Studientitel:

CONTROLING INTESTINAL COLONIZATION OF HIGH-RISK PATIENTS WITH EXTENDED- SPECTRUM BETALACTAMASE PRODUCING ENTEROBACTERIACEAE (ESBL-E) – A RANDOMIZED TRIAL (CLEAR)

Prüfsubstanz: Fosfomycin (Monuril®), Colistin (Diaröntº mono), Gentamicin (Refobacin®) or Placebo

Eudra-CT Nummer: 2013-003048-21

Clinicaltrials.gov: NCT01931592

Prüfplan-Nummer: Uni-Köln-1667

Kurzbezeichnung: CLEAR Study

Abschlussbericht (Zusammenfassung)

Final Version 1.0 – 02 May 2018

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Unterschriften

Die unterzeichnenden Autoren stimmen den Inhalten des vorliegenden Abschlussberichtes durch ihre Unterschriften zu. Die hier berichtete, klinische Prüfung wurde nach den Grundsätzen der Deklaration von Helsinki, der Guten Klinischen Praxis (GCP) sowie den geltenden Gesetzen durchgeführt.

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Köln, 04.5.18
Ort, Datum

Unterschrift

Prof. Dr. rer. medic. Martin Hellmich

Biometriker

Köln, 02.05.2018
Ort, Datum

Unterschrift

Titel der Studie	**C**ONTRO**L**ING INTESTINAL COLONIZATION OF HIGH-RISK PATIENTS WITH EXTENDED- SPECTRUM BETALACTAMASE PRODUCING **E**NTEROBACTERIACEAE (ESBL-E) – **A R**ANDOMIZED TRIAL (CLEAR)
Amendments	Protocol version v5-02, 23rd May 2014; due to revised exclusion criteria Protocol version v6-01, 15th August 2014; due to revised inclusion criteria
Art des Vorhabens	This is a phase II trial with the aim to assess the efficacy and safety of an antimicrobial regimen in the short-term and long-term eradication of ESBL-E from the intestinal flora of immunocompromised high-risk patients.
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Veröffentlichung der Studie	The study has not been published yet.
Studienzeitraum	First patient in (FPI): 22.04.2014; Last patient last visit (LPLV): 28.02.2016; Premature discontinuation of the trial: 31.05.2016; Since colistin powder production was stopped by the manufacturer we were forced to terminate the trial prematurely.
Studienziele	The target group were immunocompromised patients at high risk of bloodstream infections with colonizing bacteria. The trial objective was the assessment of efficacy and safety of an antimicrobial regimen in the short-term and long-term

	eradication of ESBL-E from the intestinal flora.
Primärer Zielparameter	Short-term intestinal eradication defined as a fecal sample negative for ESBL-E/K on day 6+/-2 and day 11+/-2 was the primary endpoint.
Sekundäre Zielparameter	• Long-term intestinal eradication d28, defined as a fecal sample, negative for ESBL-E on day 28+/-4 • Long-term intestinal eradication d42, defined as a fecal sample, negative for ESBL-E on day 42+/-4 • Short-term non-intestinal eradication, defined as a combination of ESBL-E negative samples from urine and throat on day 6+/-2 and day 11+/-2 • Long-term non-intestinal eradication d28, defined as a combination of ESBL-E negative samples from urine and throat on day 28+/-4 • Long-term non-intestinal eradication d42, defined as a combination of ESBL-E negative samples from urine and throat on day 42+/-4 • Short-term overall eradication, defined as a combination of ESBL-E negative samples from feces, urine and throat on day 6+/-2 and day 11+/-2 • Long-term overall eradication d28, defined as a combination of ESBL-E negative samples from feces, urine and throat on day 28+/-4 • Long-term overall eradication d42, defined as a combination of ESBL-E negative samples from feces, urine and throat on day 42+/-4 • Emerging presence of non-ESBL multi-drug resistant bacteria in the intestine, defined as identification of vancomycin resistant *Enterococci* (VRE), carbapenemre-sistant gram negative rods (4MRGN according to the KRINKO definition) or colistin-resistant enterobacteria (except *Proteus* and *Serratia* spp.) in a fecal sample on day 6+/-2, day 11+/-2, day 28+/-4 or day 42+/-4 • Association between the intestinal microbiome pattern and the outcome of eradication on baseline, day 6+/-2, day 11+/-2, day 28+/-4 or day 42+/-4

	• Quantitative assessment of intestinal ESBL-E burden on baseline, day 6+/-2, day 11+/-2, day 28+/-4 or day 42+/-4 • Incidence and severity of AEs • Rate of AE-related study drug discontinuations
Studiendesign	This study was conducted as double-blind, multicenter placebo-controlled, parallel-group trial. After informed consent was obtained, patients were randomized in a 2:1 ratio between active study treatment and placebo. Randomization was carried out using a 24-7-internet service. The eradication regimen consisted of seven days colistin (Diarönt® mono, powder) $2x10^6$ IU four times daily, gentamicin (Refobacin®, solution) 80 mg four times daily and fosfomycin (Monuril®, granules) 3g every 72 hours. The placebo group received appropriate manufactured placebo preparations accordingly. Each study medication was dissolved in water and given orally. For evaluation of treatment success, fecal samples (preferably stool samples, alternatively deep rectal swabs), throat swabs and urine specimen were collected on day 0 (baseline), 6+/-2, day 11+/-2, day 28+/-4 and day 42+/-4 (last follow-up). For determination of creatinine, AST, ALT and bilirubine levels, blood samples were drawn on day 0 and 6+/-2. Throughout the study period of 42 +/-4 days, adverse events (AEs), severe adverse events (SAE) and AE-related study drug discontinuations were assessed. Clinical data capture furthermore included demographics, underlying disease, cytotoxic and immunosuppressive therapies, antibiotic administration, neutropenia and occurrence of bloodstream infections with ESBL-E/K.
Prüfmedikation / Behandlungsstrategie	Trade name: Monuril ® INN (International Nonproprietary Name): Fosfomycin Presentation: granules in single-dose sachet for oral solution Dose: 3 g every 72h for 7 days (overall 3 administrations) Manufacturer: Pierre Fabre Pharma GmbH Fosfomycin is a bactericidal broad-spectrum antibiotic and inhibits bacterial cell wall biogenesis by inactivating the enzyme MurA. --- Trade name: Diarönt ® mono INN (International Nonproprietary Name): Colistin Presentation: powder for oral solution Dose: $2x10^6$ IU every 6 hours for 7 days Manufacturer: CNP Pharma GmbH Colistin is a polymyxin antibiotic and is effective against most

	gram-negative bacteria by damaging the outer membrane. Trade name: Refobacin® 80mg INN (International Nonproprietary Name): Gentamicin Presentation: oral solution Dose: 80 mg every 6 hours for 7 days Manufacturer: Merck Gentamicin is a bactericidal aminoglycoside antibiotic that works by irreversibly binding the 30S subunit of the bacterial ribosome, interrupting protein synthesis. The blinded study medications/placebo were prepared and provided by the hospital pharmacy at the University Hospital Mainz.
Behandlung / Intervention	Colistin was administered as powder, dissolved in 50-100 ml of water, containing $2x10^6$ IU four times daily for seven days at 8.00 a.m., 12.00 a.m., 4.00 p.m. and 8 p.m. Gentamicin was administered as an 80 mg oral solution dissolved in 50-100 ml of water four times daily for seven days at 8.00 a.m., 12.00 a.m., 4.00 p.m. and 8 p.m. Fosfomycin-trometamol was administered as 3 g granulate, dissolved in 200 ml of water every 72h for a period of 7 days. The first dose of fosfomycin was administered together with the first dose of colistin/gentamicin. The prepared solutions were stable for 24 hours, but were drunk immediately. To include the oral cavity into the eradication regimen, all medications were gargled for at least 10 seconds before being swallowed.
Vergleichsbedingung / -medikation	The study was a placebo-controlled study. For each IMP, a product identical in taste, form, texture and smell was provided and administered according to the same schedule as the IMP.
Gesamtzahl Patienten	Planned number of patients: 47 (31 active vs. 16 placebo) Screened patients: 121 Enrolled patients: 29 Since colistin powder production was stopped by the manufacturer we were forced to terminate the trial prematurely.
Studienpopulation	All 29 patients were qualified for the trial in accordance with the inclusion and exclusion criteria and were evaluable in the intention to treat (ITT) analysis. 22 patients received a chemotherapy with expected duration of chemotherapy associated neutropenia. Six patients would undergo an allogenic or autologous hematopoietic stem cell therapy and one patient received a high-dose corticosteroids or other im-

	munosuppressive therapy. On baseline day fecal samples of 26 patients were tested positive for ESBL-*E.coli* and two for ESBL-*K.pneumoniae*. One patient had a confirmed ESBL-*E.coli* sample on screening day only, all further samples were negative. 21 patients (13 verum/8 placebo) received the complete treatment. 5 patients (4 verum/1 placebo) discontinued the intake of study medication between the 1st und 3rd day after start of treatment. For 3 patients (1 verum/2 placebo) minor deviations related to study drug administration such as one missing dosage or delayed intake were recorded. Nearly all patients in both arms received concomitant antimicrobial agents during the study period (17/18 in verum and 10/11 in placebo arm), in most cases due to febrile neutropenia. With regard to different substance groups, only for aminoglycosides a significant difference was observed with a higher exposure in the verum group (p=0.036; see Table 1). We also assessed whether the administered antibiotic substance was potentially active against ESBL-E and whether it was individually active according to the susceptibility profile from the respective baseline ESBL-E/K isolate. In this subanalysis, antibiotic exposure was similarly high in both groups.
Einschlusskriterien	1) Fecal colonization with ESBL-E.coli or ESBL-K.pneumoniae, as confirmed by a positive sample (rectal swab or stool sample) obtained within 14 days prior to study enrolment 2) Ongoing or scheduled immunosuppression: - allogeneic or autologous hematopoietic stem cell transplantation within 14 days after enrolment **or** - chemotherapy with an expected duration of chemotherapy-associated neutropenia (<500 neutrophils/mL or white blood count <1,000 - eukocytes/mL) of at least 3 days within 14 days after enrolment **or** - solid organ transplantation within 14 days after enrolment **or** - administration of high-dose corticosteroids or other immunosuppressants for acute rejection of a solid organ transplant or for therapy or prophylaxis of graft versus host disease after stem cell transplantation or for a rheumatologic disease **or** - expected neutropenia (<500 neutrophils/mL or white blood count <1,000 leukocytes/mL) of at least 7 days due to an underlying condition, including functional neutropenia (<500 functional neutrophils/mL or functional white blood count <1,000 leukocytes/mL) 3) Age of at least 18 years

	4) Subject is not legally incapacitated 5) Written informed consent from the trial subject has been obtained
Ausschlusskriterien	1) Current or scheduled administraton of ESBL-E active antibiotic treatment1 after receipt of the most recent sample showing intestinal ESBL-E colonization and within 10 days after randomization 2) Planned selective digestive tract decolonization within 42 days following randomization 3) Known hypersensitivity or allergy to any of the components of the study treatment 4) Moderate or severe liver dysfunction at baseline, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than three times the upper limit of normal (ULN), AND a total bilirubin level greater than two times the ULN 5) Serum creatinine > 2 x the upper limit of the ULN 6) Inability to take oral medication 7) Concurrent participation in another clinical trial with an investigational drug is not permitted, unless the drug under study is related to the treatment of the underlying condition or a transplantation 8) Current pregnancy or nursing period 9) In female study participants, failure to use highly-effective contraceptive methods. The following contraceptive methods with a Pearl Index lower than 1% are regarded as highly-effective: o Oral hormonal contraception (‘pill’) o Dermal hormonal contraception o Vaginal hormonal contraception (NuvaRing®) o Contraceptive plaster o Long-acting injectable contraceptives o Implants that release progesterone (Implanon®) o Tubal ligation (female sterilisation) o Intrauterine devices that release hormones (hormone spiral) o Double barrier methods This means that the following are not regarded as safe: condom plus spermicide, simple barrier methods (vaginal pessaries, condom, female condoms), copper spirals, the rhythm method, basal temperature method, and the withdrawal method (coitus interruptus). 10) Patient has any other condition that, in the opinion of the

	investigator, would jeopardize the safety or rights of the patient participating in the study, would make it unlikely for the patient to complete the study, or would confound the results of the study. 11) Persons with any kind of dependency on the investigator or employed by the sponsor or investigator 12) Persons held in an institution by legal or official order
Darstellung der Demographie und Baseline-Charakteristika	Overall 29 patients (7 female/ 22 male) were enrolled into the study, 18 in the verum and 11 in the placebo group. Median age was in verum group 52 (range 30 to 73) and 53 (range 28 to 64) in placebo group. All 29 patients were evaluable in the intention to treat analysis. Demographic characteristics, exposure to cytostatic and immunosuppression, and median duration of neutropenias did not differ significantly between the groups as shown in Table 2.
Darstellung **Wirksamkeit**	The primary endpoint of short-term intestinal eradication differed significantly between the two groups with 11/18 (61.1%) patients in the verum group being tested negative versus 2/11 (18.2%) in the placebo group (p=0.043, Mantel-Haenszel common odds ratio estimate 0.063; 95% CI 0.006-0.702). Rates of long-term intestinal eradication were not statistically significant for both day 28 and 42 (verum: 38.9% vs. placebo: 27.3%; p=0.299, Table 3. Only two patients in verum and four in placebo group were found to be colonized in urine. None of all patients was colonized in throat. As a consequence, endpoints of non-intestinal eradication were not calculated. Of note, throughout the study, three verum patients showed colonization in urine and two verum patients in throat not detected at baseline. Please refer to Table 4 for details. A carbapenem-resistant gram-negative bacterial isolate was detected in one patient in placebo group on day 6, in another placebo patient on day 28, and in one patient in the verum group on day 28 only (non statistically significant, *K. pneumonia* in all three cases). The presence of VRE remained nearly constant during the observation period (Table 5). In none of the samples a colistin-resistant gram negative bacteria was isolated. Quantitative analysis showed a significant decrease of intestinal ESBL-E/K burden on day 6 in verum as compared to placebo group (mean: 6.14 x 10^7 CFU/g; median: 0 CFU/g vs. placebo group, mean: 2.04 x 10^8 CFU/g; median: 3.1 x 10^7 CFU/g; p=0.005). All quantitative results are shown in Table 6.
Darstellung der **Sicherheit**	Throughout the study period of 42 +/-4 days, adverse events (AEs), severe adverse events (SAE) and AE-related study drug discontinuations were assessed. Scheduled hospitalization for chemotherapy, stem cell transplantation or observation during chemotherapy-associated neutropenia, as well as

	chemotherapy-associated leukopenia, neutropenia, anemia or thrombocytopenia were not considered AEs in this study and were not documented as such. In total, 200 AEs in 17 patients compared to 118 AEs in 11 patients were reported in the verum and placebo group, respectively (p=1.000). Intensity of AEs did not differ significantly between groups (*p*=0.149) with nearly all AEs being rated CTC Grade 1 to 3 except one AE in the verum group with CTC Grade 5. 17 AEs in 17 patients in the verum group and 12 AEs in 11 patients in the placebo group were rated as probably/likely or possibly related to the study drug (p=0.115). Among these and among all AEs gastrointestinal disorders were the most frequent (Table 7 and 8). There were four (22.2%) compared to one (9.1%) treatment discontinuations in the verum and placebo arm, respectively (p=0.622). Only one study drug discontinuation was related to an AE in a patient with nausea and vomiting on day two in the verum group. Another patient in the verum arm died on day 16 after enrollment due to pulmonary sepsis constituting the only SAE in this study. Laboratory results were compared between baseline and day 6. The changes in GPT levels differed significantly between the two groups with a median increase by 6 U/l in the placebo and a median decrease by 2 U/l in the verum group (p=0.025). All other laboratory changes were similar between groups. During the study period, there was only one serious adverse event (SAE). This SAE occurred in patient CL2-03 (age 31, male) and resulted in the death of the patient. The detailed course of events was the following: The patient was enrolled in the study on 02.04.2015 and study treatment (verum) was initiated on 02.04.2015. He was in the hospital due to a metastatic nonseminomatous gonadal germ cell cancer and planned intensive chemotherapy, there were no relevant comorbidities. On the evening of the 06.04.2015, the patient presented with respiratory insufficiency and tachycardia due to a pulmonary sepsis. He needed to be transferred to the ICU on 07.04.2015. On that day, intake of study medication was incomplete (only 2 doses of gentamicin and colistin instead of 4) due to a delay caused by the patient transfer and the need for a gastric tube to be placed prior medication administration. The SAE was reported by the study site. On 08.04.2015, the last day of study medication, medication was administered completely. During the consecutive days, the patient needed to receive non-invasive and later on invasive ventilation. Further antibiotic treatment was administered. The patient status deteriorated with multi-organ failure including acute renal failure. On 15.04.2015 it was decided not to take any further curative measures in light of the poor prognosis. The patient CL2-03 died on 17.04.2015 as a

	consequence of the severe sepsis. The event was not considered related to the study drug administration neither by the study site investigators nor the sponsor. During study period, no actions have been taken because of safety or lack of efficacy due to lack of reasons for actions. All three drugs have been marketed for a number of years and have many and different indications. It is not possible for us to track their overall exposure worldwide. During the reporting period no new or potentially important safety issues have been identified. As no potential risks were recognized, no actions have been taken to detect or prevent them.
Statistische Methoden:	To gain additional safety information and observe a higher number of patients on treatment, it was decided to use a 2:1 randomization. Based on prior data we assumed that colonization with ESBL-E/K persists in 84% of patients without treatment and in 40% in the eradication arm. Aiming at 80% power and accounting for dropouts and stratification, sample size calculations resulted in a total of 47 subjects with 31 in the verum and 16 in the placebo arm to be randomized. The intention-to-treat (ITT) population included all randomized subjects with dropouts or patients with missing data counted as failures. Furthermore, a subanalysis was conducted with respect to each eradication endpoint including only those patients that did not receive any concomitant antibiotic substances tested as susceptible in the resistance testing of their specific ESBL-E/K isolate (micromodITT). The primary end point was evaluated by means of the two-sided Mantel-Haenszel test stratified by study center including calculation of the common odds ratio with 95% confidence interval (CI). Distribution of data between groups was described using count, percentage, mean, median and interquartile range and compared using Mann-Whitney *U* test, Fisher's exact test, and Kustal Wallis test, as appropriate.

ZUSAMMENFASSUNG:

Worldwide, rates of colonization and infection with extended-spectrum β-lactamase producing *Enterobacteriaceae* (ESBL-E) are increasing. In particular, in immunocompromised hosts, bloodstream infections (BSI) caused by these organisms are a major clinical challenge given the limited antibiotic treatment options and reported poor outcome rates. Taking into account, that the risk of subsequent BSI in colonized patients is the highest during periods of immunosuppression (Table 2), we conducted an eradication study for ESBL-E in this specific setting not yet targeted by previous studies.

ERGEBNISSE WIRKSAMKEIT:

Overall 29 patients (7 female/ 22 male) were enrolled into the study, 18 in the verum and 11 in the placebo group. With respect to intestinal colonization with ESBL-E/K, our eradication therapy demonstrated a short-term effect up to day 11 only. There was no significant difference observed between verum and placebo group on day 28 and 42 due to four patients in the verum group being again tested positive for ESBL-E/K. Furthermore, long-term effect was also not detected when excluding samples taken after ESBL-E active concomitant antibiotic

treatment based on the individual susceptibility profile of the respective strain. Please refer to Table 3, 4, 5 and 6 for details.

ERGEBNISSE SICHERHEIT:

Overall the study medication was well tolerated whereas, gastrointestinal disorders were the most frequent AEs. The death of patient CL2-03 was not related to the study drug administration. Patients with liver and kidney disfunction have not been enrolled into the study. Please refer to Table 7 and 8 for details.

SCHLUSSFOLGERUNG:

In conclusion, a seven day antibiotic treatment showed a short-term ESBL-E/K eradication only. Nevertheless, our trial could be an approach for further investigations on antimicrobial regimen particularly in immunocompromised high-risk patients.

Table 1: Exposure to concomitant antibiotic

	Verum group, *n*=18 (%)	**Placebo group, *n*=11 (%)**	***p***
Number of patients with any antibiotics (%)	17 (94.4)	10 (90.9)	1.000[†]
Antibiotic substances by class:			
Aminoglycosides	6 (33.3)	0 -	0.058[†]
Sulfonamides	16 (88.9)	9 (81.8)	0.622[†]
Carbapenems	8 (44.4)	5 (45.5)	1.000[†]
Beta-lactam beta-lactamase inhibitor combinations	4 (22.2)	4 (36.4)	0.433[†]
Fluoroquinolones	5 (27.8)	4 (36.4)	0.694[†]
Fosfomycin	1 (5.6ni)	0 -	1.000[†]
3rd generation cephalosporins	7 (38.9)	1 (9.1)	0.110[†]
Other antibiotics	5 (27.8)	1 (9.1)	0.362[†]
Duration: mean/median days			
Aminoglycosides	1.2/0	0/0	0.036[#]
Sulfonamides	11.8/14.5	8.5/9	0.241[#]
Carbapenems	3.9/0	3.9/0	0.921[#]
Beta-lactam beta-lactamase inhibitor combinations	1.6/0	3.4/0	0.376[#]
Fluoroquinolones	4.3/0	3.5/0	0.848[#]
Fosfomycin	0.4/0	0/0	0.434[#]
3rd generation cephalosporins	1.0/0	0.2/0	0.081[#]
Other antibiotics	2.1/0	2.8/0	0.310[#]
Number of patients with potentially ESBL-E active antibiotic (%)	16 (88.9)	10 (90.9)	1.000[†]
Number of patients with individually ESBL-E active antibiotic (%)	11 (61.1)	7 (63.6)	1.000[†]
Duration: mean/median days			
Potentially ESBL-E active antibiotic	18.9/17.5	15.8/13	0.300[#]
Individually ESBL-E active antibiotic	4.9/2.5	5.3/8	0.595[#]

[†]Fisher's exact test; [#]Mann-Whitney *U* test

Table 2: Demographic and clinical characteristics of included patients

Characteristics	**Verum group, *n*=18**	**Placebo group, *n*=11**	***p***
Age – median years (range; IQR)	52 (30-73; 24)	53 (28-64; 12)	0.840[#]
Gender (male/female)	13/5	8/3	1.000[†]
BMI – median (range; IQR)	25.5 (21.6-32.6; 6.1)	25.1 (19.7-40.3; 6.6)	0.928[#]
Underlying conditions (%)			0.387[†]
Acute leukemia	3 (16.7)	2 (18.2)	
Hodgkin lymphoma	3 (16.7)	0	
Myeloma	1 (5.6)	3 (27.3)	
Non-Hodgkin lymphoma	9 (50)	4 (36.4)	
Solid tumor	2 (11.1)	2 (18.2)	
ECOG score at randomization (%)*			0.686[#]
0	7 (38.9)	5 (45.5)	
1	8 (44.4)	4 (36.4)	

2	3 (16.7)	1 (9.1)	
3	0	1 (9.1)	
Inclusion Group (%)			0.349†
Administration of high-dose corti costeroids or other immunosup pressive therapy	0	1 (9.1)	
Allogeneic or autologous hemato poietic stem cell therapy	3 (16.7)	3 (27.3)	
Chemotherapy with expected duration of chemotherapy associate ed neutropenia	15 (83.3)	7 (63.6)	
Exposure to cytostatics (%)	16 (88.9)	9 (81.8)	0.622†
Exposure to immunosuppressants (%)	13 (72.2)	8 (72.7)	1.000†
Duration of neutropenia – median days (range; IQR)	7.5 (0-25; 7)	8 (0-29; 11)	0.804#

IQR: Interquartile range; ECOG: European Cooperative Oncology Group;
*No ECOG of 4 and 5 were reported; †Fisher's exact test; #Mann-Whitney *U* test

Table 3: Primary and secondary end points regarding intestinal eradication

End points	**Verum group, *n*=18**	**Placebo group, *n*=11**	***p***
Short-term intestinal eradication d6/11 (primary end point)	11 (61.1)	2 (18.2)	0.043§
Short-term intestinal eradication d6	15 (83.3)	2 (18.2)	0.001†
Short-term intestinal eradication d11	11 (61.1)	4 (36.4)	0.317†
Long-term intestinal eradication d28	7 (38.9)	3 (27.3)	0.299†
Long-term intestinal eradication d42	7 (38.9)	3 (27.3)	0.299†

§Two-sided Mantel-Haenszel test; †Fisher's exact test

Table 4: Detected colonization in urine and throat samples

	Verum group, n=18 (%)	**Placebo group, n=11 (%)**
Urine		
Baseline	2	4
d6	0	2
d11	0	1
d28	2*	2
d42	4**	0
Throat		
Baseline	0	0
d6	0	0
d11	1#	0
d28	0	0
d42	1#	0

*one pat on d28 in verum group was not tested positive in urine at baseline
**three pat on d42 in verum group were not tested positive in urine at baseline, one of them was tested positive on d28
#different patients.

Table 5: Presence of vancomycin-resistant enterococci in fecal samples

	Verum group, n=18 (%)	**Placebo group, n=11 (%)**	***p***
Baseline	1 (5.6)	1 (9.1)	1.000[†]
d6	2 (11.1)	3 (27.3)	0.339[†]
d11	1 (5.6)	3 (27.3)	0.269[†]
d28	1 (5.6)	2 (18.2)	0.556[†]
d42	2 (11.1)	2 (18.2)	1.000[†]

[†]Fisher's exact test

Table 6: Quantitative assessment of intestinal ESBL-E burden

	Verum group, n=18 (%)	**Placebo group, n=11 (%)**	***p***
Baseline			0.597[#]
Mean (CFU/g)	2.86×10^8	1.5×10^8	
Median (CFU/g)	2×10^7	3.85×10^7	
Day 6			0.005[#]
Mean (CFU/g)	6.14×10^7	2.04×10^8	
Median (CFU/g)	0	3.1×10^7	
Day 11			0.406[#]
Mean (CFU/g)	8.36×10^7	1.01×10^8	
Median (CFU/g)	0	1×10^6	
Day 28			0.431[#]
Mean (CFU/g)	5.92×10^8	2.88×10^8	
Median (CFU/g)	25	1.01×10^7	
Day 42			0.581[#]
Mean (CFU/g)	3×10^8	1.71×10^8	
Median (CFU/g)	0	50	
Difference baseline/d 11			0.953[#]
Mean (CFU/g)	$- 2.17 \times 10^8$	$- 4.84 \times 10^7$	
Median (CFU/g)	$- 2.16 \times 10^6$	$- 1.2 \times 10^7$	

CFU/g: Colony forming unit/gram; [#]Mann-Whitney *U* test

Table 7: Incidence of AE/SAEs per category

	Verum group, n=18	**Events n=200**	**Placebo group, n=11**	**Events n= 118**	***p***
Cardiac disorders	3	4	2	3	1.000[†]
Ear and labyrinth disorders	6	8	0	0	1.000[†]
Eye disorders	2	3	0	0	1.000[†]
Gastrointestinal disorders	13	53	9	20	0.820[†]
General disorders and administration site conditions	14	53	7	18	0.818[†]
Hepatobiliary disorders	0	0	1	1	1.000[†]
Infections and infestations	6	9	3	6	1.000[†]
Investigations	1	1	4	12	0.065[†]
Metabolism and nutrition disorders	8	9	5	15	1.000[†]
Musculoskeletal and connective tissue disorders	6	12	7	12	0.244[†]

Nervous system disorders	6	8	6	9	0.372†
Psychiatric disorders	3	6	0	0	1.000†
Renal and urinary disorders	3	8	2	2	1.000†
Reproductive system and breast disorders	0	0	1	1	1.000†
Respiratory, thoracic and mediastinal disorders	6	12	3	8	1.000†
Skin and subcutaneous tissue disorders	4	6	3	9	0.713†
Vascular disorders	3	8	1	2	1.000†

†Fisher's exact test

Table 8: Gastrointestinal events

	Verum group, events n=53 (%)	**Placebo group, events n=20 (%)**
Abdominal discomfort	1 (1.9)	0
Abdominal distension	2 (3.8)	0
Abdominal pain	3 (5.7)	0
Abdominal pain lower	1 (1.9)	0
Abdominal pain upper	1 (1.9)	1 (5.0)
Aphthous ulcer	1 (1.9)	0
Constipation	5 (9.4)	1 (5.0)
Diarrhoea	16 (30.2)	9 (45.0)
Dyspepsia	1 (1.9)	0
Gingival bleeding	0	1 (5.0)
Nausea	7 (13.2)	4 (20.0)
Oesophageal pain	0	1 (5.0)
Oral pain	3 (5.7)	0
Painful defaecation	0	1 (5.0)
Proctitis	1 (1.9)	0
Stomatitis	7 (13.2)	0
Vomiting	4 (7.5)	2 (10.0)