Sponsor:	HOVON foundation
Trial:	HOVON 112 MSC
EudraCT:	2011-003237-33
Title of study:	Treatment of severe acute GVHD after allogeneic hematopoietic stem cell transplantation with steroids versus MSC and steroids. A prospective double-blind placebo-controlled randomized phase III trial
Report date:	29Sep2025

Signature	
Name:	Prof. dr. J. Kuball
Function:	Principal Investigator
Date:	27-11-2025
Signature:	

Investigational sites & investigators with ≥1 included patients

Site Name	Site PI Name
NL-Utrecht-UMCUTRECHT	J.H.E. Kuball

Publications:
No publications yet.

Studied period:
27May2014 (date of inclusion of first patient) – 31Dec2024 (last patient last visit).

Phase of development:
Phase III

Objectives:
- To improve the response rate to treatment of grade II-IV acute GVHD involving gut and/or liver by adding MSC to standard high dose prednisolone
- To study the safety of the addition of MSC to standard treatment of severe acute GVHD as compared to standard treatment alone
- To study quality of life
- To study cost-effectiveness
- To study the (immunological) phenotype before and after application of MSC/placebo of responders and non-responders in both groups at different sites
- To study the immunological genotype of responders and non-responders as well as donors in both groups
- To study the incidence of relapse of the underlying disease (e.g. hematological malignancy)
- To study progression free survival (of the underlying disease)
- To study overall survival

Methodology:
HO112 was a prospective, double-blind placebo-controlled randomized phase III trial. Patients who received an allo-SCT for malignant or non-malignant disorders who develop grade II-IV acute GVHD involving gut and/or liver were randomized to either standard treatment consisting of high dose prednisolone plus placebo or high dose prednisolone plus Mesenchymal Stromal Cells (MSC).

Number of patients:
Planned: 200
Enrolled: 39
Analyzed: 39

Diagnosis and main criteria for inclusion:
Inclusion criteria:
- Any age;

- Previously treated with allo-SCT/ DLI;
- Grade II-IV acute GVHD involving gut and/or liver according to appendix A (confirmed by histology of involved tissues, however, the first infusion of MSC/placebo can be given without final histological confirmation);
- WHO performance 0-3;
- Negative pregnancy test (if applicable);
- Patients must be willing and capable to use adequate contraception during therapy (if applicable) ;
- Written Informed Consent by the patient and/or parent(s) or legal guardian(s).

Exclusion criteria:

- Patients with active, uncontrolled infection;
- Rapid progressive hematological malignancy;
- Patients pre-treated with prednisolone > 1 mg/kg for GVHD, for more than 72 hours prior to randomization/application of MSC/placebo;
- Known uncontrolled toxicity for DMSO;
- Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, cancer, etc.)
- Any psychological, familial, sociological and/or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

Investigational Medicinal Product(s), dose and mode of administration:
MSC or placebo was given intravenously at day 1, day 8, and day 22.

Comparator(s), dose and mode of administration:
Placebo consisted of a 10% DMSO-solution in Physiological Salt Solution and Human Serum Albumin. It was given intravenously at day 1, day 8, and day 22.

Criteria for evaluation - Efficacy:
Primary endpoint:
Proportion of patients in each treatment arm who experience a CRGVHD or PRGVHD at day 57, without treatment failure (initiation of secondary treatment, progression/relapse, or death.

Secondary endpoints:

- Proportion of patients in each treatment arm who experience a CRGVHD or PRGVHD at indicated days after initiation of study-treatment, without treatment failure (initiation of secondary treatment, progression/relapse, or death)
- Time to CRGVHD or PRGVHD
- Amount of immune suppression at indicated days (and cumulative exposure of steroid till above mentioned time points)
- The (immunological) phenotype before and after application of MSC/placebo of responders and non-responders in both groups at different sites
- The immunological genotype of responders and non-responders as well as donors in both groups
- Quality of life at indicated days

- Cost-effectiveness as determined by hospital admission days from randomization until day 57 calculated against the price of MSC
- Relapse of the underlying disease (e.g. hematological malignancy)
- Incidence and severity of chronic GVHD
- Progression-free survival, defined as time from randomization until progression or relapse (of the underlying disease), or death whichever the cause
- Overall survival, defined as time from randomization until death whichever the cause. Patients still alive at the date of last contact, will be censored

Criteria for evaluation - Safety:

- Adverse events

Statistical methods:

After an inclusion period of nearly 3 years between May 2014 en May 2017 the trial was put on hold due to slow accrual. Despite a proposed amendment the trial could not be reopened and therefore a total of 39 patients were randomized and treated on the protocol. Twenty one patients were randomized to the MSC arm and 18 patients to the placebo arm.

Summary of efficacy results:

Median age was 44 years (IQR 17-62 years, range 1-75 years) with no significant difference between the two arms. There was an overall male predominance of 62% in the MSC arm and 83% in the placebo arm. Severity of acute GVHD was equally distributed in both arms (MSC arm 33% grade 2, 57% grade 3 and 10% grade 4 vs 22% grade 2 and 78% grade 3 in the placebo arm). Median time from transplantation to randomization was 2.3 months (not different between arms). The majority of patients received 3 infusions on protocol (81% in MSC vs 67% in placebo arm). Less patients had at least one serious adverse event in the MSC (33%) compared to the placebo arm (61%).

The primary endpoint of the study was complete or partial resolution of aGVHD at day 57 after first infusion of MSC or placebo. In the 21 patients treated with MSC 14 patients (67%) reached the primary endpoint vs 8 patients (44%) in the placebo arm. Median follow up of the 15 patients still alive is 109 months (IQR, 96-108 months). Overall survival was improved in patients treated with MSC compared to placebo, however due to the low patient numbers this was not analyzed to be a significant difference.

Summary of safety results:

There were 13 SAE's in the placebo arm vs 9 SAE's in the MSC arm.

Less patients had at least one serious adverse event in the MSC (33%) compared to the placebo arm (61%).

Most SAE's were related to infections as was anticipated in this immunocompromised patient cohort. No SAE could be directly related to infusion of the MSC. Six SAEs resulted in death of the patient, 4 in the patients treated with prednisone+placebo and 2 in the patients treated with prednisone+ MSC. In the longterm follow up of patients that received MSC, no new safety concerns were noted.

Conclusions:
Randomized controlled trials with ATMPs have proved to be difficult in an academic setting, however the HOVON 112 trial shows the potential of MSC in the treatment of aGVHD also in a first line setting. MSC have few side effects and appear to have clinically meaningful beneficial effects in grade II-IV aGVHD patients translating in an improved CR/PR rate and overall survival.