Safety, tolerability and gut microbIota AnalysiS of an Oral microbiotherapy in amyotrophic lateral sclerosis; an open-label phase 1b pilot trial

Adèle Hesters* (1), Pierre-François Pradat (1), François Salachas (1), Giorgia Querin (1), Emilie Plantamura (2), Juliette Jouve (2), Hervé Jullien de Pommerol (2), Véronique Danel-Brunaud (3), Gaëlle Bruneteau (1,4)

1. APHP, Pitié-Salpêtrière Hospital, Department of Neurology, Paris ALS Center, Neurosciences Clinical Investigation Center, Paris, France 2. MaaT Pharma, Lyon, 69007, France. 3. Department of Neurology, ALS Center, Lille University Hospital Center, Lille, France. 4. Alliance on Clinical Trials for ALS-MND (ACT4ALS-MND), Neuroscience Clinical Investigation Center,Paris Brain Institute, Paris, France.

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INTRODUCTION

The pathogenesis of Amyotrophic lateral sclerosis (ALS) is multifactorial and involves complex host-environment interactions. The gut microbiota (GM), a key player of these interactions, can communicate with the central nervous system via the gut-brain axis. Preclinical and clinical evidence suggests an impact of GM dysbiosis on the pathogenesis of ALS and on the variability of the disease course. Interestingly, several of the mechanisms involved in ALS can be modulated by the GM e.g., energy homeostasis, oxidative stress levels, mitochondrial function, neuroinflammation.

› Restoring and maintaining symbiosis may thus constitute a unique opportunity to simultaneously address several of these ALS processes.

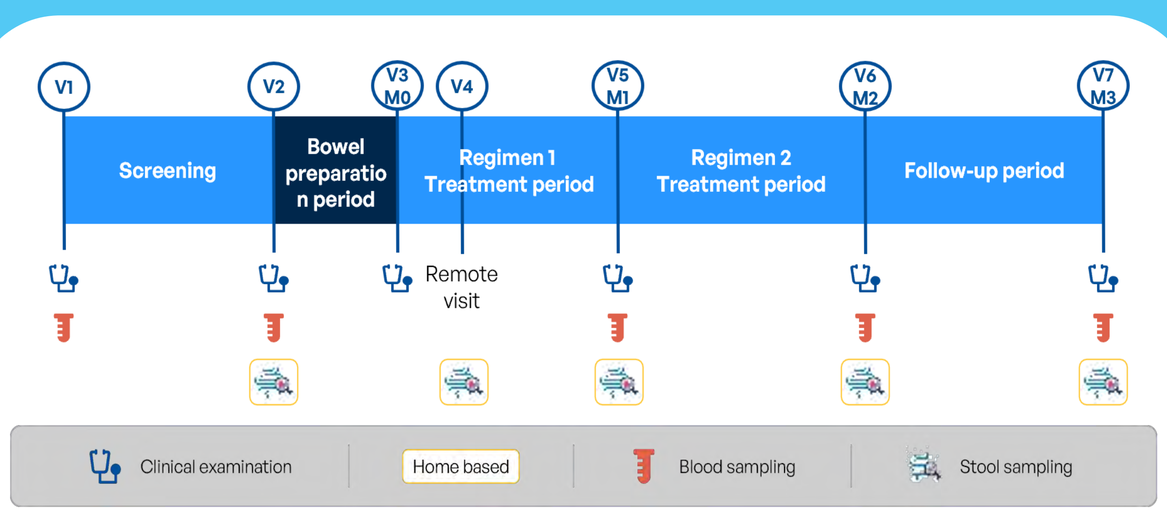
The IASO trial is a phase 1b pilot study (NCT05889572) aiming to assess the safety and tolerability of multiple doses of MaaT033, an oral Microbiome Ecosystem Therapy (MET), in patients with ALS and to analyze the composition and evolution of the GM before considering a larger randomized controlled efficacy study.

METHODS

MaaT033

- MaaT033 is a freeze-dried, high richness, high-diversity, full-ecosystem, fecal microbiota medicinal product, formulated as delayed-release capsules and derived from pooled allogenic human fecal material.

Study flowchart



Main Inclusion, non-inclusion criteria

- Male or female subjects, between18 and 80 years old
- ALS meeting the revised El Escorial criteria for possible, probable, laboratory-supported probable, or definite ALS
- Time since first motor deficit at screening: 6 to 24 months
- Slope of progression of ALS Functional Rating Scale - revised (ALSFRS-R) from date of symptom onset: between 0.4 and 1.1

Study design

Open label

Up to 15 patients

2 months treatments, 1 month follow-up

Study objectives

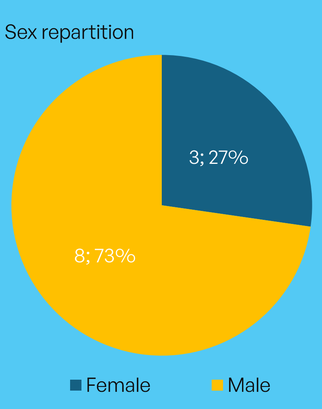
Primary: Assess MaaT033 treatment safety and tolerability
- o Incidence of treatment-related adverse events (TEAE) grade >3
- o Physical examinations
- o ALS clinical evaluations (ALSFRS-R scores, SVC)
- o Laboratory safety parameters
- o TEAE (solicited and unsolicited; serious)

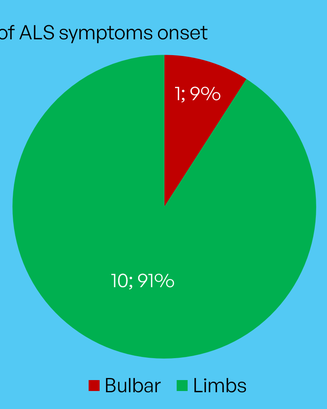
Secondary: Analyze the gut microbiota composition and evolution, to identify disease/ mechanistic biomarkers sensitive to study treatment for future chronic use
- o Microbiome engraftment, beta and alpha diversity indices.
- o Disease/mechanistic biomarkers in blood or feces: NfL, neutrophil/ lymphocyte ratio, IL-2, IL-6 , IL-8, IFNg, TNFa, MCP-1, TGFb, sCD14, CRP, sLBP, creatinin and SCFA.

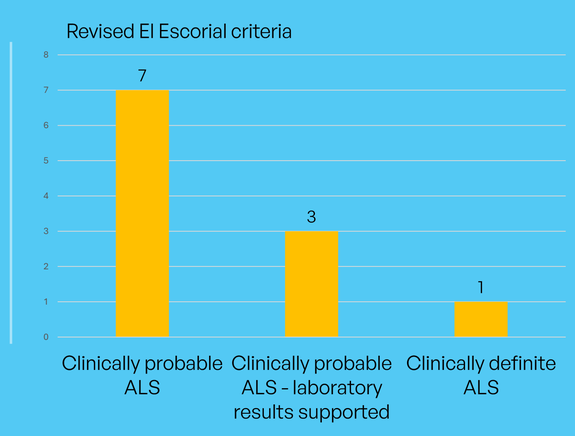
- Subjects with a non-invasive ventilation, a tracheotomy and /or a gastrostomy
- Known autoimmune diseases, inflammatory disorders or chronic infections
- Subject with white blood cells < 4000/ mm3; Polynuclear neutrophils < 1.5 G/ L
- Active infection requiring systemic antimicrobial therapy within 2-week prior to screening visit or between screening and baseline.
- Medical condition requiring proton pump inhibitors
- GI obstruction or perforation, bleeding. Toxic megacolon. Severe forms of inflammation of the intestinal tract.
- Gastric emptying disorders

RESULTS

Demographics (first 11 patients): Median age of 59 (34; 74) years-old







A first review by the study Data Safety Monitoring Board based on the clinical data of the first 8 patients having received at least one dose of MaaT033 (6 of them with at least one month of MaaT033 treatment) determined:

- MaaT033 was generally well tolerated with a good safety profile.
- No serious or severe adverse events were observed.
- No infectious events could be related to MaaT033.

CONCLUSION

- This is the first trial testing an oral full ecosystem microbiotherapy as a potential intervention to slow disease progression by acting simultaneously on several of the key ALS pathways.
- The DSMB recommended that the trial continues without modifications.

STUDY STATUS

14 patients received at least one dose of MaaT033

Recruitment completed

Active sites

Study read out 2H 2024

CONTACTS

Pr. Gaëlle Bruneteau (PUPH)**,** Neurology Department AP-HP Uniiversity Hospital Pitié Salpêtrière

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contact@maat-pharma.com