Synopsis

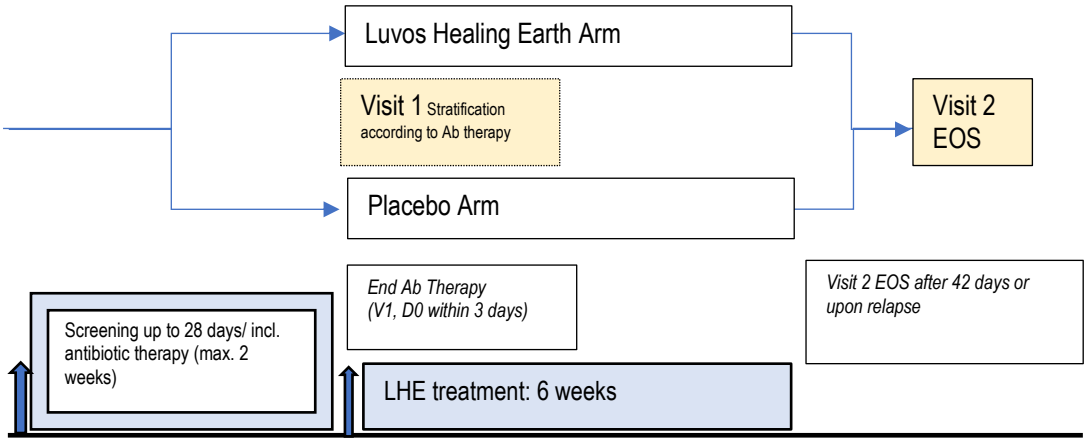
Study title	**A Randomized, double-blind, placebo controlled multicenter Study of the Clinical Performance and Safety of LUVOS® HEILERDE imutox in Patients with recurrent *Clostridioides difficile* infection.**
Short title	LUVCDIPLA
Study objectives	Primary objective is the reduction of the incidence of primary or secondary recurrences in patients successfully treated with Standard of Care anti-infective therapy of CDI. Secondary objectives are the reduction in clinical symptoms in case of a further recurrence, the Clinial Cure rate after 6 weeks of therapy, and the evaluation of the safety of Luvos® Heilerde
Test product(s)	Luvos® Heilerde imutox (LHE) Granulate Placebo Granulate
Indication	Patients with mild to moderate *Clostridioides difficile* infections and a (minimum) first recurrence of the disease
Coordinating Investigatoral	Prof. Dr. med. Maria Vehreschild, Universität Frankfurt
Diagnosis and main criteria for inclusion	• Females and Males aged > 18 years with proven mild to moderate *Clostridioides-difficile* Infection (white blood cell count of <15.000 cells/ml and a serum creatinine level < 1.5 mg/dl) • Patients with a first or multiple recurrence of CDI diagnosed by the primary care or hospital physician, and treated with anti-infectives (max. of 14 days) according to current guidelines, and which fulfil the criteria of "Clinical Cure".
Study design	Prospective, randomized, placebo controlled, double-blind, mulicenter, two-way parallel group PMCF clinical investigation
Methodology	Patients receive after the first examination for 6 weeks either • Group 1 LUVCDIPLA - 0g of LHE per day: Placebo-Granules of microcrystalline cellulose with sea sand and coloring 3 x 1 sachet pd

	• Group 2 LUVCDIGRA: 19,5 g Luvos® Healing Earth (LHE) pd: Sachet of granulate 3 x 1 pd (3 x 6,5g pd LHE imutox)
Planned study dates	Subject recruitment is planned to commence in 2nd quarter 2021, with an estimated enrolment duration of 24 months, and a six week treatment phase per patient. Anticipated study dates (clinical part) are accordingly April 2021-June 2023.
Planned number of study centers	10-30
Planned number of countries	1 (Germany)
Number of patients	A maximum total of 330 patients (N=314 evaluable; 157 per group) if only primary infections are included. In total, a minimum of 114 patients (N=108 evaluable,; 54 per group) if only secondary or multiple recurrent infections are included. depending on the actual distribution of patients with first or further infection that will be included into the study.
Primary endpoint	• Occurrence of a first or second CDI recurrence, with a new episode of diarrhea, positive stool test for toxigenic C. difficile following clinical cure of the first infection.
Secondary endpoints	• Global cure as defined as clinical cure of the first infection or recurrence episode and no CDI recurrence through week 6 • Global cure as defined as clinical cure of the recurrent (Secornd/further) infection or recurrence episode and no CDI recurrence through week 6 • Overall Clinical Cure after first of further infection. • Reduction of the patient's clinical symptoms in case of a further recurrence episode • Safety: Adverse events
Plan for statistical analysis	Both groups will be compared statistically regarding the clinical performance of LHE at avoiding further recurrences

Description Design

This clinical trial is a prospective, randomized, stratified placebo-controlled, multicenter, double-blind clinical trial (PMCF) in a two-way paralel group design. Inclusion in the trial (randomization, V1, DO) will occur within 3 days of successful antibiotic therapy during the screening phase.

Figure 1: Study design Scheme



Abbrev: Ab=Antibiotic; EOS=End of Study.

Patient population, Inclusion- / Exclusion Criteria

Subjects may be enrolled in the clinical trial only if they meet all of the following inclusion criteria and none of the following exclusion criteria.

Inclusion criteria:

1) Patients with the first occurrence of CDI and patients with the second (or multiple) occurrence of CDI (i.e., recurrence 1-x), and who:
   a) have fully completed 14 days or less of CDI antibiotic therapy,
   b) meets the criteria for "cure," and
   c) Can have visit 1 (inclusion examination) within 3 days;
2) Presence of written informed consent.
3) Age ≥18 years
4) Ability to understand the purpose and risks of the study and provide a signed and dated informed consent form and consent to the use of protected health information (in accordance with national and local privacy regulations applicable to subjects).
5) Patients must be willing and able to participate in all examinations and procedures required by the protocol.
6) In women of childbearing potential, willingness and use of effective contraceptive measures throughout the duration of this clinical trial.

Exclusion criteria

1. Patients who must continue to take their other therapies (except antibiotics) for any underlying conditions that may be present during the therapy phase, but for which a change in dose or medication is necessary during the therapy phase, or for whom additional concomitant therapy is required that, at the discretion of the investigator, precludes inclusion
2. Patients with short bowel syndrome or intestinal stomas
3. Patients with severe or complicated course of CDI (leukocytosis >15,000/µl, serum creatinine ≥ 1.5 mg/dl, hypotension requiring treatment, intensive care treatment, ileus, toxic megacolon, perforation, colectomy), including patients requiring prior antibiotic CDI therapy of more than 14 days duration
4. Patients who need to take antibiotics regularly, i.e. also or with high probability during the study, due to other diseases
5. Patients who need to continue antibiotic therapy (beyond visit 1) due to infectious disease of other organs, or have undergone antibiotic therapy (except against CDI) within the 4 weeks prior to inclusion (visit 1) in this study.

6. Known allergic reactions to healing clay or other loess preparations.
7. Inability to understand the study protocol
8. Multimorbid patients in a health condition that, at the discretion of the investigator, precludes inclusion
9. Patients with Crohn's disease, ulcerative colitis
10. Taking anticonvulsants (epilepsy)
11. Use of antiarrhythmic drugs
12. Under treatment with chemotherapeutic agents
13. Chronic liver disease (Child-Pugh B and C)
14. Chronic renal insufficiency (glomerular filtration rate < 60 ml/min/1.73m² body surface area)
15. Concurrent participation in another clinical trial
16. Previous participation in this study
17. Individuals who are in regulatory placement.
18. Individuals who are in a personal or financial dependency to the sponsor or a study center
19. Pregnancy or desire to become pregnant. The use of Luvos® healing clay during pregnancy is safe and poses no risk to participants.

Study Flow Chart

	Screening & Antibiotic - Phase [b]	Visit 1 and Enrolment	Treatment initiation	Interim-visit V-Z1	Visit 2 EOS[§]
	Screening		Treatment phase		
Visit plan	**D-28 to D-4**	**D –3 to D-1**	**D 0**	**Optional (D1-D41)**	**D 42 (+/- 5 Days)**
Informed consent		X			
Randomisation		X			
Start of randomized p.o. LHE treatment			X[a]		
Medical history, concomittant diseases and –medication		X			
Physical exam & vital signs		X		(X)	
Symptom scores (stool frequency & -consistency/24h, pain (VAS)), overall well being		X		(X)	X
AEs [c]		X	Capture in Pt. Diary	(X)	X
Provide study medication for 4 weeks, patient diary		X			
Check Sachets, patient diary					X
Overall assessment patient and investigator to efficacy and tolerability					X

Table 1: Flow Chart

[§] Visit 2 is performed 6 weeks after the start of treatment with LHE. In case of recurrence before D42, visit 2 is performed within 5 days after the recurrence is detected.
[a] Start of patient's treatment phase on day D0 (max. 3 days) after last antibiotic use
[b] Diagnosis by clinician or primary care physician. Antibiotic phase (e.g., fidaxo-micin 10 days)
[c] Adverse events, as well as daily dose of test product are recorded daily by the patient in the patient diary. The patient is asked about possible adverse events during the scheduled visits.