HERACLES: A PHASE II SINGLE-ARM PROSPECTIVE STUDY TO ASSESS THE EFFICACY OF FECAL MICROBIOTA TRANSFER (FMT) IN THE TREATMENT OF STEROID-REFRACTORY GASTRO-INTESTINAL PREDOMINANT aGVHD POST ALLO-HSCT

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Background

Steroid-refractory acute graft-versus-host disease (SR-aGVHD) is associated with 80% mortality rates and reduced quality of life (QoL). There is no approved standard of care for SR-aGVHD second-line treatment. In view of the poor prognosis and limited therapeutic options, there is an urgent need to identify effective therapies to improve patients' outcomes. Fecal Microbiota Transfer (FMT) might be beneficial to substantially improve the prognosis. Indeed, higher gut microbial diversity is strongly associated with increased survival in GvHD patients, and recent studies reported promising results for SR-aGVHD patients treated with FMT. Further evaluations to confirm the efficacy and safety of FMT for aGVHD is warranted. The ongoing phase 2 study (HERACLES) investigates the efficacy of a pooled FMT biotherapeutic, MaaT013. Promising results were obtained with a mono-donor FMT biotherapeutic, MaaT012, in the reconstruction of gut microbiota diversity after induction chemotherapy. We now expect that full ecosystem gut microbiota restoration with the MaaT013 biotherapeutic could be an effective treatment of gastrointestinal-predominant SR-aGVHD, and thereby reduce the risk of life-threatening complications after allogeneic HSCT.

- ✓ Single-arm, multicenter prospective
- ✓ 5 European countries
- ✓ Up to 30 reference centers
- ✓ ClinicalTrials.gov Id: **NCT03359980**
- ✓ First Patient In: August 2018

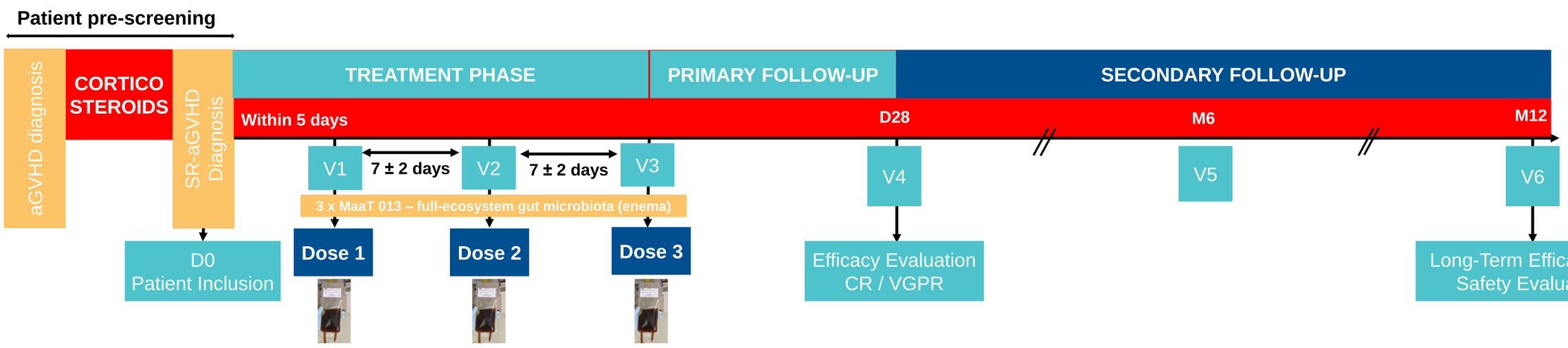
Competitive recruitment of 32 patients

MaaT013

- ✓ Standardized industrial production of MMRB Platform: MaaT Microbiome Restoration Biotherapeutics
- ✓ Pooled-donor, conditioned, full-ecosystem restoration
- ✓ 3 x 150 mL enemas administered 1 week apart from each other
- ✓ Obtained from rigorously screened healthy donors

MMRB: MaaT Microbiome Restoration Biotherapeutic

Study Flow Chart



Methods

Inclusion Criteria

- ➢ First episode of **Stage 3 or 4 gastrointestinal (GI) aGVHD** with gut predominance if associated with other organs, **resistant to a first line therapy with steroids**
- ➢ Age ≥18 years-old
- ➢ Allo-HSCT with any type of donor, stem cell source, GVHD prophylaxis or conditioning regimen
- ➢ Patients able to have a minimum of 12 hours discontinuation of systemic antibiotics, during which to administer the enema
- ➢ Signature of informed consent

Exclusion Criteria

- ➢ Grade IV hyper-acute GVHD
- ➢ Late onset aGVHD
- ➢ Overlap chronic GVHD
- ➢ Acute GVHD after donor lymphocytes infusion
- ➢ Relapsed/persistent malignancy requiring rapid immune suppression withdrawal
- ➢ Active uncontrolled infection according to the attending physician
- ➢ Systemic drugs other than corticosteroids for GVHD treatment
- ➢ Absolute neutrophil count < 0.5 x 10^9/L
- ➢ Absolute platelet count < 10,000
- ➢ Patient with negative EBV serology

Key Objectives

PRIMARY

- ➢ **Evaluation of MaaT013 efficacy in treating gastrointestinal-predominant SR-aGVHD** through the assessment of **Complete Response** (CR, according to modified Seattle / Glucksberg criteria) and **Very Good Partial Response** (VGPR, defined by Martin et al, BBMT 2009)

SECONDARY

- ➢ Safety evaluation
- ➢ Evaluation of MaaT013's impact on overall / steroid-free / progression-free/ relapse-free / GVHD-free survival, maintenance of response, relapse of the initial disease at D28, M6 and M12 post inclusion
- ➢ Evaluation of MaaT013's impact on infectious events, Multi-Drug Resistant Bacteria (MDRB) carriage, clinical symptoms of skin/liver aGVHD associated with SR-GI-aGVHD

Study Design

- **Patient pre-screening phase**

Patients diagnosed with gastrointestinal-predominant aGVHD will be identified. Only patients with steroid refractory aGVHD will be included in the study.

- **Treatment phase**

Patients receive their first MaaT013 enema within 5 days after diagnosis of steroid resistance (V1). Two additional enemas follow a week apart from each other at V2 and V3. The total number of treatments will depend on patient's tolerance. Visits are planned with clinical and biological evaluations from D0 through D16.

- **Follow-up phases**
  - ➢ Primary: Patients' response (CR and VGPR) will be evaluated at D28 post inclusion.
  - ➢ Secondary: Patients will be more closely followed up to 6 months; with survival, long term safety and chronic GVHD expression up followed up to 12 months after inclusion.

At inclusion (V1), before each dosing (V2, V3), and 28 days post inclusion (V4), patients' faeces and blood are collected. Safety monitoring is performed with the corresponding blood analyses. Exploratory measures on faeces include characterization of gut microbiota composition and evolution, impact of MaaT013 on metabolism and gut inflammation. Immune system phenotyping will be performed by flow cytometry on peripheral blood mononuclear cells (PBMCs), and by ELISA on plasma. Patients' QoL will be assessed using a standard EQ-5D-5L questionnaire.

Results

The study was launched in May 2018 and enrolment is ongoing. Overall, **32 patients are planned to be enrolled and treated**, to assess GI response, overall response rates, and MaaT013's safety profile. The first results (primary follow-up) are expected in **Q4 2019**.