable 350th patient will be enrolled (175 per arm).

11.6 End of study

The follow-up according to the protocol is 2 years and 1 month for the first phase according to the primary outcome (severe malnutrition according to PG-SGA). One year more and 12 months of follow-up are expected for the second phase.
Study duration will be 48 months for patient accrual (starting from the first patient enrolled) for all transplant patients (36 months of enrolment in both phases and 12 months of follow-up for all the studied outcomes) and 6 months for statistical analysis, drafting of the final report and paper. The study will end when the 350th patient will be evaluated for the last follow-up.
In addition, the whole study can be discontinued by the coordinating investigators in case of undercurrent illness, adverse events, protocol violation, or toxicity considered excessive or in case of futility (sample size and study population). Moreover, patients may withdraw from the study upon their request at any time, the investigator may discontinue the patient treatment if toxicity is considered excessive or if there is evidence of disease progression while under treatment.
In summary, the study will be performed in 4.5 years from the first patient enrolled.

11.7 Data collection

Investigators must enter the information required by the protocol into the electronic Patient Data Collection Forms (e-CRFs). The CRFs will be electronically forwarded to the study data management center. One print-out version of the CRF will be retained at the investigational site. Once the CRFs are received by the data management center, their receipt will be recorded, and they will be forwarded to the responsible data management staff for processing.

11.8 Data Management and Quality Control

Database management and quality control for this study are under the responsibility of the ASST Spedali Civili di Brescia.
The Clinical Trial Center will act as Data Management Center and quality control, providing for comprehensive statistical analyses, data management, and administrative support throughout the course of the study. At the Clinical Trial Center, expert personnel will review the e-CRFs for completeness and accuracy. Errors, omissions or questions will be entered on data query forms, which will be returned to the investigational site for resolution. After the investigator response is received at the Data Management Center, the resolutions will be entered into the database. A copy of the signed data query form will be kept with the print-out of the e-CRFs.
Quality control audits of all key safety and efficacy data in the database will be made at designated times during the study. When the database has been declared to be complete and accurate, the database will be locked and unblinded.
The study will use remote data-entry (RDE) on electronic case report forms (e-CRFs) that will be entered, transmitted and stored electronically. A print-out of the compiled e-CRFs will be stored at the investigational center and at the Coordinating Centre, to be used as a backup copy. Electronic signatures are required together with combined identification codes/passwords before access is granted to the computerized system and at the start of a data entry session. To guarantee the secrecy of the data, but also to avoid manipulation and loss of data, precautionary action (hardware and software) are taken.

11.9 Data Transmission and Protection

The study will use remote data-entry (RDE) on electronic case report forms (e-CRFs) that will be entered, transmitted and stored electronically. A print-out of the compiled e-CRFs will be stored at the investigational center and at the Coordinating Centre, to be used as a backup copy. Electronic signatures are required together with combined identification codes/passwords before access is granted to the computerized system and at the start of a data entry session.
To guarantee the secrecy of the data, but also to avoid manipulation and loss of data, precautionary action (hardware and software) are taken.
In particular:

- At the Coordinating Centre:
- access to data collected from the participating centers is reserved only to authorized members of Coordinating Centre
- the database is located on a server that is protected with a password, that is changed periodically
- access to the database is protected with a password and is only accessible by responsible persons of Coordinating Centre
- periodical back-ups will guarantee secure copies, to allow retrieval of both stored data and the data-collection system

- the patient is registered and identifiable with a code, to guarantee anonymity.
- At the participating Centre:
- Each Investigator will receive a personal digital certificate and a "username" and a "password". Only these investigators will be authorized to enter data on the e-CRFs.

11.10 Network

Network resources (GITMO Centers)
Two GITMO centers (Brescia, Cuneo, Reggio Emilia) will participate in the study on a competitive strategy. All the centers will be previously prepared by CRO to conduct the study according to GCP rules.
The CRO will manage the entire study according to study plan:

1. Patients enrollment and randomization
2. Study Registration
3. Submission to the local ethical committee
4. Statistical analysis

The experimental treatment will be delivered by DHL from the coordinating center for each patient enrolled within 24 hours.

12. Ethical and legal aspects

12.1 Ethical Conduct of the Study

The study will be conducted according to the principles of Good Clinical Practice (GCP) as reported in current Italian and European legislation.
The responsible investigator will ensure that this study is conducted in agreement with the declaration of Helsinki and the Italians laws and regulations, whichever provides the greatest protection of the patient. The protocol has been written and the study will be conducted according to the ICH Harmonized Tripartite Guideline for GCP, issued by the European Union. The responsible Local Ethical Committee approval must be obtained before starting the trial. A copy of the patient informed consent form must be submitted to the appropriate authority or committee, together with the protocol for written approval. Written approval of the protocol and informed consent by the responsible and appropriate authority or committee must be obtained prior to recruitment of patients to the study. The investigator must inform the appropriate authority or committee of subsequent protocol amendments, which must be approved by this one.

12.2 Responsibility

The ASST Spedali Civili di Brescia will act as the Sponsor and will be responsible for the Data Management Center and quality control, providing for data management and administrative support throughout the course of the study.
This trial is being organized under the auspices of GITMO, in that it involves the principal centers active in transplantation of any kind of hematopoietic stem cells (HSCT) in Italy.

12.3 Investigators' responsibility

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the EU Clinical Trial Directive 2001/20/EC and 2005/28/EC.
Investigators must enter study data in electronic CRFs. The Investigator will permit study-related monitoring visits and audits by the sponsor or its representatives, EC review, and regulatory inspection(s) (e.g., FDA, AIFA, ethics committee, etc), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.
The Investigator, or a designated member of the Investigator's staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to the sponsor representative so that the accuracy and completeness may be checked.

12.4 Ethics committee/IRB Approval

The Local Ethical Committee approval of the study must be obtained before starting the trial. The investigator must inform the appropriate authority or committee of subsequent protocol amendments, which must be approved by this one. The trial will not be initiated until the investigator obtains written approval of the study from the appropriate Ethics Committee/IRB. All correspondence with the Local Ethical Committee should be retained in the Investigator File Copies of IRB/IEC. Approvals should be forwarded to the Sponsor of Study (ASST Spedali Civili di Brescia). After the clinical trials office of ASST Spedali Civili di Brescia has received approvals it will proceed with the opening of the center to the registration of patients.
The Investigator is responsible for notifying the Ethics Committee of any serious deviations from the protocol, or anything else that may involve added risk to subjects.
Any advertisements used to recruit subjects for the study must be reviewed and approved by the Ethics Committee prior to use.

12.5 Protocol amendments

Any amendment to this protocol must be agreed to by the Principal Investigators and Sponsor. Written verification of EC approval will be obtained before any amendment, which affects subject safety or efficacy, is implemented.
Amendments that are administrative in nature do not require EC approval but will be submitted to the IRB/EC for information purposes.

12.6 Protocol deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was prepared) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the Investigator will notify the EC in writing of such deviation from protocol.

12.7 Informed Consent

Before enrolling in this study, the investigator is responsible for obtaining written informed consent and information forms from the patient, or legally acceptable representative, after adequate explanation of the aims and methods. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.
The acquisition of informed consent forms and information forms should be documented in the patient medical records, as required by ICH GCP, and the information and informed consent forms should be signed and personally dated by the patient, or a legally acceptable representative, and by the physician who conducted the information and informed consent discussion. The original signed information and informed consent forms should be retained in accordance with institutional policy, and a copy of the signed forms should be provided to the patient or legally acceptable representative.
All patients will be informed of the aims of the study, the potential benefit, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol, whenever he/she wants. This will not prejudice the patient's subsequent care. They will be informed as to the strict confidentiality of their data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. This must be done in accordance with the local regulatory requirements. Witnessed written informed consent must be obtained for all patients included in the study or their legally authorized guardian/representative, before they are enrolled. Record the name of the witness and the date that informed consent is obtained in the patient's hospital notes.

12.8 Subject confidentiality

Access to clinical data is exclusively reserved to authorized personnel only. Investigators will verify and ensure the strict confidentiality of patient records in compliance with standards on privacy and personal data by the Italian legislation. Patient names will never appear in any communication and/or correspondence. Personal names will be required to access original patient medical records for verification and monitoring of clinical data. It is mandatory to inform patients that their medical records could be verified without breach of confidentiality of personal data.
Regulatory authorities and/or IEC/IRB may request access to all source documents, data capture records, and other study documentation for one-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.
The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations (Low n. 675/1996 and amendments) and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).
The name of the patient will not be asked by the Sponsor. An identification number will be automatically attributed to each patient enrolled in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, date of birth will also be reported on forms.

12.9 Study Records Retention

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and

records be retained by the Investigator for as long as needed to comply with national and international regulations.
The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

12.10 Insurance Policy

Insurance coverage will be provided for each center participating in the study, as per local applicable law and regulation. Insurance conditions will meet good local standards, as applicable.

13. Experimental FSMP material and management

The Investigator Brochure of Modulen-IBD ® can be downloaded at the following URL:
https://www.nestlehealthscience.it/prodotti/modulen/ibd

14 Publication of study results

All data produced are property of study Sponsor (ASST Spedali Civili di Brescia). It is the responsibility of the study coordinating Centre to publish study results after its completion. Participating Centers are not allowed to publish single center experiences before publication of the multicentre study. Participating Centres and Authors will be listed according to their overall contribution to the study. Principal Investigator and/or Writing Committee will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to ASST Spedali Civili di Brescia at least 30 days before submission. The Writing Committee of the study will publish the final results of the trial. The Chairman of the Committee and ASST Spedali Civili di Brescia study coordinator must approve all publications, abstracts and presentations pertinent to the study presented at conferences and/or meetings. This applies to any data on the entire study population or patients' subgroups. Titles of manuscripts and/or abstracts should include the term "ASST Spedali Civili di Brescia". All manuscripts will also include an "Acknowledgments" section, which will mention all investigators who contributed to the study.

14.1 Authorship

The final report of the study findings will be written by the Study Coordinator in the light of analyses carried out at the Data Centre. An advanced draft of the manuscript will be submitted to the Data Centre for review by the study coordinator.

14.2 Responsibility for publication

Manuscript/s will be sent to major scientific journals after revision by the study coordinator.
All manuscripts will include an appropriate acknowledgment section, mentioning all Investigators who have contributed to the study, as well as supporting bodies. The Writing Committee, the Study coordinator and the Data Centre must approve all publications, abstracts and presentations based on patients included in this study. This is applicable to any individual patient registered in the study, or any subgroup of the study patients. Publications cannot include any analysis of any of the study end points unless the final results of the study have already been published by the Study Coordinator.

15 Abbreviations

FSMP Food for special medical purposes
PG-SGA Patient Generated Subjective General Assessment
GLIM Global Leadership Initiative on Malnutrition
BW Body Weight
BMI Body Mass Index
BIA Bioimpedance Analysis
GVHD Graft Versus Host Disease
RFS Relapse Free Survival
GRFS GVHD Relapse Free Survival
TDEE Total Daily Energy Expenditure
OS Overall Survival
DEXA Dual Energy X-ray Absorptiometry
MUD Matched unrelated donor
MRD Matched related donor
ONS Oral Nutritional Support
TDEE Total Daily Energy Expenditure
NGT NasoGastric Tube
BST Best Supportive Treatment
PN Parenteral Nutrition
EN Enteral Nutrition
PROMs Patients Reported Outcome Measures
NRM Non Relapse Mortality
IBD Inflammatory Bowel Disease
GI Gastro Intestinal
TR Treatment Ratio
AE Adverse Event
ADR Adverse Drug Reaction
SAE Serious Adverse Event
USAE Unexpected Serious Adverse Event

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