Pooled fecal allogenic microbiotherapy for refractory gastrointestinal acute graft-versus-host disease: results from the early access program in Europe

Florent Malard, MD, PhD
Sorbonne University, INSERM
Clinical Hematology and Cellular Therapy Dpt.
Saint-Antoine Hospital
Paris, France

Disclosures

I have the following relationships to disclose:

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Fecal microbiotherapy (FMT) and gastro-intestinal acute GvHD

- Treatment of GI-aGvHD is an **unmeet medical need**
- Link between gut microbiota dysbiosis and GvHD outcomes is **well established.**
- FMT was proven to be **safe and effective** in highly immunosuppressed patients.

➔ **Promising results with FMT for SR-GI-aGvHD in case reports and small series**

Abbreviations: SR-GI-aGVHD, steroid-refractory gastro-intestinal acute graft-versus host disease

aGvHD after ruxo resistance/intolerance: unmet medical need, poor survival

nature > nature reviews disease primers > primers > article

Primer | Published: 08 June 2023

Acute graft-versus-host disease

Florent Malard, Ernst Holler, Brenda M. Sandmaier, He Huang & Mohamad Mohty

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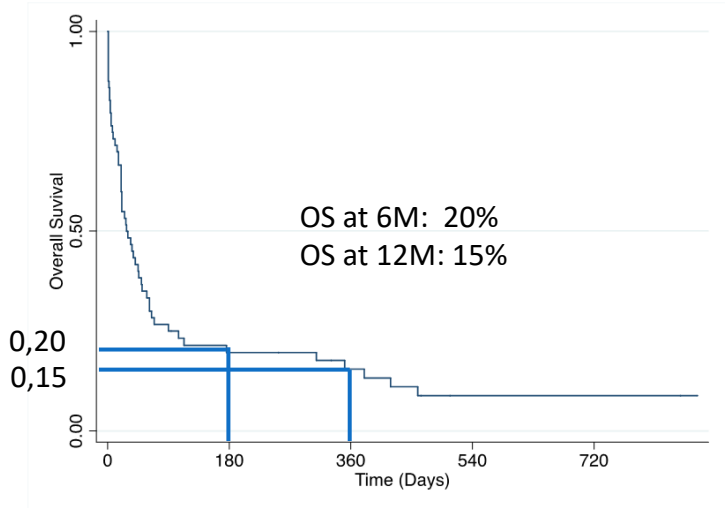
Ruxolitinib resistance or intolerance in steroid-refractory acute graft-*versus*-host disease — a real-world outcomes analysis

Sameem Abedin,[1] Nahid Rashid,[2] Mark Schroeder,[3] Rizwan Romee,[4] Mary Nauffal,[5] Muhamad Alhaj Moustafa,[6] Mohamed A. Kharfan-Dabaja,[6] Jeanne Palmer,[7] William Hogan,[8] Mehrdad Hefazi,[8] Samantha Larson,[9] Shernan Holtan,[10] Zachariah DeFilipp,[11] Reena Jayani,[12] Bhagirathbhai Dholaria,[12] Joseph Pidala,[13] Farhad Khimani,[13] Michael R. Grunwald,[14] Candace Butler,[14] and Mehdi Hamadani[1]

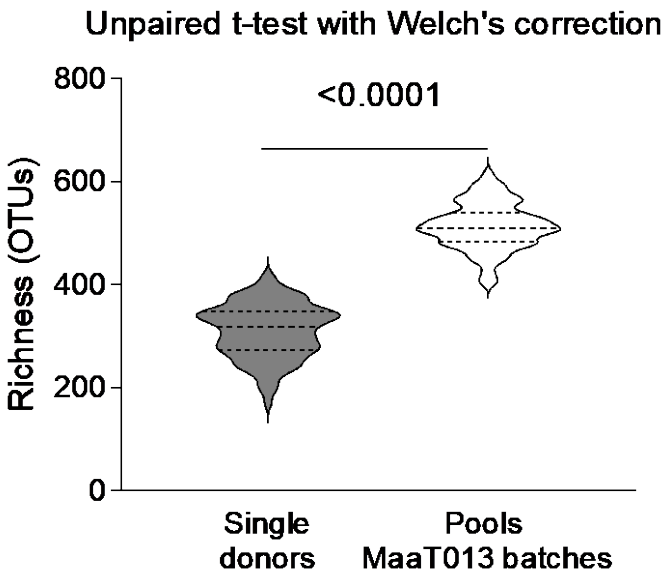
No validated treatments are available for acute GvHD that is refractory to steroids and ruxolitinib, and therefore **it remains an unmet medical need**



Median survival of 28 (range: 15-253) days

Abedin et al, 2021
Malard et al, 2023

MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: GvHD response (all patients)



Significant increase of pooled product richness when compared to mono-donor products

ODD status from EMA and FDA

Characteristics
Pooled microbiota: a high-richness, high-diversity, full ecosystem, containing Butycore™, 24 months stability at -80°C

Administration
3 doses (150 mL enema bag) within 2 weeks

Available Clinical Data
- ✓ HERACLES Phase 2 Clinical Trial, n=24,
- ✓ Early Access Program, data on n=140, ongoing (> 150 patients treated as of March 2024)

Efficacy evaluation (GI ORR at Day28)
Complete response, Very Good Partial Response, Partial Response

Malard et al, eclinical medicine 2023

MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: Early Access Program (EAP)

- **In France: Authorized by the French regulator (ANSM) with Governing protocol for use**
- **In other countries in Europe: compassionate use**

Data from 140 patients treated from July 2018 to October 2022, in 26 European sites (France, Italy, Spain, Austria, Germany)

Indications:

- Adult patients with GI-aGvHD
- Known resistance to, or dependence on, corticosteroids (CS) alone or with failure of other lines of treatments
- GvHD with overlap syndrome

Contra-indications:

- Active uncontrolled infection
- Relapsed/ persistent malignancy requiring rapid immune suppression withdrawal
- Current or past veno-occlusive disease or other uncontrolled complication
- Absolute neutrophil count < 500/uL
- Absolute platelet count <10 000/uL
- Patients with negative EBV serology
- Current or past evidence of toxic megacolon, bowel obstruction or GI perforation
- Pregnancy, breastfeeding
- Known allergy to trehalose and maltodextrin

MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: Early Access Program (EAP)

Characteristics	All patients (N=140)
• **Age, median (range)**	58 (12-74)
• **Gender**	
○ Male	77 (55%)
○ Female	63 (45%)
• **Disease**	
○ Acute myeloid leukemia	55 (39%)
○ Myelodysplastic syndrome	26 (19%)
○ Myeloproliferativesyndrome	17 (12%)
○ Lymphoma	15 (11%)
○ Acute lymphoblastic leukemia	15 (11%)
○ Other	12 (9%)

MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: aGvHD characteristics

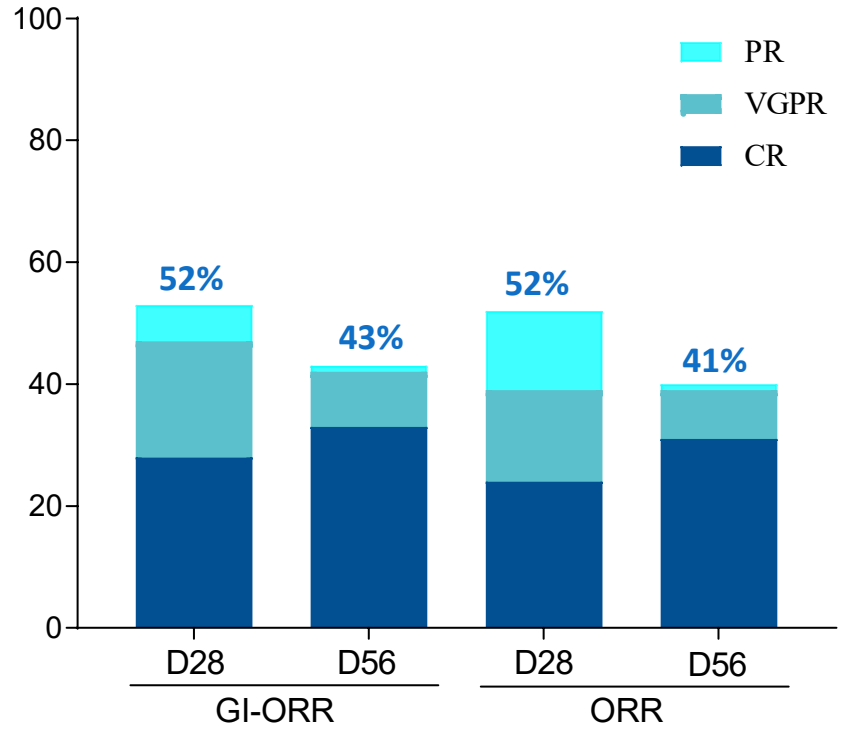
Characteristics	All patients (N=140)
• **Steroid status**	
○ Steroid resistance	**115 (82%)**
○ Steroid dependence	25 (18%)
• **Type of aGvHD**	
○ Classical	86 (61%)
○ Late onset	13 (9%)
○ Overlap syndrome	20 (14%)
○ Hyper-acute	20 (14%)
○ Chronic	1 (1%)
• **aGvHD grade at the time of ATU request (Harris, 2016)**	
○ I	0
○ II	16 (11%)
○ III	**68 (49%)**
○ IV	**56 (40%)**
• **GvHD organ involvement at inclusion**	
○ GI only	**84 (60%)**
○ GI + skin	**34 (24%)**
○ GI + liver	8 (6%)
○ GI + skin + liver	6 (4%)
○ Missing data for skin and liver	8 (6%)

MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: aGvHD prior therapies

Characteristics	All patients (N=140)
• **Median number of previous treatments for aGvHD (including CS) (range)**	**2 (1-6)**
○ **CS**	**140 (100%)**
○ **Ruxolitinib**	**121 (84%)**
• **Median number of MaaT013 doses administered (range)**	3 (1-6)
• **Route of MaaT013 administration**	
○ Enema	139 (99%)
○ Nasogastric tube	1 (1%)

MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: aGvHD response (all EAP patients)

D28 response, N (%)	GI Stage 1 N= 18	GI Stage 2 N= 28	GI Stage 3 N= 38	GI Stage 4 N= 56	Total N=140
• **GI-ORR**	12 (67%)	20 (71%)	24 (63%)	18 (32%)	**73 (52%)**
○ CR	10 (56%)	13 (46%)	10 (26%)	6 (11%)	**39 (28%)**
○ VGPR	1 (6%)	7 (25%)	9 (24%)	9 (16%)	**26 (19%)**
○ PR	1 (6%)	0	5 (13%)	3 (5%)	**8 (6%)**
Response, N (%)					
• **ORR**	12 (67%)	19 (68%)	25 (66%)	18 (32%)	**74 (52%)**
○ CR	8 (44%)	12 (43%)	9 (24%)	5 (9%)	**34 (24%)**
○ VGPR	3 (17%)	7 (25%)	5 (13%)	6 (11%)	**21 (15%)**
○ PR	1 (6%)	0	11 (29%)	7 (13%)	**18 (13%)**



Sustainable response at D56

Abbreviations: CR, complete response; VGPR, very good partial response; PR, partial response; ORR, overall response rate; GI, gastro-intestinal

N=138 for Day 56, 2 missing data

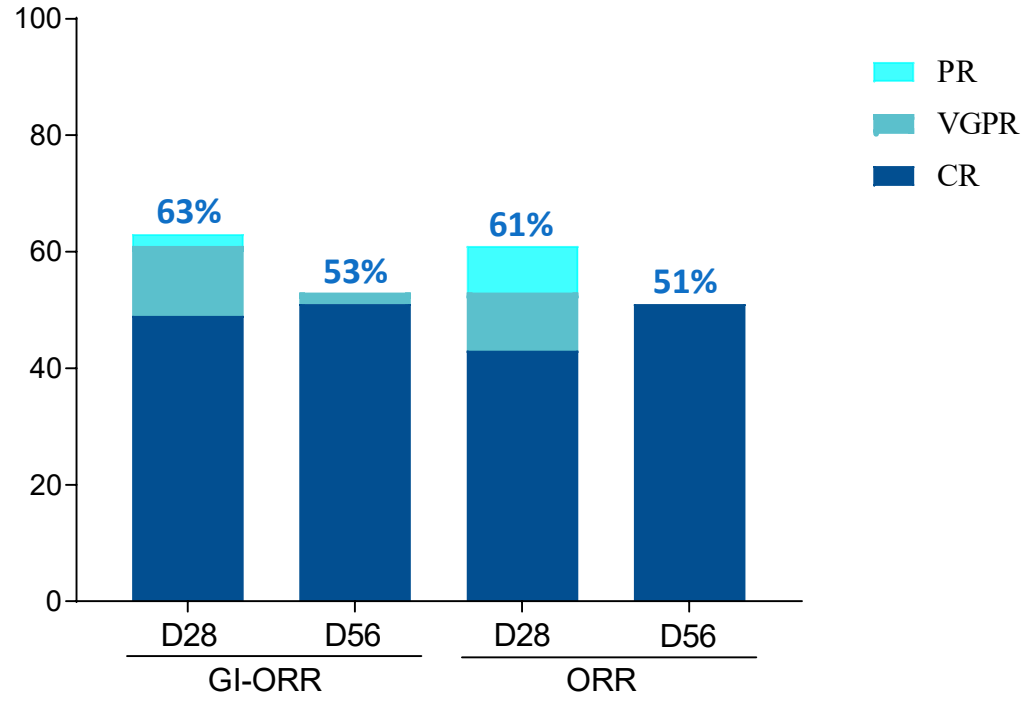
MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: aGvHD response in steroid- dependent versus steroid-refractory patients

GI response N (%)	SR-aGvHD, N= 115	SD-aGvHD, N= 25
GI-ORR	**54 (47%)**	**20 (80%)**
CR	**25 (22%)**	**14 (56%)**
VGPR	20 (17%)	6 (24%)
PR	9 (8%)	0

Abbreviations: CR, complete response; VGPR, very good partial response; PR, partial response; ORR, overall response rate; GI, gastro-intestinal

MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: aGvHD response in the ruxolitinib-refractory patients treated with MaaT013 as 3rd line (n=49)

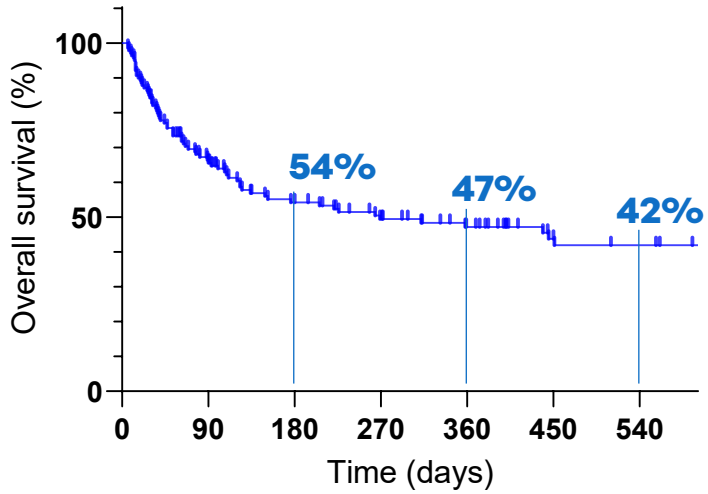
Response N (%)	Ruxolitinib refractory in 2nd line, MaaT013 in 3rd line N=49	
	GI-ORR	ORR
ORR	**31 (63%)**	**30 (61%)**
CR	**24 (49%)**	**21 (43%)**
VGPR	6 (12%)	5 (10%)
PR	1 (2%)	4 (8%)

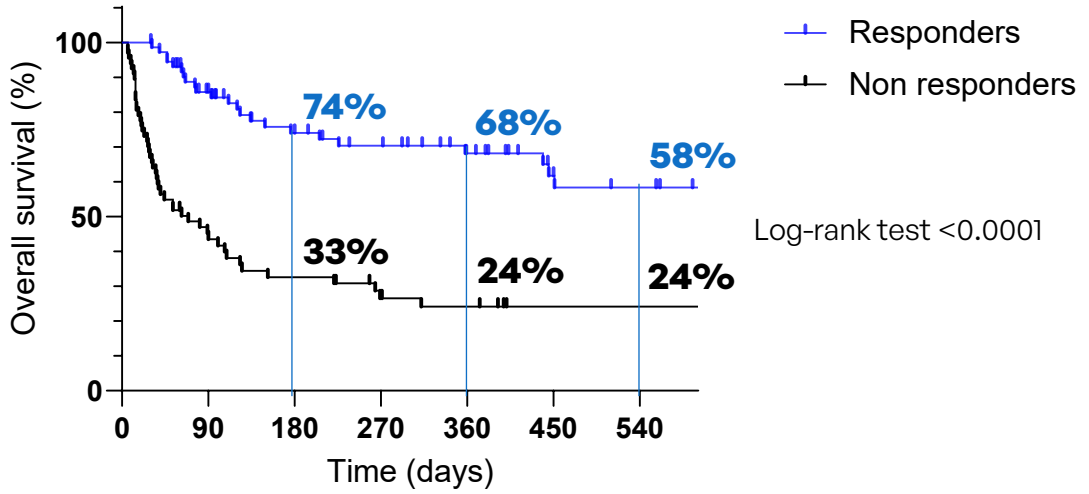


High rates of CR and VGPR
Sustainable response at D56

Abbreviations: CR, complete response; VGPR, very good partial response; PR, partial response; ORR, overall response rate; GI, gastro-intestinal

MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: Overall Survival (All EAP patients, n=140)

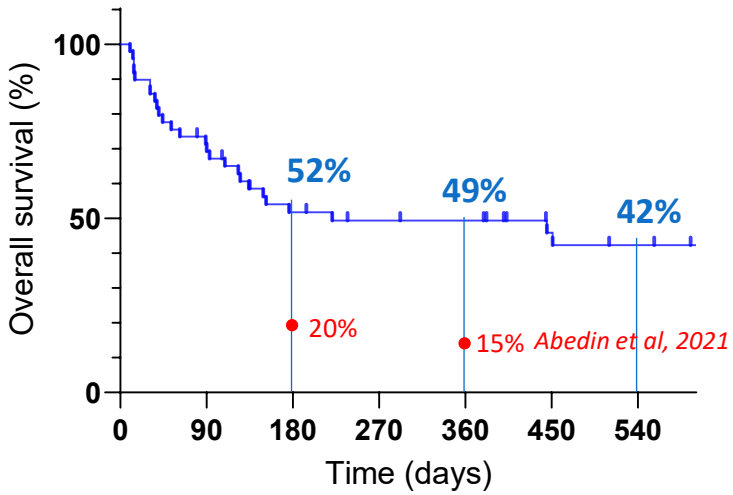


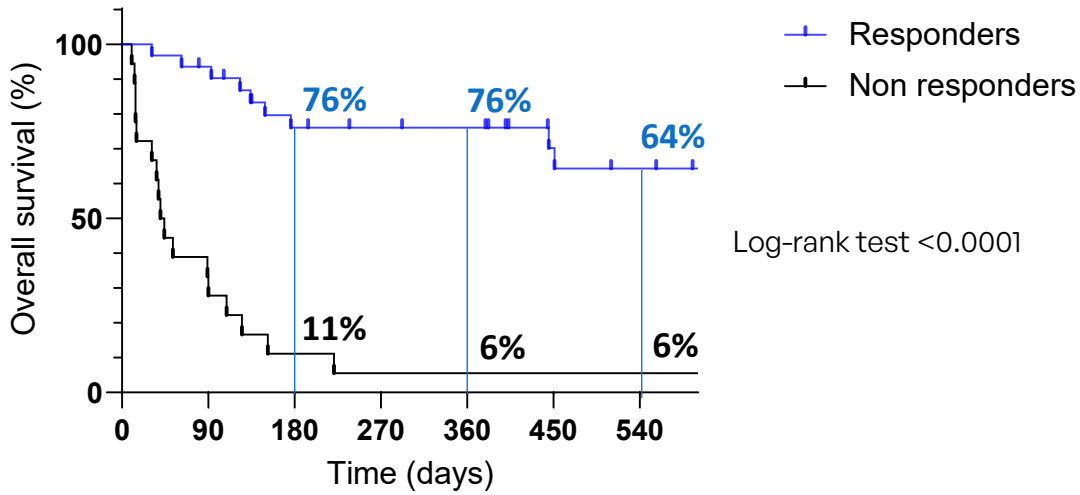


Clinical response to MaaT013 translates to increased overall survival

Abbreviations: CR, complete response; VGPR, very good partial response; PR, partial response

MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: Overall Survival in steroid- and ruxolitinib- refractory patients treated as 3rd line (n=49)





Clinical response to MaaT013 translates to increased overall survival

Abbreviations: CR, complete response; VGPR, very good partial response; PR, partial response

MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: Safety profile

- Overall safety is very good compared to historical data in such heavily pre-treated and fragile population
- 2 paediatric patients (aged 12 and 15) treated with MaaT013: well tolerated (no AE) and good efficacy
- 35 pharmacovigilance cases reported in 33 patients
- Among them, 22 cases possibly related to MaaT013 by the physician or the company, including 10 bacteremia and 6 sepsis
- 70 deaths reported: GvHD in 28, severe infection in 24, relapse in 11, hemorrhage in 2, neurological complications post allo-HCT in 1, respiratory distress in 1, cardiac arrest in 2 and unknown cause for 1 patient.
- No causality link with MaaT013 administration has been identified.

- **No report of pathogen transmission**
- **Only 2 cases of non-pathogenic commensal bacteria associated with infectious events**

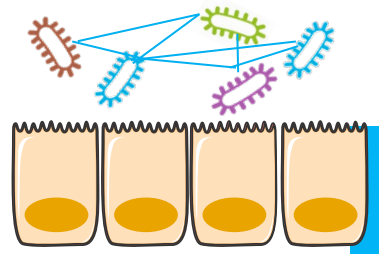
MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: potential mechanism of action with restoration of homeostasis and gut barrier

MaaT013 *resets microbial network*

Restoration of microbial homeostasis and network

↗ diversity
Eradication of MDRB, pathobiont growth inhibition

Remission of symptoms



1

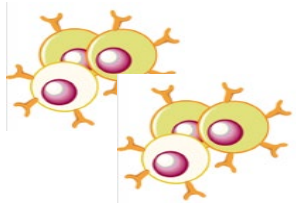
Restoration of barrier
Integrity
(~~SEPSIS~~)

Regulatory T cells

2

Butyrate
Immunoregulation
(IL-10; TGF-b)

3



Immune homeostasis
restoration

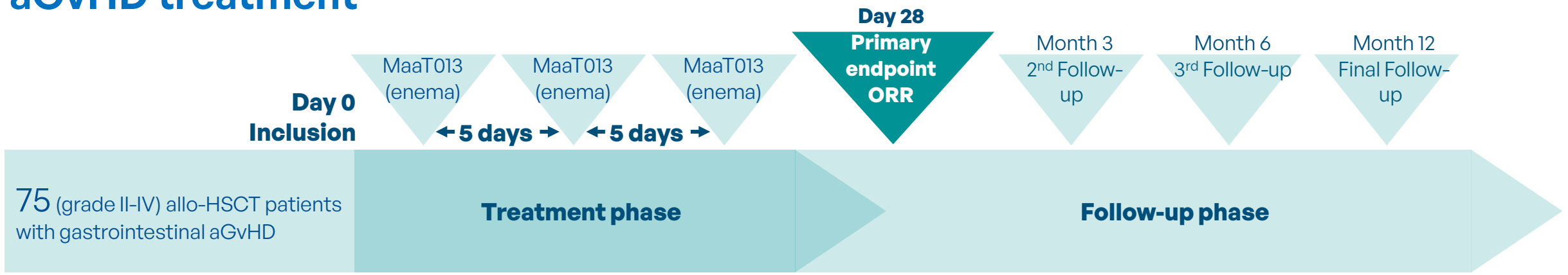
Proposed mechanism of action: MaaT013 restores microbiome diversity, regenerates gut barrier' s protective effect, and significantly curbs inflammation
(based on preclinical and clinical studies)

MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: Conclusions

- **MaaT013 is highly effective therapy for SR- and SD-GI- aGvHD**
  - D28 GI-ORR 52% and ORR 52%
- **Excellent responses in the ruxolitinib-refractory patients (MaaT013 as 3rd line), with high rates of CR and VGPR at D28, maintained at D56**
  - D28 GI-ORR 63% and ORR 61%
  - D56 GI-ORR 53% and ORR 51%
- **High overall survival in this severe population**
- **Innovative mechanism of action based on immune modulation**
- **Overall safety is very good**
- **Further investigation currently ongoing in a phase 3 trial (NCT04769895)**

Abbreviations: ORR, overall response rate; GI, gastro-intestinal; SR-aGVHD, steroid-refractory acute graft-versus-host disease; SD-aGVHD, steroid-dependent acute graft-versus-host disease

The ARES Phase 3 study: MaaT013 as 3rd line agent in GI aGvHD treatment



- Pivotal single-arm study of MaaT013
- Targeting 3rd line in patients with GI aGvHD who are refractory to both steroids and ruxolitinib
- Primary endpoint: GI response at Day 28
- Sites initiated in Europe in Q1 2022 (France, Germany, Spain, Italy, Austria, Belgium)
- First patient included in March 2022
- **Positive review by DSMB in October (N=30): favorable benefit/risk ratio, with "high efficacy and low toxicity."**

ClinicalTrials.gov Identifier: NCT04769895

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Thank you!

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