Title: A Single-Arm, Open-Label, Single-Center Phase I-II Study of the Safety and Feasibility of Sulforaphane in Promoting Early Hematopoietic Recovery After Umbilical Cord Blood Transplantation

NCT Number: SFN-UCBT-2025

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Clinical Study Protocol

Protocol Title	A Single-Arm, Open-Label, Single-Center Phase I-II Clinical Study on the Safety and Feasibility of Sulforaphane in Promoting Early Hematopoietic Recovery Following Umbilical Cord Blood Transplantation
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Version Number	2.0
Version Date	2025-07-07

Confidentiality Statement

Investigator's Statement

I hereby confirm that I have thoroughly reviewed this study protocol and acknowledge that it contains all necessary components for the proper conduct of the study. I fully understand my responsibilities associated with this protocol.I agree to perform all related duties in strict compliance with Chinese laws and regulations, the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and this study protocol. I affirm that no procedures outlined in this study will be initiated until the protocol has received approval from the Ethics Committee and informed consent has been obtained from the subject. Any modifications to the protocol require prior approval by the Ethics Committee before implementation, except when immediate action is necessary to eliminate an immediate hazard to the subject's safety, rights, and welfare. I understand and commit to adhering to all requirements regarding the maintenance and confidentiality of original source data.

Principal Investigator：　　Date：

Clinical Research Unit: Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College

Table of Contents

Abbreviations

Abbreviation/Acronym	Term
AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
Ara-C	Cytarabine
AST	Aspartate Aminotransferase
Bu	Busulfan
CR	Complete response
CRF	Case report form
CsA	Cyclosporine A
CY	Cyclophosphamide
DFS	Disease-free survival
EBV	Epstein - Barr Virus
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
FEV1	Forced Expiratory Volume in 1 second
Flu	Fludarabine
FVC	Forced Vital Capacity
GRFS	GVHD-free and relapse-free survival
GVHD	Graft-versus-host disease
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B virus
HCMV	Human Cytomegalovirus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HSC	Hematopoietic stem cells
HSPC	Hematopoietic stem cell transplantation
LVEF	Left Ventricular Ejection Fraction
MDS	Myelodysplastic Syndromes
Mel	Melphalan
MMF	Mycophenolate Mofetil
NIH	National Institutes of Health
NR	No response
NRM	Non-relapse mortality
NYHA	New York Heart Association
OS	Overall survival
PR	Partial response
RFS	Relapse-free survival

SAE	Severe adverse event
SFN	Sulforaphane
SS	Safety Set
TP-Ab	Treponema Pallidum Antibody
TRM	Transplant - related mortality
UCB	Umbilicol cord blood
UCBT	Umbilicol cord blood transplantation
ULN	Upper Limits of Nomal

1 Synopsis

Date of Protocol Synopsis	2025-07-07
Study Dietary Supplement Name	Antioxidant Sulforaphane
Clinical Trial Phase	I-II
Study Title	A Single-Arm, Open-Label, Single-Center Phase I-II Clinical Study on the Safety and Feasibility of Sulforaphane in Promoting Early Hematopoietic Recovery Following Umbilical Cord Blood Transplantation
Planned Study Period	2025-09-01 to 2027-12-31

Study Objectives:

Phase I: To evaluate the safety and feasibility of oral sulforaphane administration during the peri-infusion period in adults undergoing UCBT.

Phase II: To demonstrate the non-inferiority of neutrophil recovery time in patients receiving umbilical cord blood (UCB) units cryopreserved for ≥10 years with concomitant sulforaphane administration, compared to the efficacy observed in patients receiving UCB units cryopreserved for <10 years without sulforaphane.

Study Population:

1. Patients with high-risk hematologic malignancies: including AML, ALL, and high-risk MDS;
2. Age and Sex: ≥18 years old, no gender restriction;
3. Karnofsky score ≥70%, and Eastern Cooperative Oncology Group (ECOG) performance status ≤2.

Planned Sample Size:

Phase I will enroll 4 patients. Upon meeting the safety evaluation criteria in Phase I, Phase II will enroll 32 patients for observation.

Study Design Overview:

Umbilical cord blood (UCB) is rich in hematopoietic stem/progenitor cells and immune cells, and is used for transplantation in various hematologic diseases due to advantages such as lower HLA matching requirements and fewer transplant-related complications. As of March 2025, over 280,000 public UCB units are cryopreserved in 7 (8) public cord blood banks in China, with units cryopreserved for ≥10 years accounting for 26%, raising

concerns regarding their clinical utility. Our preliminary studies indicate that long-term cryopreservation impairs mitochondrial function in UCB hematopoietic stem/progenitor cells, leading to reduced reconstitution capacity and impaired megakaryocytic differentiation. Intervention with the antioxidant sulforaphane (SFN) can partially rescue this cryopreservation-induced functional impairment. These findings are based on studies in immunodeficient animals. Whether SFN intervention can promote hematopoietic reconstitution after transplantation using long-term cryopreserved (≥10 years) UCB in patients urgently requires clinical investigation. This project proposes a single-arm, open-label, single-center Phase I-II clinical study to evaluate the safety and feasibility of the dietary supplement SFN in promoting early hematopoietic recovery after UCBT. It aims to assess the safety and feasibility of SFN use during the peri-infusion period in adult transplant patients receiving long-term cryopreserved UCB, and to elucidate the impact of peri-infusion SFN use on neutrophil engraftment. This project will provide scientific guidance for promoting the clinical application of long-term cryopreserved UCB, and key data for optimizing UCBT strategies and expanding its application scope.

Inclusion Criteria （subjects suitable for inclusion in this study must meet all of the following criteria）:

1. Patients with high-risk hematologic malignancies: including AML, ALL, and high-risk MDS diagnosed according to World Health Organization (WHO) criteria;
2. Age and Sex: ≥18 years old, no gender restriction;
3. Karnofsky score ≥70%, and Eastern Cooperative Oncology Group (ECOG) performance status ≤2;
4. Selection of unrelated umbilical cord blood: Donor-recipient HLA high-resolution match ≥4/6, 7/10, and post-thaw CD34+ cell count ≥0.83 × 10^5/kg (recipient body weight). Furthermore, only UCB units cryopreserved for ≥10 years meeting the above criteria are available from Chinese public cord blood stem cell banks for the patient.

Exclusion Criteria (subjects who meet any of the following criteria will be excluded from participation in this study):

1. Patients with positive results for the following pathogens: Human Immunodeficiency Virus (HIV-1/2), Human Cytomegalovirus (HCMV-DNA), Epstein-Barr Virus (EBV-DNA), Hepatitis B (Hepatitis B surface antigen [HBsAg] positive or Hepatitis B virus DNA [HBV-DNA] positive), Hepatitis C antibody (HCV-Ab) positive, or Treponema pallidum antibody (TP-Ab) positive;
2. Active bacterial, viral, fungal, or parasitic infections judged by the investigator to be clinically significant at screening;
3. Availability of an HLA-identical willing donor and eligibility for allogeneic hematopoietic stem cell transplantation from that donor;
4. Prior history of gene therapy or allogeneic hematopoietic stem cell transplantation;
5. First-degree relatives with known or suspected familial cancer syndromes (including but not limited to hereditary breast and ovarian cancer syndrome, Lynch syndrome, familial adenomatous polyposis, etc.);
6. Diagnosis of a major psychiatric disorder or predisposition that would severely impair the ability to participate in the clinical study; or history of psychotropic drug abuse unable to abstain;
7. History of major organ impairment, including:
    (1) Hepatic impairment: Liver function tests indicating AST or ALT > 3 × ULN; total serum bilirubin > 2.5 × ULN; or if consistent with Gilbert's syndrome, total bilirubin > 3 × ULN and direct bilirubin > 2.5 × ULN; history of bridging fibrosis, cirrhosis, or presence of active hepatitis.
    (2) Cardiac impairment: Left ventricular ejection fraction (LVEF) <45% at screening; New York Heart Association (NYHA) Class III or IV congestive heart failure; severe arrhythmia requiring treatment; uncontrolled hypertension (systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg despite antihypertensive medication), or history of hypertensive emergency, hypertensive encephalopathy, or unstable angina; myocardial infarction, coronary artery bypass graft, peripheral artery bypass graft/implantation surgery, or stent placement within 12 months prior to enrollment; clinically significant valvular heart disease; estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m².
    (3) Pulmonary impairment: FEV1/FVC <60% and/or diffusing capacity <60% of predicted value; evidence of clinically significant pulmonary hypertension requiring medical intervention.
8. Uncorrectable coagulation dysfunction or history of severe hemorrhagic disorder;
9. Any other condition considered by the physician to render the subject unsuitable for hematopoietic stem cell transplantation;

10. Known allergy to the investigational product or its components;
11. Participation in another interventional clinical study within 3 months prior to screening or current participation;
12. Administration of live vaccines within 6 weeks prior to screening;
13. Pregnant or lactating women;
14. Poor compliance with the study protocol expected from the subject;
15. Any other condition considered by the investigator to make the subject unsuitable for participation in this clinical trial;
16. Unwillingness to provide pre-existing diagnostic evidence or undergo bone marrow examination before treatment, and unwillingness to undergo bone marrow and blood examinations after treatment;
17. Diagnosis of acute promyelocytic leukemia;
18. Clinically significant gastrointestinal abnormalities that may affect the intake, transport, or absorption of SFN (e.g., inability to swallow, chronic diarrhea, intestinal obstruction, etc.), or subjects with total gastrectomy;
19. Subjects with a definite tendency for gastrointestinal bleeding, whom the investigator considers at risk for major gastrointestinal hemorrhage;
20. History of solid organ transplantation.

Investigational Product:

Name of Dietary Supplement: Antioxidant Sulforaphane

Dosage Form: Tablet

Specification: 30 mg/tablet

Route of Administration: Oral administration, two tablets each time, three times daily, taken with meals or after meals (recommended to be taken with a fat-containing meal).

Source of Dietary Supplement: A sulforaphane-yielding supplement containing glucoraphanin and active myrosinase, manufactured by Nutramax Laboratories Consumer Care, USA. Brand Name: Avmacol® Extra Strength. Detailed component information is provided in the protocol appendices. To avoid confounding factors, the dietary supplement used in this study protocol will be from a single production batch.

Dosing Regimen:

Administration from day -1 (one day before transplantation) to day +7 (seven days after transplantation).

Concomitant Therapy:

1. During the study period, concomitant medical conditions and any adverse events (AEs) should be actively managed after evaluating the relationship between the AE and the investigational product. Prophylactic treatment may also be administered if necessary (Nausea and Vomiting: Nausea and vomiting may occur in most subjects during chemotherapy. Appropriate antiemetic therapy is recommended to prevent or alleviate nausea and vomiting. Prophylactic use of antiemetics, such as prochlorperazine or ondansetron, is recommended during chemotherapy. Increased monitoring of electrolytes and electrocardiogram is advised during medication use).
2. Unrelated umbilical cord blood transplantation.

Prohibited Medications: /

Follow-up Duration:

Treatment Period: Approximately ±10 days

Completion of Primary Endpoint Assessment: 2 months post-transplantation

Follow-up Period: 1 year

Criteria for Discontinuation of Investigational Product:

Discontinuation of investigational product does not equate to withdrawal from the study. Subjects who discontinue the investigational product should continue to complete subsequent study visits as required by the protocol (unless they meet criteria for study withdrawal). Study treatment must be discontinued if any of the following criteria are met:

1. The subject is unwilling to continue receiving the investigational product. In accordance with the Declaration of Helsinki and the informed consent form, the subject has the right to withdraw at any stage of the trial without affecting their future medical care and rights.
2. Occurrence of an adverse event that does not improve or is intolerable after optimal medical treatment, and the investigator judges that discontinuation of treatment is necessary.
3. Subjects who discontinue the study are required to complete all examinations for the primary endpoints (the investigator should confirm whether subjects who withdraw consent are willing to complete all procedures of the final visit).
4. For all subjects who withdraw from the study due to adverse events or laboratory abnormalities, follow-up must be conducted until the

symptoms (or laboratory values) return to their pre-study state or are deemed non-clinically significant, and the results recorded in the CRF.

5. Criteria for subject study discontinuation also include loss to follow-up. If a subject misses a visit without withdrawing consent, the investigator should make every effort to contact the subject and record the contact attempts in the CRF. The investigator has the right to discontinue a subject's participation in the study if it is judged that continuation poses an unacceptable risk.

Criteria for Exclusion from Analysis:

Failure to receive the planned dose of SFN (<50% of the planned dose)

Study Endpoints:

Primary Endpoints:

(1) Safety: Incidence of adverse events, including non-hematological adverse events of Grade 3 or higher.

(2) Efficacy: Time to neutrophil recovery after UCBT.

Secondary Endpoints:

(1) Time to platelet engraftment.

(2) Relationship between CD34+ cell dose and trilineage engraftment.

(3) Incidence of acute and chronic GVHD.

(4) Incidence of primary and secondary graft failure.

(5) Incidence of severe (Grade 3 or higher) infections.

(6) Transplant-related mortality, relapse rate, duration of response, 1-year disease-free survival, overall survival (OS), and GVHD-free relapse-free survival (GRFS).

(7) Incidence of pre-engraftment syndrome.

(8) Length of hospital stay (length of stay, number of days with fever, number of days on parenteral nutrition within the first 100 days post-transplant).

(9) Immune reconstitution (kinetics of immune and hematopoietic stem cell recovery).

(10) Incidence of oral intolerance and vomiting.

(11) Volume of red blood cell transfusions and volume of platelet transfusions.

All patients will be followed up until 1 year after transplantation.

Sample Size Determination and Statistical Methods:

(1) Basis for Sample Size Determination:

Based on clinical practice, Phase I will enroll 4 adult patients to evaluate the

safety and feasibility of oral sulforaphane during the peri-infusion period of UCBT. The Phase II objective is to demonstrate the non-inferiority of neutrophil recovery time in patients receiving UCB units cryopreserved for ≥10 years with sulforaphane, compared to the efficacy in patients receiving UCB units cryopreserved for <10 years without sulforaphane. Historical data indicate a mean neutrophil recovery time of 18 days (standard error: 4 days) in patients receiving UCB cryopreserved for <10 years without sulforaphane. The expected neutrophil recovery time for patients receiving UCB cryopreserved for ≥10 years with sulforaphane is 18 days. Recovery time not exceeding 20 days is considered non-inferior to the effect observed with UCB cryopreserved for <10 years. Using a one-sided, one-arm non-inferiority z-test, with a Type I error (α) of 0.025 and Type II error (β) of 0.2 (power=80%), the Phase II study requires a total of 32 adult patients.

(2) Statistical Analysis Methods:

Quantitative data will be described using medians (interquartile range) or mean ± standard deviation. Comparative analyses will employ the t-test or Wilcoxon test based on whether the data conform to a normal distribution. Qualitative data will be described using absolute numbers/frequencies, with comparative analyses using the chi-square test or Fisher's exact test. The analysis of post-transplant blood cell recovery time will utilize the Fine-Gray competing risks model to account for early death and primary graft failure as competing events, reporting the subdistribution hazard ratio (sHR). Between-group comparisons for cumulative incidence will be performed using Gray's test.

2 Research Background

Hematopoietic stem cell (HSC) transplantation represents a potentially curative therapy for a variety of hematologic disorders. The primary clinical sources of HSCs include bone marrow, mobilized peripheral blood, and umbilical cord blood (UCB). Among these, UCB offers distinct advantages such as rapid availability, less stringent HLA matching requirements, lower incidence of severe chronic graft-versus-host disease (GVHD), and a theoretically lower risk of latent viral transmission. Consequently, the application of UCB transplantation (UCBT) has been progressively expanding.

Globally, over 8 million UCB units are stored in both public and private banks, with China's inventory exceeding 2.4 million units. Despite this substantial reserve, the clinical utilization rate remains disproportionately low, with only approximately 80,000 reported UCBT cases worldwide and about 42,000 in China, translating to an overall usage rate of less than 2%. A significant contributing factor to this underutilization is clinician apprehension regarding the efficacy of long-term cryopreserved units. Data from Chinese public cord blood banks indicate that as of March 2025, from a

total inventory exceeding 280,000 units, more than 70,000 (approximately 26%) have been cryopreserved for 10 years or longer. This substantial portion of the inventory represents a critical, yet underused, resource.

While some studies suggest that UCB units cryopreserved for extended periods (up to 19 years) retain engraftment potential, a prevailing preference for shorter-term cryopreserved units persists in clinical practice, largely based on empirical observation rather than robust scientific evidence. Our preliminary investigations have systematically demonstrated that the cryopreservation process and duration can impair the hematopoietic reconstitution capacity of UCB-derived hematopoietic stem and progenitor cells (HSPCs), potentially due to accumulated damage such as mitochondrial dysfunction and oxidative stress, while sparing immunologic function. Notably, we have found that treatment with the antioxidant sulforaphane (SFN) can partially rescue this functional impairment in preclinical models.

Sulforaphane (C6H11NOS2), an isothiocyanate derived from its precursor glucoraphanin found in cruciferous vegetables, is a potent inducer of cytoprotective enzymes via the Nrf2 pathway. Its antioxidant and potential cytoprotective properties make it a compelling candidate for mitigating cryopreservation-induced cell damage. Commercially available SFN-containing supplements have been utilized in other registered clinical trials, supporting its safety profile for human consumption.

This clinical study is therefore designed to translate these preclinical findings into a clinical setting. We hypothesize that SFN administration in the peri-transplant period to adult patients undergoing UCBT with long-term cryopreserved (≥10 years) UCB will promote early hematopoietic recovery, achieving engraftment rates comparable to those observed with shorter-term cryopreserved units. Confirming this hypothesis would significantly increase the available donor pool by "reawakening" this dormant inventory, thereby enhancing patient access to this potentially life-saving therapy and maximizing the return on investment in public cord blood banking. This trial aims to provide the necessary clinical evidence to address a critical unmet need in the field of transplantation medicine.

3 Study Objectives

Primary Objectives:

(1) To determine the safety and feasibility of SFN use during the peri-infusion period of UCBT in adults.

(2) To determine the impact of SFN use during the peri-infusion period

of UCBT on hematopoietic recovery, particularly neutrophil engraftment.

Secondary Objectives:

(1) To establish a high-quality clinical cohort of adult patients transplanted with long-term cryopreserved umbilical cord blood.

4 Study Design

This is a single-arm, open-label, single-center study. Phase I will enroll 4 patients. Upon meeting the safety evaluation criteria in Phase I, Phase II will enroll 32 patients for observation.

5 Study Population

5.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for the study:

(1) Patients with high-risk hematologic malignancies: including Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), or high-risk Myelodysplastic Syndromes (MDS) diagnosed according to World Health Organization (WHO) criteria.

(2) Age and Sex: ≥18 years old, no gender restriction.

(3) Karnofsky Performance Status (KPS) score ≥70%, and Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.

(4) Selection of Unrelated Donor Umbilical Cord Blood (UCB): The UCB unit must meet the following criteria: donor-recipient high-resolution HLA match ≥4/6 or 7/10, and a post-thaw CD34+ cell dose ≥0.83 × 10^5/kg (recipient body weight). Furthermore, only UCB units cryopreserved for ≥10 years meeting these criteria are available for the patient from Chinese public cord blood stem cell banks.

5.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation:

(1) Positive test results for any of the following: Human Immunodeficiency Virus (HIV-1/2), detectable Human Cytomegalovirus DNA (HCMV-DNA), detectable Epstein-Barr Virus

DNA (EBV-DNA), Hepatitis B (positive for Hepatitis B surface antigen [HBsAg] or detectable Hepatitis B virus DNA [HBV-DNA]), positive Hepatitis C antibody (HCV-Ab), or positive Treponema pallidum antibody (TP-Ab).

(2) Active bacterial, viral, fungal, or parasitic infection judged by the investigator to be clinically significant at the time of screening.

(3) Availability of an HLA-identical willing donor and eligibility for allogeneic hematopoietic stem cell transplantation from that donor.

(4) Prior receipt of gene therapy or allogeneic hematopoietic stem cell transplantation.

(5) First-degree relative(s) with a known or suspected hereditary cancer syndrome (including, but not limited to, hereditary breast and ovarian cancer syndrome, Lynch syndrome, familial adenomatous polyposis, etc.).

(6) Diagnosis of a major psychiatric disorder or condition that would severely impair the ability to participate in the clinical study; or history of substance abuse related to psychotropic drugs and inability to abstain.

(7) History of significant organ dysfunction, including:

1) Hepatic: Liver function tests indicating AST or ALT > 3 × Upper Limit of Normal (ULN); total serum bilirubin > 2.5 × ULN; or, if consistent with Gilbert's syndrome, total bilirubin > 3 × ULN with direct bilirubin > 2.5 × ULN; history of bridging hepatic fibrosis, cirrhosis, or presence of active hepatitis.

2) Cardiac: Left ventricular ejection fraction (LVEF) <45% at screening; New York Heart Association (NYHA) Class III or IV congestive heart failure; severe arrhythmia requiring treatment; uncontrolled hypertension (systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg despite antihypertensive medication), or history of hypertensive emergency, hypertensive encephalopathy, or unstable angina; myocardial infarction, coronary artery bypass grafting, peripheral artery bypass graft/implantation surgery, or stent placement within 12 months prior to enrollment; clinically significant valvular heart disease; estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m².

3) Pulmonary: FEV1/FVC ratio <60% and/or diffusing capacity for carbon monoxide (DLCO) <60% of predicted value; evidence of clinically significant pulmonary hypertension requiring medical

intervention.

(8) Uncorrectable coagulation dysfunction or history of a severe hemorrhagic disorder.

(9) Any other condition considered by the physician to render the subject unsuitable for hematopoietic stem cell transplantation.

(10) Known allergy or hypersensitivity to the investigational product (sulforaphane) or any of its components.

(11) Participation in another interventional clinical study within 3 months prior to screening or current participation.

(12) Administration of live attenuated vaccines within 6 weeks prior to screening.

(13) Pregnant or lactating women.

(14) Poor compliance with the study protocol expected from the subject, as judged by the investigator.

(15) Any other condition considered by the investigator to make the subject unsuitable for participation in this clinical trial.

(16) Unwillingness to provide valid pre-existing diagnostic evidence or undergo bone marrow examination before treatment, and/or unwillingness to undergo bone marrow and blood examinations after treatment.

(17) Diagnosis of acute promyelocytic leukemia (APL).

(18) Clinically significant gastrointestinal abnormalities that may affect drug intake, transport, or absorption (e.g., inability to swallow, chronic diarrhea, intestinal obstruction, etc.), or subjects who have undergone total gastrectomy.

(19) Subjects with a definite tendency for gastrointestinal bleeding, whom the investigator judges to be at risk for major gastrointestinal hemorrhage.

(20) History of solid organ transplantation.

5.3 Criteria for Withdrawal and Discontinuation

(1) Subjects may withdraw their informed consent and leave the study at any time if they are unwilling to continue participation. Subjects deciding to withdraw should notify the investigator promptly.

(2) The reason for withdrawal must be recorded in the Case Report Form (CRF), including the date of and reason for withdrawal.

(3) Subjects who discontinue the study are required to complete all procedures specified for the final visit (the investigator should confirm whether subjects who withdraw consent are willing to complete all final visit procedures).

(4) All subjects who withdraw due to adverse events or laboratory abnormalities must be followed up until the symptoms (or laboratory values) return to their pre-study state or are deemed non-clinically significant. The results of this follow-up must be recorded in the CRF.

(5) Criteria for study discontinuation also include loss to follow-up. If a subject misses a scheduled visit without formally withdrawing consent, the investigator must make reasonable efforts to contact the subject and document these contact attempts in the CRF. The investigator has the right to discontinue a subject's participation if it is judged that continuation poses an unacceptable risk to the subject.

5.4 Criteria for Exclusion from Analysis

Failure to receive the planned dose of SFN (defined as receiving <50% of the total planned dose).

6 Investigational Product

Name of Dietary Supplement: Antioxidant Sulforaphane

Dosage Form and Strength: 30 mg/tablet

Route of Administration: Oral administration, two tablets each time, three times daily, to be taken with meals or after meals (recommended to be taken with a fat-containing meal).

Source of Dietary Supplement: A sulforaphane-yielding supplement containing glucoraphanin and active myrosinase, manufactured by Nutramax Laboratories Consumer Care, USA. Brand Name: Avmacol® Extra Strength. Detailed component information is provided in the protocol appendices. To minimize variability, the dietary supplement used in this study will be from a single manufacturing batch.

7 Dosing Regimen

(1) Administration starts on day -1 (one day before transplantation) and

continues until day +7 (seven days after transplantation).

If vomiting occurs after drug intake and intact tablets are visible in the vomitus, the dose should be re-administered based on the number of tablets identified.

8 Prohibited Medications

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9 Transplant Protocol

Conditioning Regimen: A dose-stratified design is used, adjusting intensity based on patient age and comorbidities:

(1) For patients aged ≤50 years and ECOG ≤1: Myeloablative regimen (Flu/Bu/Cy or Flu/Bu/Mel):

1) Flu/Bu/Cy: Fludarabine (Flu) 30mg/m² daily for 4 days; Busulfan (BU) 0.8mg/kg every 6 hours for 4 days; Cyclophosphamide (Cy) 60mg/kg daily for 2 days.

2) Flu/Bu/Mel: Flu and Bu as above; Melphalan (Mel) 80-100mg/m² daily for 1 day.

(2) For patients aged >50 years or ECOG ≥2: Myeloablative regimen (Flu/Ara-C/Bu/Mel):

1) Flu 30mg/m² daily for 4 days; Granulocyte Colony-Stimulating Factor (G-CSF) 5μg/kg daily for 3 days; Cytarabine (Ara-c) 1.5-2.0g/m² daily for 3 days; Bu 0.8mg/kg every 6 hours for 3 days; Mel 80-100mg/m² daily for 1 days.

For patients with a history of meningeal leukemia, high-risk factors for meningeal leukemia, or extramedullary disease: Add Semustine (250 mg/m²) or Thiotepa (8-10 mg/kg daily for 1 day).

For patients with active disease (not in remission) at transplantation: Add Decitabine (20 mg/m²/day for 3 days) or Thiotepa (8-10 mg/kg daily for 1 day).

GVHD Prophylaxis: Cyclosporine A (CsA) combined with short-course Mycophenolate Mofetil (MMF).

(1) CsA: Starting on day -1 at 2.5 mg/kg/day via continuous 24-hour intravenous infusion, targeting a blood concentration of 200-300 ng/mL. After granulocyte engraftment, switch to oral administration at twice the intravenous dose. CsA tapering begins at 2 months post-transplant based on disease relapse risk, GVHD, and infection status, with discontinuation planned at 5-6 months post-transplant.

(2) MMF: 30 mg/kg/day (in two divided doses), starting on day +1. Tapering begins after granulocyte engraftment, with gradual discontinuation by 3-4 months post-transplant.

Other Supportive Care:

Other supportive care measures will be administered according to the institution's standard transplant protocols.

10 Other/Concomitant Therapies

(1) Transfusion Support: All blood products used during the transplant process must be irradiated.

(2) Treatment of Underlying Conditions: e.g., antihypertensive medication for hypertensive patients; antiviral therapy for patients with chronic hepatitis B with regular monitoring of liver function and HBV-DNA levels.

(3) Other Disease-Related Supportive Therapies.

(4) From the date of signing the informed consent form until the final study visit, the investigator must record all treatments for underlying conditions, supportive care, and concomitant medications (including start/stop dates and indications) in the subject's source documents and the CRF.

11 Study Schedule

11.1 Screening Period (Approximately 2 Weeks)

(1) Medical History Collection:

1) Medication history prior to disease onset.

2) Recent history of infections.

3) Pregnancy status.

4) Prior history of transplantation.

(2) Standard Pre-Transplant Workup:

1) Bone marrow examination (bone marrow aspirate/biopsy, immunophenotyping, cytogenetics, molecular studies, etc.).

2) Complete blood count with reticulocytes, comprehensive biochemistry panel, coagulation profile, thyroid function tests, urinalysis, stool routine plus occult blood test, immunoglobulin levels, immune function assessments (T, B, NK cells, TCR repertoire, etc.).

3) Pulmonary function tests, cardiac ultrasound, abdominal ultrasound, chest CT/X-ray, electrocardiogram, head MRI, etc.

4) Pathogen testing: HIV-1/2, HBsAg, HBV-DNA, HCV-Ab, TP-Ab, CMV-DNA, EBV-DNA, etc.

5) Multidisciplinary team assessment.

11.2 Treatment Period

(1) Pre-transplant Baseline: Collect samples for serum cytokines, immune cell subsets, etc.

(2) Day 0 to 1 Year Post-Transplant: Monitor complete blood count daily post-transplant until neutrophil/platelet/reticulocyte engraftment, then periodically thereafter. Donor chimerism assessments will be performed on days +3, +5, +7, +14, +21, +28, and at months 2, 3, 6, 9, and 12 post-transplant to monitor dynamic changes.

11.3 Follow-up Period

(1) Assessments at Months 1, 2, 3, 4, 6, 9, and 12 post-transplant: Immune cell subsets, acute GVHD grading (Glucksberg/IBMTR criteria), chronic GVHD assessment (NIH criteria), monitoring of CMV/EBV viral load, infection surveillance, etc.

(2) All patients will be followed until 1 year post-transplant: Outcomes including non-relapse mortality (NRM), disease-free survival (DFS), overall survival (OS), and GVHD-free relapse-free survival (GRFS) will be calculated.

12 Endpoints

12.1 Efficacy Endpoints

(1) Neutrophil Engraftment: The first of three consecutive days with an absolute neutrophil count (ANC) ≥ 0.5 × 10^9/L after transplantation.

(2) Platelet Engraftment: The first of seven consecutive days with a platelet count ≥ 20 × 10^9/L without transfusion support after transplantation.

(3) Primary Graft Failure (PGF): Failure to achieve neutrophil recovery (as defined above) by day +28, or donor chimerism <5% in whole blood or bone marrow at day +28.

(4) Relapse: Reappearance of ≥5% blasts in the bone marrow after achieving complete remission (CR); or detection of blasts in the peripheral blood on two separate occasions at least one week apart; or development of new extramedullary disease.

(5) Transplant-Related Mortality (TRM): Death from any cause other than relapse of the underlying disease.

(6) Overall Survival (OS): The time from the initiation of study treatment (transplantation) to death from any cause.

(7) Relapse-Free Survival (RFS): The time from the date of first achieving CR to the date of disease relapse or death from any cause, whichever occurs first.

(8) Disease-Free Survival (DFS): The time from the date of achieving CR after transplantation to the date of disease relapse or death from any cause, whichever occurs first.

(9) GVHD-free, Relapse-Free Survival (GRFS): The time from transplantation to the occurrence of any of the following events: grades III-IV acute GVHD, chronic GVHD requiring systemic treatment, disease relapse, or death from any cause, whichever occurs first.

12.2 Safety Endpoints

(1) Tolerance of SFN in UCBT patients and incidence of grade 3-4 non-hematological toxicities. Dose modifications or interruptions will be determined based on grading according to CTCAE (Common Terminology Criteria for Adverse Events).

(2) Transplant-related complications: Incidence of acute GVHD,

incidence of infections, and TRM.

13 Adverse Events and Serious Adverse Events

All Adverse Events (AEs) occurring from the time of signing the informed consent form until the final study visit will be recorded. AEs will be graded and recorded according to the NCI CTCAE version 5.0.

13.1 Adverse Events

13.1.1 Definition of an Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product or undergoing a medical procedure, which does not necessarily have a causal relationship with this treatment or procedure. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the research intervention. This includes any new event or worsening of a pre-existing condition relative to the baseline state. Adverse Events include Serious Adverse Events (SAEs), non-serious AEs, and abnormal laboratory findings.

13.1.2 Collection and Recording of Adverse Events

All AEs occurring from the date of signing the informed consent form until the final study visit must be recorded. The investigator should report all AEs using concise medical terminology.

13.1.3 Criteria for Determining the Severity of Adverse Events

The severity of AEs will be graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, on a scale from Grade 1 (mild) to Grade 5 (death related to AE).

Grading	Criteria
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (IADL)*.

Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care Activities of Daily Living (ADL)†.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to Adverse Event.

*Instrumental Activities of Daily Living (IADL) refer to activities such as cooking, shopping, using the telephone, managing money, etc.

†Self-care Activities of Daily Living (ADL) refer to activities such as bathing, dressing and undressing, eating, using the toilet, taking medications, and not bedridden.

Note: It is important to distinguish between the severity of an adverse event and its intensity. The term "severe" is used to describe intensity, which does not necessarily qualify an event as a Serious Adverse Event (SAE). For example, a headache may be intense ("severe" in intensity) but is not an SAE unless it meets the specific SAE criteria.

13.1.4 Criteria for Assessing the Relationship between an Adverse Event and the Investigational Product

The investigator shall analyze the relationship between an adverse event and the investigational product based on the principles of causality assessment, categorized into five classes: "Definitely Related," "Probably Related," "Possibly Related," "Definitely Not Related," and "Cannot Be Determined." Events judged as "Definitely Related," "Probably Related," "Possibly Related," or "Cannot Be Determined" are considered Adverse Drug Reactions (ADRs). The investigator must record all ADRs using medical terminology.

Causality	**Reasonable Temporal Relationship?**	**Consistent with Known Adverse Reaction Profile**	**Alternative Etiology Plausible**
Definitely Related	Yes	Yes	Yes
Probably Related	Yes	Yes/No	Uncertain
Possibly Related	No	No	Uncertain
Definitely Not Related	No	No	Yes

Cannot Be Determined	Essential information for assessment is unavailable

13.2 Serious Adverse Events (SAEs)

13.2.1 Definition of a Serious Adverse Event:

A Serious Adverse Event (SAE) is any adverse event that meets one or more of the following criteria:

(1) Results in death or is life-threatening;

(2) Requires inpatient hospitalization or prolongation of existing hospitalization;

(3) Results in persistent or significant disability/incapacity;

(4) Is a congenital anomaly/birth defect;

(5) Is another medically significant event that, based on appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above.

The following hospitalizations are generally not considered SAEs:

(1) Hospitalization due to disease progression in subjects who have withdrawn or dropped out from the study;

(2) Pre-planned hospitalizations for routine treatment or observation of the condition under investigation, without worsening of the condition;

(3) Hospitalizations that were scheduled prior to the subject's enrollment in the study, with no worsening of pre-existing symptoms;

(4) Treatment in an emergency room or outpatient setting that does not meet any of the SAE criteria above and does not result in hospitalization;

(5) Pregnancy itself is not an SAE. However, it must be reported on the SAE form or a dedicated pregnancy form and followed up to document the outcome, including spontaneous abortion, elective termination, birth details, and the presence or absence of congenital anomalies.

13.2.2 Reporting of Serious Adverse Events

If a subject experiences a Grade 5 (fatal) SAE during the study period (from the date of signing the informed consent until the final visit) that is assessed by the investigator as possibly related to the investigational product, the investigator must complete an SAE report form. This report must be submitted to the local Institutional Review Board (IRB)/Ethics Committee (EC) at the study site within 24 hours of the investigator becoming aware of the event. The report must be signed and dated by the investigator.

Medical Ethics Committee of Institute of Hematology & Blood Diseases Hospital, CAMS & PUMC

Telephone: +86-22-23909095

Email: ec@ihcams.ac.cn

Address: 288 Nanjing Road, Tianjin, China

14 Data Management

Case Report Forms (CRFs) will be used for data collection in this study.

The research site will designate specific personnel to enter data from the CRFs into the study database. A separate designated person will verify the consistency between the database entries and the source CRF data.

The data manager will check the data in the database against the clinical study protocol. Any discrepancies or queries will be documented in a Data Query Form, which will be sent to the investigator for resolution. All Data Query Forms shall be retained.

The data manager will be responsible for exporting the final, cleaned data from the database for statistical analysis.

15 Statistical Analysis

15.1 Analysis Sets

Full Analysis Set (FAS): Includes data from all enrolled subjects. Used for reporting compliance and all baseline characteristics. The primary efficacy

analysis will be based on the FAS.

Safety Set (SS): Includes all enrolled subjects who received at least one dose of the study intervention and have at least one post-treatment safety assessment. Safety analyses will be based on the SS.

15.2 Statistical Methods

Quantitative data will be described using medians (interquartile range) or mean ± standard deviation. Comparative analyses will employ the Student's t-test or the Wilcoxon rank-sum test based on the normality of the data distribution. Qualitative data will be described using absolute numbers and frequencies, with comparative analyses using the Chi-square test or Fisher's exact test, as appropriate. The cumulative incidence of post-transplant hematological recovery will be estimated using the Fine-Gray competing risks model to account for competing events (e.g., early death, graft failure). Comparisons of cumulative incidence curves between groups will be performed using Gray's test.

16 Ethics

16.1 Ethical Requirements

The conduct of this study will adhere to the principles of the current version of the Declaration of Helsinki (2013), relevant regulations, and the approval opinions of the Ethics Committee.

Before the study begins, the investigator must obtain written approval from the relevant regulatory bodies for the study protocol, informed consent form (ICF), subject recruitment procedures, and any other written information to be provided to subjects. During the study, any amendments to the protocol, ICF, etc., must receive written approval from the relevant regulatory bodies before implementation.

16.2 Informed Consent

The investigator or their authorized representative is responsible for explaining the study background, the pharmacological characteristics of the investigational product, the study procedures, and the potential benefits and risks of participation to each potential subject (if applicable), and/or the subject's parent(s)/legal guardian(s). Written informed consent, signed and dated by the subject (if applicable), the subject's parent(s)/legal guardian(s), and the investigating physician, must be

obtained before any study-specific procedures are performed (i.e., before screening examinations).

The final ICF text shall include: the study purpose, procedures, subject responsibilities, foreseeable benefits, risks, and inconveniences; availability of treatment for study-related injury; access to study data and confidentiality of subject information.

The ICF must be approved in writing by the relevant regulatory bodies and written in a language understandable to the subject (if applicable) and/or the subject's parent(s)/legal guardian(s). The subject (if applicable), the subject's parent(s)/legal guardian(s), and the investigator obtaining consent must all sign and date the ICF. The original signed ICF shall be retained by both the investigator and the subject (or their guardian). If significant new information relevant to the study emerges, a revised ICF must be prepared, submitted for regulatory approval, and re-consent must be obtained.

For subjects who cannot personally participate in the consent process, written informed consent must be obtained from the subject's parent(s)/legal guardian(s), and all study procedures must be fully explained to them.

16.3 Subject Confidentiality

The investigator is responsible for maintaining subject anonymity. Subject identification on the CRF or other study documents shall use only subject initials, numbers, and/or a unique code, not the subject's name. The investigator must maintain a confidential subject identification list that links the subject's code to their name and contact information. The investigator must ensure the confidentiality of all documents that could identify individual subjects.

17 Study Management

17.1 Training

Prior to the initiation of the clinical study, the investigators shall receive training on the study protocol. They must thoroughly read and understand the content of this clinical study protocol, unify data recording methods and assessment criteria, and strictly adhere to the protocol during conduct.

17.2 Quality Control and Quality Assurance

All observations and abnormal findings obtained during the clinical study must be promptly and carefully verified and recorded to ensure data reliability. The investigator will enter the information required by the protocol into the CRFs. The accuracy and completeness of the CRF entries will be verified by monitors.

18 Anticipated Study Timeline and Completion Date

The anticipated study timeline is as follows:

September 2025 - December 2025: Complete enrollment of 4 patients in Phase I and conduct a preliminary evaluation of the safety and feasibility of SFN use during the peri-transplant period.

December 2025 - December 2026: Complete enrollment of 32 patients in Phase II and evaluate the impact of peri-transplant SFN use on hematopoietic engraftment parameters.

First Subject Enrolled: September 2025

Last Subject Completed: December 2027

Data Management, Statistical Analysis, and Clinical Study Report: Clinical data from all subjects will be collected by December 2027 for statistical analysis to elucidate the safety and feasibility of peri-transplant SFN use and its impact on hematopoietic engraftment.

19 Confidentiality and Publication of Results

The investigators shall maintain the confidentiality of all information and data related to this study. Research results or materials shall not be cited or published without the consent of the sponsoring institution.

20 References

21 Appendic

Trial Flow Chart

Process	**Screening Period**	**Conditioning Regimen Period**		**Transplantation Time (SFN Administration Time)**												**Safety Follow - up**	**Survival Follow - up**
	D - 28 to D - 8	**D - 7 to D - 2**	**D-1**	D0 (+1)	D1 (+2)	D2 (+3)	D3 (+4)	D4 (+5)	D5 (+6)	D6 (+7)	D7 (+8)	D8 to D30	D14	D21	D28	30 days after transplantation	30 days, 60 days, 90 days, 120 days, 180 days, 270 days, 365 days after transplantation
Time Window (days)																	
Baseline Data																	
Sign Informed Consent Form	X																
Demographic Data	X																
Medical History and Treatment History	X																
Inclusion/Exclusion Criteria	X																
Laboratory Tests and Other Examinations																	
Pulmonary Function	X																
Electrocardiogram (ECG)	X		If necessary														

Cardiac ultrasound	X																
Chest CT/X - ray	X																
Abdominal ultrasound	X		If necessary														
Complete Blood Count + Reticulocyte	X	X	X	X	X	X	X	X	X	X	X	X（Tested daily before three - lineage engraftment）	X	X	X		
Blood Biochemistry	X		X		X		X		X		X	X					
Thyroid Function	X																
Coagulation Function	X	If necessary															
Routine Urine Test	X	If necessary															
Routine Stool Test	X	If necessary															
Etiological Detection (HIV - 1/2, HBsAg, HBV - DNA, HCV - Ab, TP - Ab)	X																
CMV - DNA	X				X		X		X		X						
EBV - DNA	X				X		X		X		X						
Immunoglobulin	X										X	X	X		X		

Immune Function (T, B, NK, TCR, etc.)	X															X	X
Other Clinical Evaluations and Examinations																	
Karnofsky Score	X																
HCT - CI	X																
ECOG Score	X																
Physical Examination	X		X	X	X	X	X	X	X	X							
Vital Signs	X		X	X	X	X	X	X	X	X							
Body Weight	X		X	X	X	X	X	X	X	X							
GF												X	X		X		
GVHD												X	X		X		X
PES			X	X	X	X	X	X	X	X	X	X	X		X		
Infection			X	X	X	X	X	X	X	X	X	X	X		X	X	X
Bone Marrow Examination																	

Bone Marrow Morphology	X														X		X
Immunophenotyping	X														X		X
Karyotype	X														X		X
Minimal Residual Disease	X														X		X
Chimerism	X									X			X	X	X		X
Patient - Reported Outcome (PRO) Scale Filling																	
EQ - 5D - 5L Scale	X			X		X		X		X			X		X		
Medication and Subject Management																	
SFN Administration				X	X	X	X	X	X	X	X						
Concomitant Medication/Treatment				X	X	X	X	X	X	X	X						
Adverse Events				X	X	X	X	X	X	X	X						
Survival Follow - up				X	X	X	X	X	X	X	X	X	X		X	X	X

Notes:

1) Medical History and Treatment History: Document all prior diagnoses and treatments, including findings from the initial diagnosis and relevant therapeutic history. This includes medical history and treatments other than AML/ALL/MDS, such as: prior history of cardiac disease (e.g., heart failure, coronary artery disease, angina pectoris), history of other malignancies (if applicable, details of treatment history should be collected whenever possible), thrombotic events within 6 months prior to randomization, hypertension, history of psychoactive substance abuse, history of recent live vaccination and any planned vaccinations, and history of organ transplantation.

2) Baseline Assessments: All baseline results must be obtained within 28 days prior to randomization. For abdominal ultrasound, cardiac ultrasound, and chest CT or X-ray, results acknowledged by the Investigator as valid are acceptable.

3) Microbiological Serology/PCR Testing: Must include testing for Human Immunodeficiency Virus (HIV-1/2), Human Cytomegalovirus (HCMV-DNA), Epstein-Barr Virus (EBV-DNA), Hepatitis B (positive Hepatitis B surface antigen [HBsAg] or detectable Hepatitis B virus DNA [HBV-DNA]), Hepatitis C antibody (HCV-Ab), and Treponema pallidum antibody (TP-Ab).

4) Blood Pregnancy Test: Required only for female subjects of childbearing potential.

5) Bone Marrow Examinations: Include bone marrow cytomorphology, immunophenotyping, chromosome karyotype, bone marrow pathology, and assessment for Minimal Residual Disease (MRD).

- Bone Marrow Cytomorphology: Must be sent to the central laboratory for analysis. The sample used for screening should be collected after the last prior therapy and within 28 days prior to randomization (historical slides meeting these criteria are acceptable; samples outside this window are not permitted – a new sample must be collected if the window is exceeded).

- Immunophenotyping and Chromosome Karyotype (Screening): For the screening period, results from tests performed after the last prior therapy and within 28 days prior to randomization may be accepted if acknowledged by the Investigator (results from Grade A tertiary hospitals or qualified third-party laboratories are acceptable). Immunophenotyping is only required during the screening period. Bone marrow samples are required in principle; however, peripheral blood may be substituted if no bone marrow sample is available and the Investigator has sufficient grounds to deem it adequate for analysis. Enrollment confirmation may proceed without awaiting this result if the Investigator confirms the diagnosis based on available information.

- Chromosome Karyotype: Is required only during screening (Note: enrollment confirmation does not require this result to be available) and at the time of definitive treatment discontinuation. Bone marrow samples are required for testing; peripheral blood may be used only if a bone marrow sample cannot be obtained.

- Minimal Residual Disease (MRD): Is required only during the treatment period and at the time of definitive treatment discontinuation (not during

screening). All MRD assessments must be sent to the central laboratory for analysis.

6) Concomitant Medications/Therapies: The collection period for concomitant medications/therapies spans from 28 days prior to randomization until the end of the safety follow-up period (within 30 ± 7 days after the last dose of study drug). All concomitant medications/therapies used by the subject and the reasons for their use must be fully documented in the source records and the electronic Case Report Form (eCRF). After the safety follow-up period ends, only concomitant medications and therapies related to Adverse Events (AEs) or Serious Adverse Events (SAEs) associated with the investigational product are recorded.

7) Survival Follow-up: Beginning 30 days after the subject's last dose of study drug, survival follow-up should be conducted every 90 days (±14 days). For subjects who are randomized but do not receive study treatment, the start date for follow-up is the randomization date. Any new anti-leukemia treatments initiated should be recorded. Follow-up continues until the subject reaches the mortality endpoint, is lost to follow-up, the study is completed, or the sponsor terminates the study.

Adverse Events of Special Interest

1) Gastrointestinal Intolerance: Nausea, vomiting, bloating, abdominal pain, diarrhea, constipation. Record their frequency, severity, and relationship to dosing time (e.g., related to fasting/post-meal administration?).

2) Allergic or Hypersensitivity Reactions: New onset rash, urticaria, skin itching, etc.

Parameters to be Monitored

1) Laboratory Tests: Complete blood count (CBC), blood biochemistry, urinalysis, stool routine.

2) Vital Signs and Physical Examination: Weight, temperature, blood pressure, respiration, heart rate. Pay attention to skin (rash), abdomen (tenderness), etc.

3) Patient-Reported Outcomes (PROs) and Compliance Records:

4) Record the subject's daily intake of SFN, any missed doses, and any subjectively reported symptoms (e.g., mild nausea, fatigue).

5) Standardized Questionnaires: Use instruments such as the Gastrointestinal Symptom Rating Scale (GSRS) or the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) to quantify the severity and frequency of gastrointestinal or other symptoms.