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

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Disclosures

I have the following relationships to disclose:

1. **Employment/leadership position/advisory role:** *No*
2. **Stock ownership or options:** No
3. **Patent royalties/licensing fees:** No
4. **Honoraria:** BMS, Therakos/Mallinckrodt, Sanofi, JAZZ Pharmaceuticals, Gilead, Novartis, Astrazeneca and MSD,
5. **Manuscript fees:** No
6. **Research funding:** No
7. **Subsidies or donations:** No
8. **Endowed departments by commercial entities:** No
9. **Gifts and others:** No
10. **Off-label use:** This presentation may include discussion of off-label use of some drugs.

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

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Nature Reviews Disease Primers **9**, Article number: 27 (2023) | Cite this article

15k Accesses | **9** Citations | **41** Altmetric | Metrics

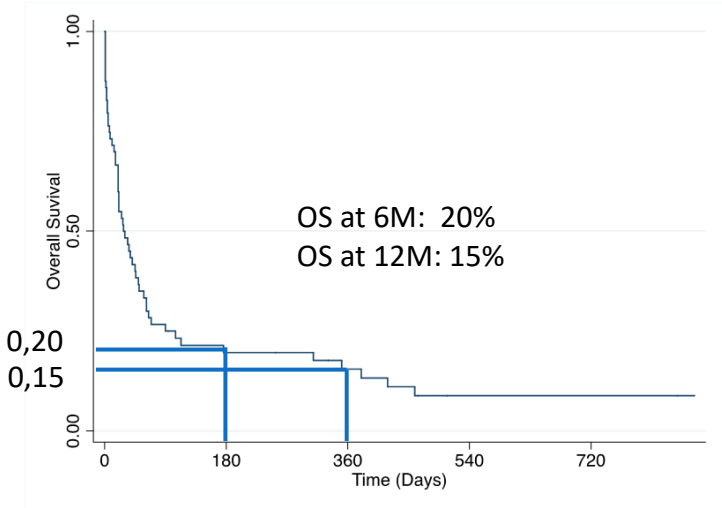
Br J Haematol. Author manuscript; available in PMC 2022 Nov 1.
Published in final edited form as:
Br J Haematol. 2021 Nov; 195(3): 429–432.
Published online 2021 Jul 12. doi: 10.1111/bjh.17700

PMCID: PMC9293486
NIHMSID: NIHMS1817932
PMID: 34254289

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]

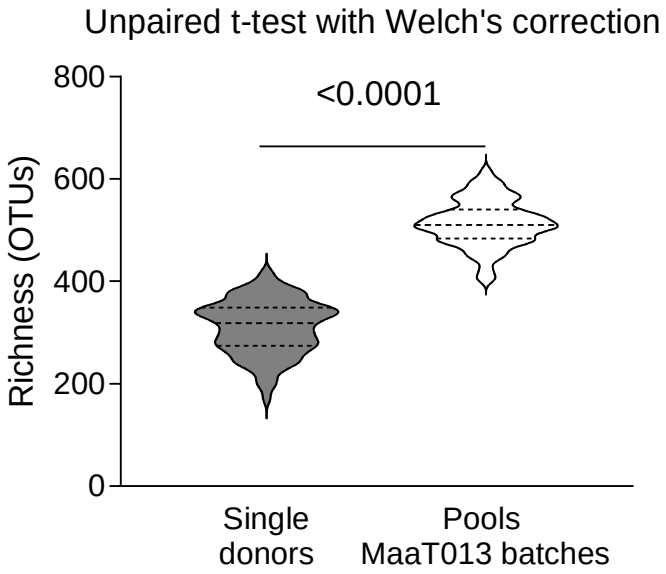
No validated treatments are available for acute GvHD that is refractory to steroids and ruxolitinib, and therefore **it remains an unmet medical need**



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



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=154, ongoing (> 170 patients treated as of Oct 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 154 patients treated from July 2018 to April 2024, in 27 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=154)
• **Age, median (range)**	57 (12-74)
• **Gender**	
○ Male	84 (55%)
○ Female	70 (45%)
• **Disease**	
○ Acute myeloid leukemia	61 (40%)
○ Myelodysplastic syndrome	27 (18%)
○ Myeloproliferative syndrome	18 (12%)
○ Lymphoma	16 (10%)
○ Acute lymphoblastic leukemia	18 (12%)
○ Other	14 (9%)

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

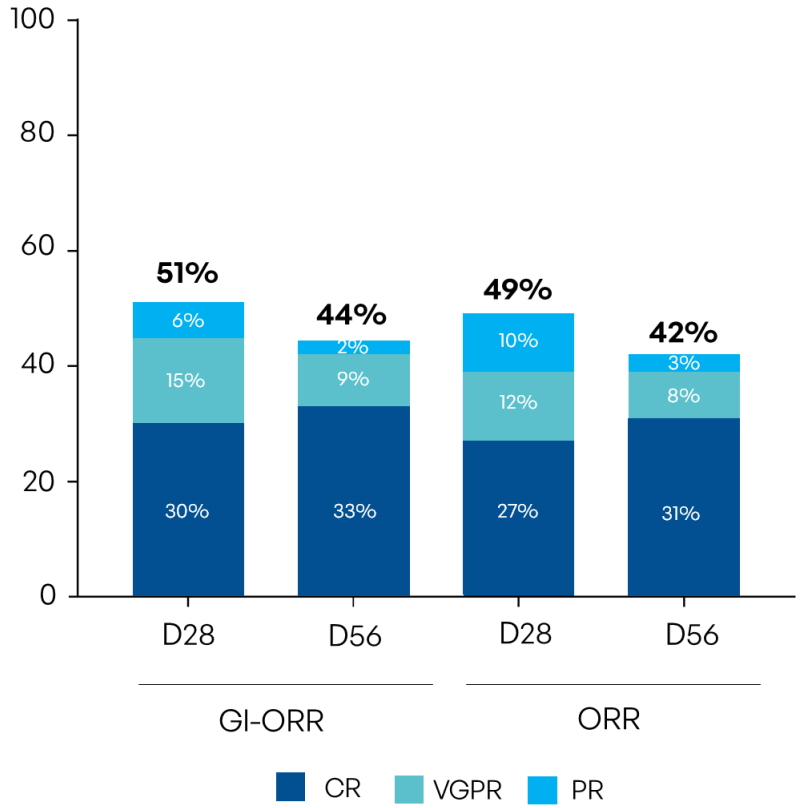
Characteristics	All patients (N=154)
• **Steroid status**	
○ Steroid resistance	**128 (83%)**
○ Steroid dependence	26 (17%)
• **Type of aGvHD**	
○ Classical	93 (60%)
○ Late onset	16 (10%)
○ Overlap syndrome	24 (16%)
○ Hyper-acute	20 (13%)
○ Chronic	1 (1%)
• **aGvHD grade at the time of ATU request (Harris, 2016)**	
○ I	0
○ II	20 (13%)
○ III	**73 (47%)**
○ IV	**61 (40%)**
• **GvHD organ involvement at inclusion**	
○ GI only	**94 (61%)**
○ GI + skin	**38 (25%)**
○ GI + liver	9 (5%)
○ GI + skin + liver	7 (5%)
○ Missing data for skin and liver	6 (4%)

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

Characteristics	All patients (N=154)
• **Median number of previous treatments for aGvHD (including CS) (range)**	**3 (1-6)**
○ **CS**	**154 (100%)**
○ **Ruxolitinib**	**139 (90%)**
• **Median number of MaaT013 doses administered (range)**	3 (1-6)
• **Route of MaaT013 administration**	
○ Enema	153 (99%)
○ Nasogastric tube	1 (1%)

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

Response N (%)	GI-ORR		ORR	
	Day 28 N=154	Day 56 N= 151	Day 28 N=154	Day 56 N= 151
ORR	**78 (51%)**	**66 (44%)**	**74 (49%)**	**64 (42%)**
CR	**46 (30%)**	**50 (33%)**	**41 (27%)**	**47 (31%)**
VGPR	23 (15%)	13 (9%)	19 (12%)	12 (8%)
PR	9 (6%)	3 (2%)	15 (10%)	5 (3%)



Sustainable response at D56

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

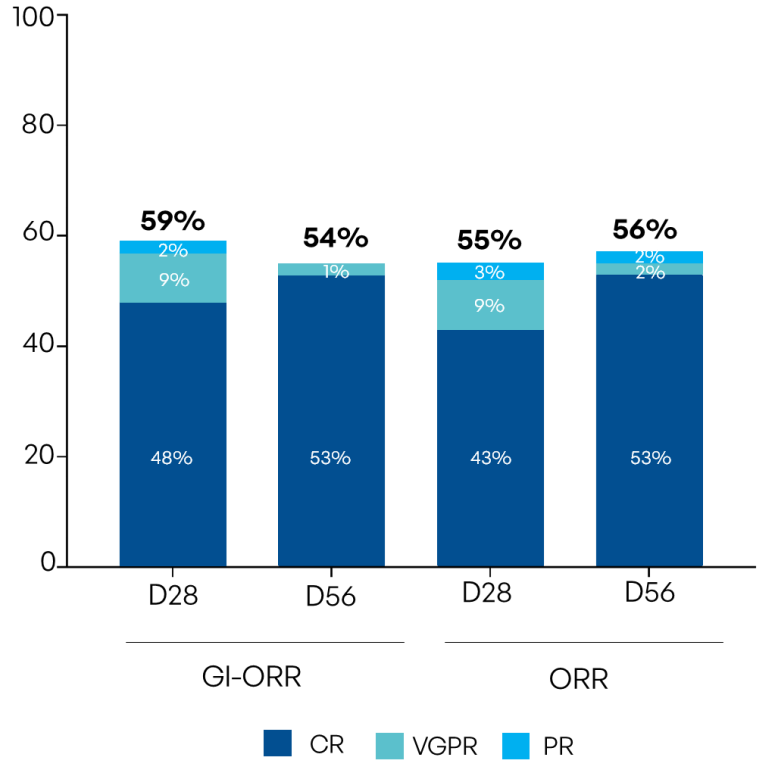
MaaT013, an immunosuppressant sparing agent to restore the microbiome and treat aGvHD: aGvHD response in steroid- dependent versus steroid-refractory patients

GI response N (%)	SR-aGvHD, N= 128	SD-aGvHD, N= 26
GI-ORR	**57 (45%)**	**21 (81%)**
CR	**28 (22%)**	**18 (69%)**
VGPR	20 (16%)	3 (12%)
PR	9 (7%)	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=58)

Response N (%)	GI-ORR		ORR	
	Day 28 N=58	Day 56 N= 57	Day 28 N=58	Day 56 N= 57
ORR	**34 (59%)**	**31 (54%)**	**32 (55%)**	**32 (56%)**
CR	**28 (48%)**	**30 (53%)**	**25 (43%)**	**30 (53%)**
VGPR	5 (9%)	1 (2%)	5 (9%)	1 (2%)
PR	1 (2%)	0	2 (3%)	1 (2%)

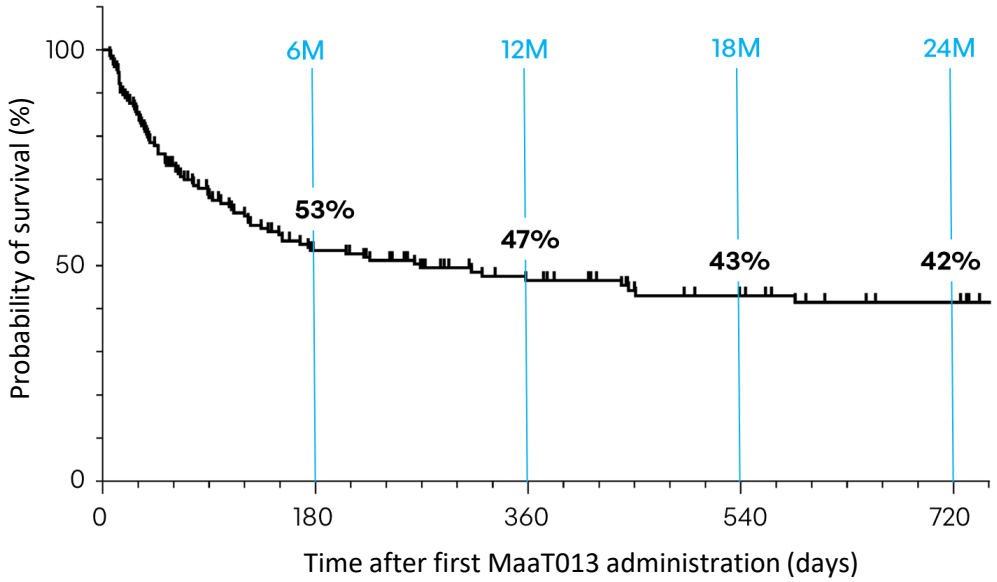


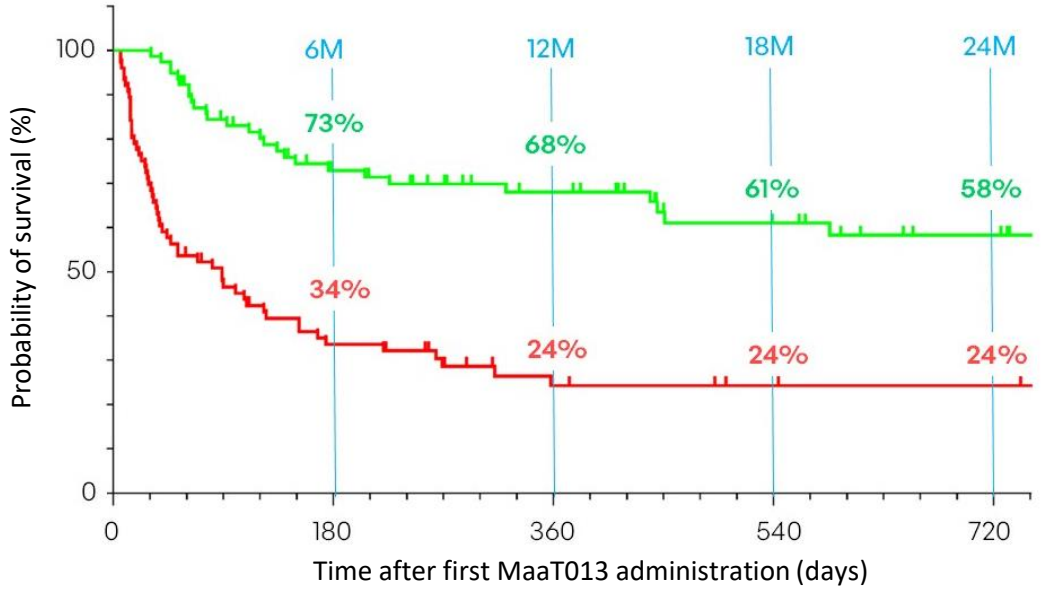
High rates of CR and VGPR

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=154)



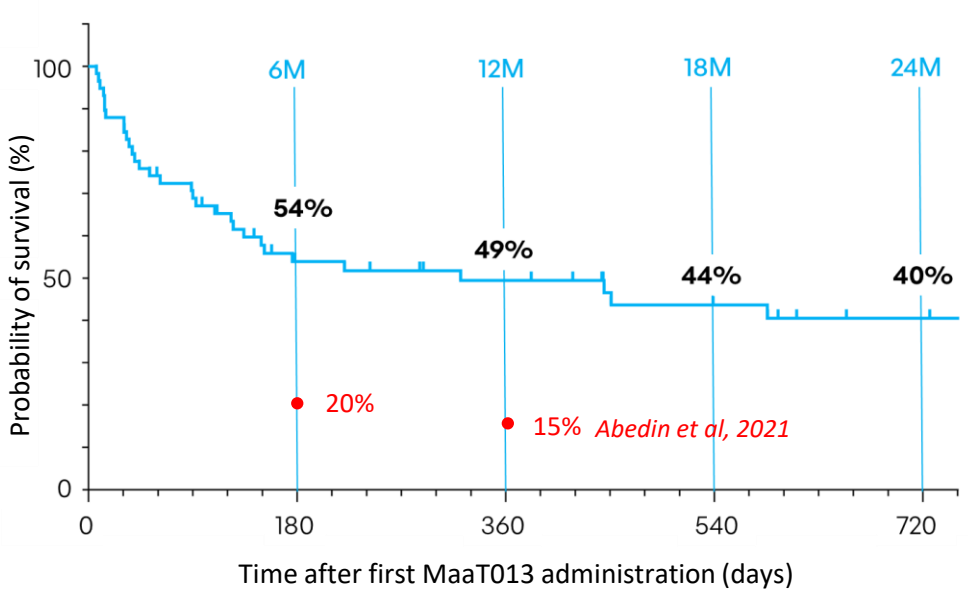


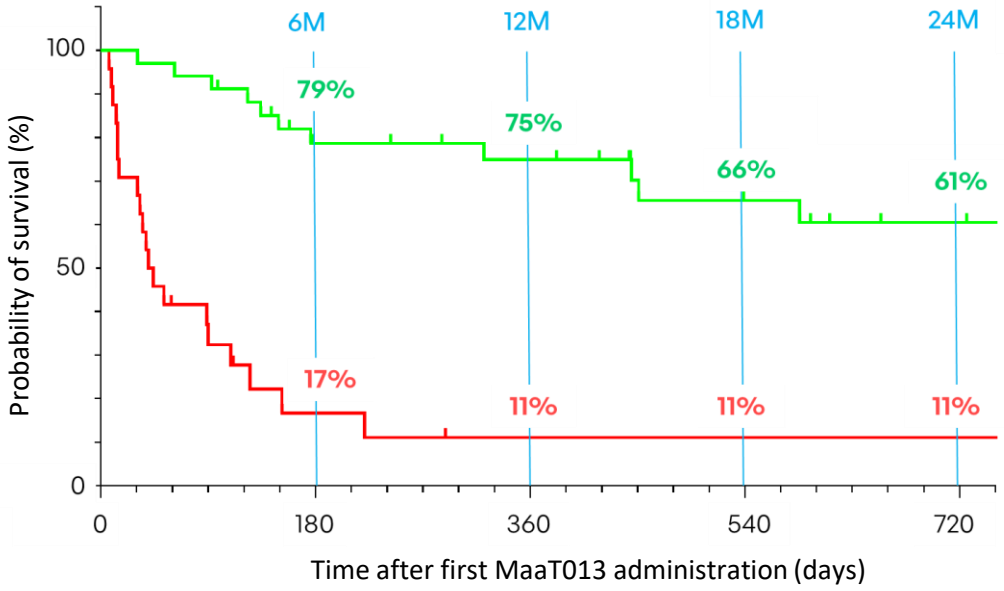
Log-rank test <0.0001

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=58)





Log-rank test <0.0001

Clinical response to MaaT013 translates to increased overall survival

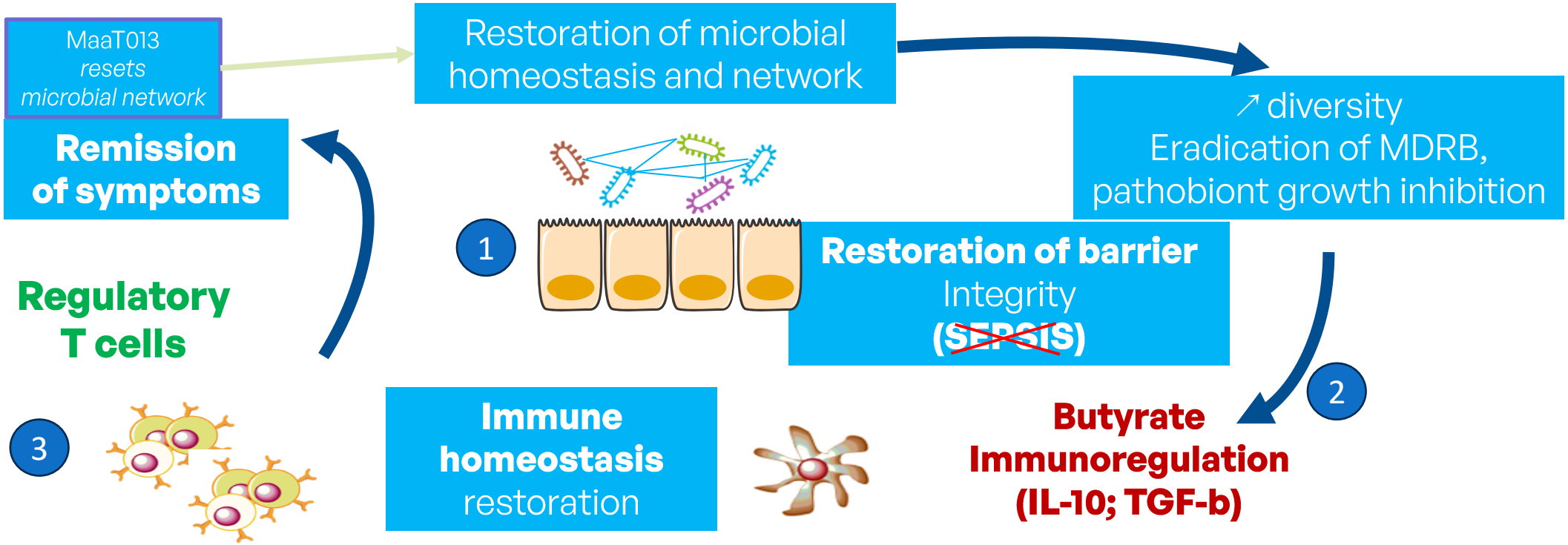
Abbreviations: CR, complete response; VGPR, very good partial response; PR, partial response

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
- 37 pharmacovigilance cases reported in 34 patients
- Among them, 24 cases possibly related to MaaT013 by the physician or the company, including 13 bacteremia and 6 sepsis
- 83 deaths reported: GvHD in 34, severe infection in 30 (incl 5 COVID-19), relapse in 11, hemorrhage in 2, neurological complications post allo-HCT in 2, respiratory distress in 1, cardiac arrest in 2 and natural death for 1 patient.
- No causality link with MaaT013 administration has been identified.

- **No report of pathogen transmission**

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



Proposed mechanism of action: MaaT013 restores microbiome diversity, regenerates gut barrier' s protective effect, and significantly curbs inflammation

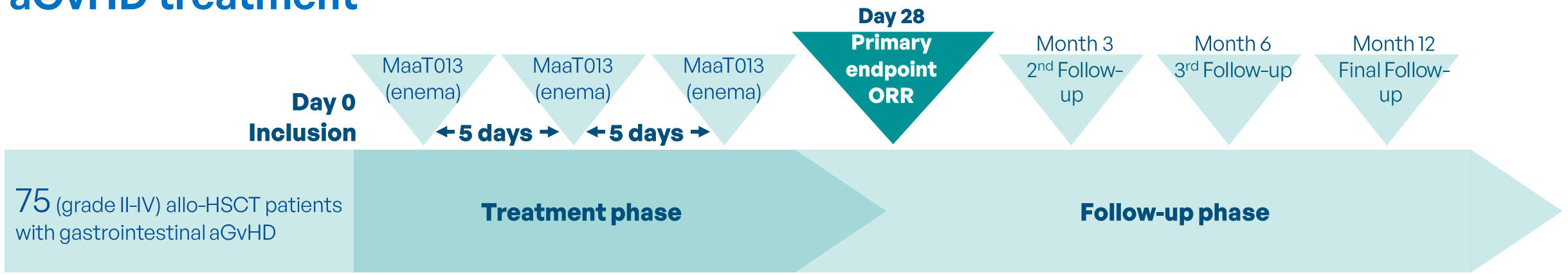
(based on preclinical and clinical studies)

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 51% and ORR 49%
- **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 59% and ORR 55%
  - D56 GI-ORR 54% and ORR 56%
- **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; **Last patient included in October 2024**
- **Positive review by DSMB in October (N=30): favorable benefit/risk ratio, with "high efficacy and low toxicity."**
- **Top line results expected in January 2024**

ClinicalTrials.gov Identifier: NCT04769895

Acknowledgments

Patients, Caregivers and Healthy Donors involved

- Michael Loschi, Thomas Cluzeau (CHU Nice)
- Faezeh Legrand, Reynier Devillier, Angela Granata, Valerio Maisano (Institut Paoli Calmettes)
- Anne Huynh, Sarah Guenounou, Cécile Borel (Institut Universitaire du Cancer Toulouse)
- Corentin Orvain, Sylvie François (CHU Angers)
- Amandine Charbonnier, Delphine Lebon (CHU Amiens)
- Deborah Desmier, Niels Moya (CHU Poitiers)
- Jean-Baptiste Mear, Faustine Lhomme, Stanislas Nimubona (CHU Rennes)
- Caroline Lejeune, Jérôme Cornillon (ICL St Priest en Jarez)
- Amandine Le Bourgeois, Patrice Chevallier (CHU Nantes)
- Clémence Médiavilla (CHU Bordeaux)
- Helene Labussière-Wallet (CHU Lyon)
- Marie-Anne Couturier (CHU Brest)
- Claude-Eric Bulabois, Martin Carré (CHU Grenoble)
- Hélène Lanic, Vincent Camus (Centre Henri Becquerel, Rouen)
- Sylvain Chantepie (CHU Caen)
- Patrice Ceballos, Jean-Jacques Tudesq (CHU Montpellier)
- David Beauvais (CHRU Lille)
- Gabrielle Roth Guépin (CHU Nancy)
- Etienne Daguindau (CHU Besançon)
- Karin Bilger (CHU Strasbourg)
- Stefan A. Klein (Mannheim, Germany)
- Jaime Sanz, Pedro Chorao (La Fe, Valencian, Spain)
- Sarah Altmeyer (Homburg, Germany)
- Francesca Patriarca (Udine, Italy)
- Francesco Saraceni (Ancona, Italy)
- Jakob D. Rudzki (Innsbruck, Austria)
- Florent Malard, Mohamad Mohty (Hôpital Saint-Antoine, AP-HP)
- MaaT Pharma’s team

Thank you!