Pooled allogenic fecal microbiotherapy MaaT013 for the treatment of steroid-refractory gastrointestinal acute graft-versus-host disease: results from the phase IIa HERACLES study and expanded access program

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INTRODUCTION

- **Steroid refractory gastrointestinal acute graft-versus-host disease (SR-GI-aGvHD)** is an important **unmet medical need.** The link between gut microbiota dysbiosis and GvHD outcomes is well established. Fecal microbiotherapies are reported to be **safe** in immunocompromised patients and have shown **promising results** in SR-GI-aGVHD.
- **MaaT013** is a **pooled allogenic fecal Microbiome Ecosystem Therapy** administered as enema, aiming at improving microbial diversity, richness and functionality.
- Here we report clinical outcomes from a **76-patient cohort with SR-GI-aGvHD** treated with the **MaaT013**: 24 patients were treated in the prospective, single-arm, phase IIa, HERACLES study (NCT03359980) while 52 patients were treated in an expanded access program (EAP).

METHODS

MaaT013 characteristics
Pooled microbiota: a high-richness, high-diversity, full ecosystem (10^{11} CFU/bag), containing Butycore™

Treatment protocol
3 doses *(150 mL enema bag for direct colonic delivery)*

Efficacy evaluation (GI response at Day 28)
Proportion of patient achieving a GI complete response (CR), Very Good Partial Response (VGPR), or Partial Response (PR) compared to Day 0

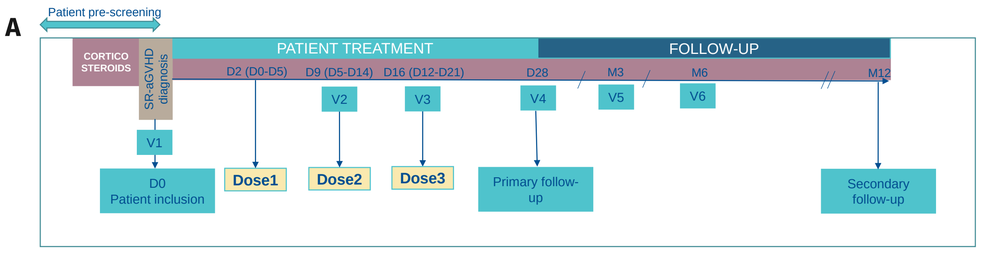
PATIENTS' CHARACTERISTICS

Characteristics	HERACLES (N=24) N (%)	EAP (N=52) N (%)
Age, median [range]	61 [20;69]	57 [18; 73]
Gender		
Male	16 (67%)	31 (60%)
Female	8 (33%)	21 (40%)
Diagnosis		
AML	9 (38%)	23 (44%)
MPS	6 (25%)	10 (19%)
MDS	3 (13%)	8 (15%)
ALL	2 (8%)	6 (12%)
Others	4 (17%)	5 (10%)
Graft source		
Bone marrow	1 (4%)	6 (12%)
PBSC	23 (96%)	45 (87%)
UCB	0	1 (2%)
Type of donor		
Related	11 (46%)	22 (42%)
Unrelated	13 (54%)	30 (58%)
Median number of previous GvHD treatment lines including CS [range]		
	1 [1-1]	3 [1-6]
Previous aGvHD treatment lines		
CS	24 (100%)	52 (100%)
Ruxolitinib	-	40 (77%)
Anti-TNFa	-	15 (29%)
ECP	-	11 (21%)
Methotrexate	-	9 (17%)
Others	-	18 (35%)
Steroid status		
Steroid resistance	24 (100%)	43 (83%)
Steroid dependence	0	9 (17%)
Number of MaaT013 dose received		
1 dose	24 (100%)	52 (100%)
2 doses	22 (92%)	45 (87%)
3 doses	12 (50%)	37 (71%)
aGVHD grade at inclusion (Glucksberg criteria)		
I	0	0
II	0	3 (6%)
III	23 (96%)	49 (94%)
IV	1 (4%)	0
GvHD organ involvement at inclusion		
GI	24 (100%)	52 (100%)
Skin	13 (54%)	15 (32%)
Liver	6 (25%)	6 (13%)

AML: acute myeloid leukemia; MPS: myeloproliferative syndrome; MDS: myelodysplastic syndrome; ALL: acute lymphoblastic leukemia; PBSC: peripheral blood stem cells; UCB: umbilical cord blood; CS: corticosteroids; ECP: extracorporeal photopheresis; GI: gastrointestinal

HERACLES

HERACLES: a phase 2 european clinical trial (NCT03359980) evaluating MaaT013 as 2nd line therapy in 24 patients with steroid-refractory gastrointestinal aGvHD

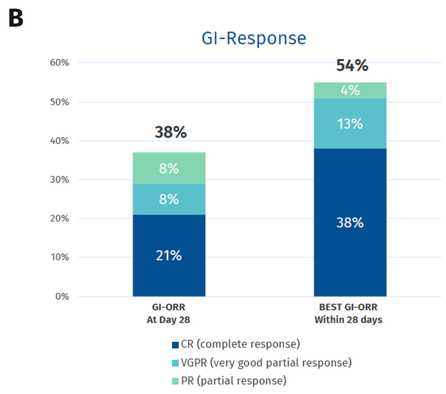


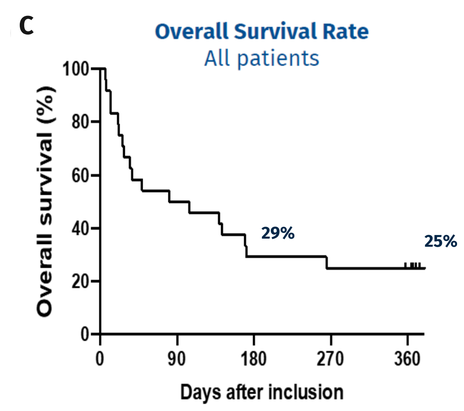
Main inclusion criteria

- **Grade III - IV aGvHD with gut predominance,** if involvement of other organs, resistant to a first line therapy with steroids
- ≥ 18 years old
- **Allo-HSCT** : any type of donor, stem cell source, GvHD prophylaxis or conditioning regimen
- ≥ 12 hours discontinuation of systemic antibiotics

Main exclusion criteria

- **Grade IV hyperacute GvHD**
- Overlap cGvHD
- aGvHD after donor lymphocyte infusion
- Relapsed/persistent malignancy requiring immunosuppression withdrawal
- **Other systemic drugs than corticosteroids for GvHD treatment**
- Toxic megacolon or gastrointestinal perforation





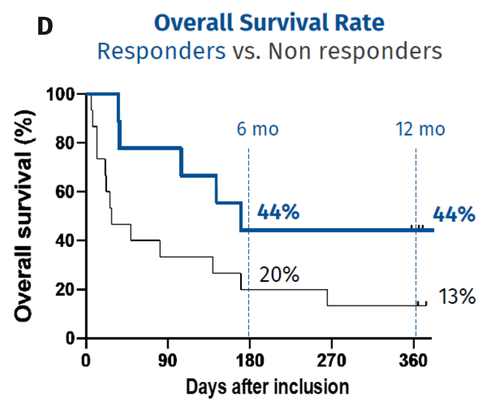
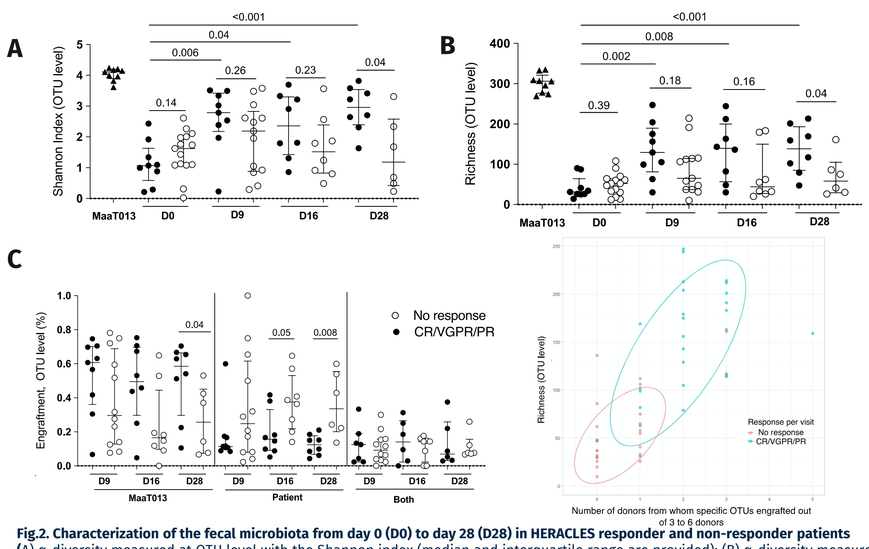


Fig 1 : Patients' response and outcomes after MaaT013 treatment in HERACLES (n=24) (A) HERACLES study flow chart (B) Response rate at day 28 (D28) and best GI response until D28 (GI-BOR-D28). (C) Overall survival in all patients (D) Overall survival according to response to MaaT013 at day 28. P=0.047, logrank test.



α-diversity indexes are significantly increased after MaaT013 treatment in responding patients

Higher proportions of engrafted MaaT013-derived species in the total composition of responder microbiota

Excellent tolerance reported – reviewed by an independent data safety and monitoring board

39 adverse events reported within 24 hours of MaaT013 administration, including 4 serious adverse events: 1 cerebral infarction (Grade 4) , 1 thrombotic microangiopathy (Grade 3), 1 general physical health deterioration (Grade 5), 1 *Escherichia* sepsis (Grade 3). The *E. coli* strain isolated from the blood sample of the patient was not identified in the MaaT013 received by the patient.

Fig.2. Characterization of the fecal microbiota from day 0 (D0) to day 28 (D28) in HERACLES responder and non-responder patients
(A) α-diversity measured at OTU level with the Shannon index (median and interquartile range are provided); (B) α-diversity measured at OTU level with the Richness index (median and interquartile range are provided) (C) Colonization by MaaT013 or "engraftment" defined as the proportion of OTUs in the stool coming from MaaT013. Engraftment measured at OTU level (median and interquartile range are provided). A to C: CR is for complete response; VGPR, very good partial response; PR, partial response. Response was evaluated at day 28. Statistical significance evaluated using Mann-Whitney test (D) Richness versus number of donors from whom specific OTUs engrafted (out of 3 to 6 donors). Clinical GI response was evaluated at each visit. Ellipse size is set to include 70% of the number of observations for each group.

EXPANDED ACCESS PROGRAM (EAP)

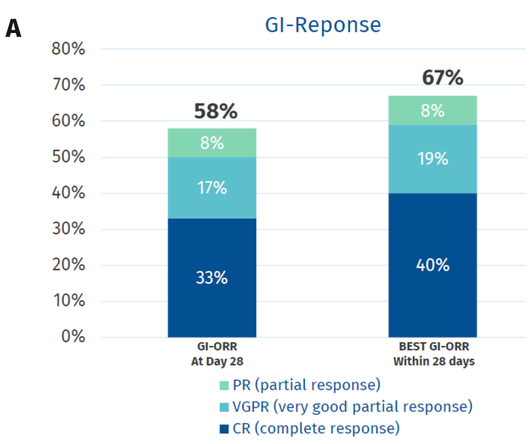
EAP program objective

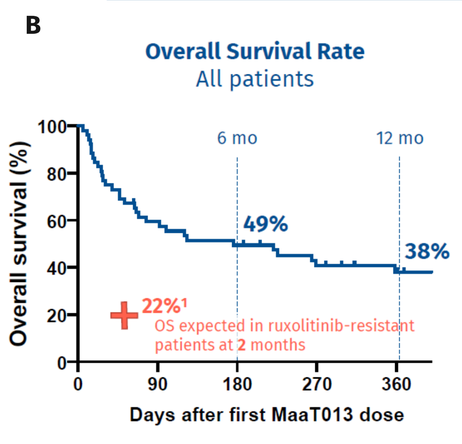
Patients not eligible to HERACLES → **EAP Expanded Access Program** → *Broader patient population* → *Ongoing in France*

- Steroid refractory / dependent
- Acute GVHD with gut involvement, grade II to IV
- Any line of treatment
- MaaT013 used as a monotherapy and/or combination therapy

52 patients treated

Very promising efficacy results in the EAP population
GI-response strongly correlates with survival, especially in patients previously treated with ruxolitinib (77% of EAP patients)





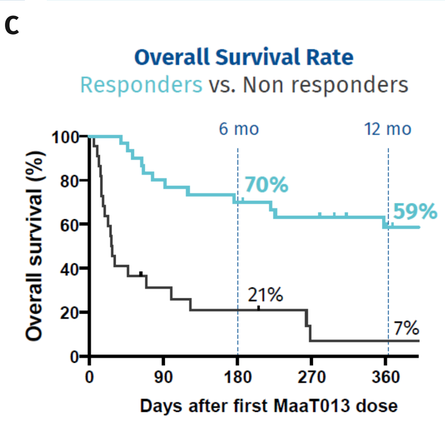


Fig. 3 : Patients' response and outcomes after MaaT013 treatment in the expanded access program (n=52)
(A) Gastrointestinal overall response rate at day 28 (D28) and best GI response achieved until D28 in early access program. (B) Overall survival after first MaaT013 administration, in the EAP (C) Overall survival according to response to MaaT013 in EAP
[1]Jagasia et al, Blood, 2020

Overall safety is good
- GI symptoms reported in 2 patients (abdominal pain, anorectal disorder)
- Infectious complications in 6 patients out of 52 (arthritis bacterial, sepsis, Escherichia bacteremia, bacterial translocation, bacteroides infection, septic shock)

CONCLUSION

- Treatment of 76 SR-GI-aGvHD patients with **MaaT013 is safe** and translates into a **high response rate in patients with SR-GI-aGvHD** : D28 GI-ORR **38% and 58% in HERACLES and EAP respectively**
- The **benefit on GI-response positively and significantly impacted OS in responding patients** : 44% and 62% M12 OS in HERACLES and EAP responding patients respectively, when compared to non-responding patients (13% and 7% respectively at M12) and compared to previous reports (Castilla-Llorente, 2014; Jagasia, 2020; Abedin, 2021)
- MaaT013 is currently being evaluated in a European **Phase 3 clinical trial** in 75 patients with steroid- and ruxolitinib-refractory aGvHD patients (NCT04769895)