Clinical trial results:
Effects of antibiotics on micobiota, pulmonary immune response and incidence of ventilator-associated infections

Summary

EudraCT number	2018-000492-32
Trial protocol	DE
Global end of trial date	17 February 2023

Results information

Result version number	v1 (current)
This version publication date	07 March 2024
First version publication date	07 March 2024

Trial information

Trial identification

Sponsor protocol code	AMIII

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité -Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 February 2023
Global end of trial reached?	Yes
Global end of trial date	17 February 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Main objective of the trial is to study the effect of antibiotic therapies on pulmonary immunoglobulin A (IgA) in mechanically ventilated patients. Based on data from mouse models and a pilot study from our research group, we assume that antibiotic therapies reduce pulmonary IgA level.

Protection of trial subjects:

To determine the suitability of a patient, the inclusion and exclusion criteria are checked that there are no comorbidities or allergies that would constitute an exclusion criterion and that the inclusion criteria for inclusion in the antibiotic or control group are met.
Assessment of the patient's clinical stability and evaluation of the risk of bronchoscopy by the investigator based on the patient's medical history, continuously recorded vital signs, clinical examination and ECG. Bronchoscopy is performed by an experienced examiner under continuous monitoring. To prevent and control possible complications, patients who are in an unstable clinical situation were excluded in advance. The strict use of concomitant medication in accordance with the information for healthcare professionals and the exclusion or premature discontinuation of patients for whom this is not guaranteed represents a further risk-minimizing measure.
To minimize the risk of emergency situations occurring, only patients in a stable clinical situation were included and in which the antibiotic therapy was carried out in accordance with the approval and specialist information.

Background therapy:

Patients who have received antibiotic therapy for 7-10 days within standard care are eligible for inclusion in the AMIII- arm, because effects of clinically revelant broad-spectrum antibiotic therapies were to be studied. Therefore, the treatment arm encompasses 24 different currently widely used IMPs with activity against gram-positive, gram-negative and anaerobic bacteria as well as combination therapies, as long as antibiotic therapies followed SMPCs and were carried out according to national guidelines.
Patients who have not received any antibiotic therapy for at least 90 days are eligible for inclusion in the control arm.

Evidence for comparator: -	
Actual start date of recruitment	18 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	5
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at one study center in Germany, between 07/05/2019 (date of first enrollment) and 15/04/2020 (LPLV).
Using the available documentation systems inpatients on the intensive care unit (18 beds) and the two home respiratory wards (12+13 beds) were daily-screened according inclusion routine parameters by the study team.

Pre-assignment

Screening details:

Adults inpatients invasive or intermittent invasive ventilation via tracheostomy tube either no antibiotic therapy for a longer period (≥90 days) or completed antibiotic therapy (7-10 days) with efficacy in the gram-positive, gram-negative and anaerobic range as part of the clinical routine in accordance with the approval were screened.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AMIII-group

Arm description:

Inpatients with invasive or intermittent invasive ventilation via tracheostomy tube with completed course of 7-10 days of antibiotic therapy with antimicrobial activity against Gram-negative, Gram-positive and anaerobic bacteria according to SmPC and to marketing authorization. Treatment ended ≥ 5x elimination half-time of the trade product prior AND not more than 72hrs prior to inclusion. Brochoscopy was performed using a local anesthesia of the bronchi (Lidocain) and concomitant medication administered for sedation (Midazolam/ Propofol) during brochoscopy outside of routine clinical practice.

Arm type	Active comparator
Investigational medicinal product name	Amoxicillin Trihydrate
Investigational medicinal product code	SUB00504MIG
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

within standard care according to SmPCs

Investigational medicinal product name	CLAVULANIC ACID
Investigational medicinal product code	58001-44-8
Other name	SUB06642MIG
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

within standard of care and according to SmPCs

Investigational medicinal product name	Ampicillin
Investigational medicinal product code	SUB00508MIG
Other name	AMPICILLIN SODIUM
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:	
within standard care and according to SmPCs	
Investigational medicinal product name	Sulbactam
Investigational medicinal product code	SUB04617MIG
Other name	SULBACTAM SODIUM
Pharmaceutical forms	Powder for concentrate and solution for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
within standard care and according to SmPCs	
Investigational medicinal product name	Cefazolin
Investigational medicinal product code	SUB01107MIG
Other name	CEFAZOLIN SODIUM
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
within standard care and according to SmPCs	
Investigational medicinal product name	CEFEPIME HYDROCHLORIDE
Investigational medicinal product code	123171-59-5
Other name	SUB01113MIG
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
within standard care and according to SmPCs	
Investigational medicinal product name	CEFTAZIDIME
Investigational medicinal product code	72558-82-8
Other name	SUB07422MIG
Pharmaceutical forms	Powder for concentrate and solution for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
within standard care and according to SmPCs	
Investigational medicinal product name	Ceftazidime Pentahydrate
Investigational medicinal product code	SUB01134MIG
Other name	
Pharmaceutical forms	Powder for concentrate and solution for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
within standard care and according to SmPCs	
Investigational medicinal product name	Avibactam
Investigational medicinal product code	SUB179984
Other name	AVIBACTAM SODIUM
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
within standard care and according to SmPCs	
Investigational medicinal product name	Ceftolozane
Investigational medicinal product code	SUB167761
Other name	CEFTOLOZANE SULFATE
Pharmaceutical forms	Powder for concentrate and solution for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
within standard care and according to SmPCs	

Investigational medicinal product name	Tazobactam Sodium
Investigational medicinal product code	SUB04682MIG
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
within standard care and according to SmPCs

Investigational medicinal product name	Ceftriaxone Disodium
Investigational medicinal product code	SUB26591
Other name	CEFTRIAXONE DISODIUM
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
within standard care and according to SmPCs

Investigational medicinal product name	Ciprofloxacin
Investigational medicinal product code	SUB182757
Other name	CIPROFLOXACIN HYDROGEN SULPHATE
Pharmaceutical forms	Powder for solution for injection/infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:
within standard care and according to SmPCs

Investigational medicinal product name	Ciprofloxacin Hydrochloride Monohydrate
Investigational medicinal product code	86393-32-0
Other name	SUB25858
Pharmaceutical forms	Powder for solution for injection/infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:
within standard care and according to SmPCs

Investigational medicinal product name	Ciprofloxacin lactate
Investigational medicinal product code	SUB01317MIG
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:
within standard care and according to SmPCs

Investigational medicinal product name	Clarithromycin
Investigational medicinal product code	SUB06641MIG
Other name	
Pharmaceutical forms	Film-coated tablet, Powder for solution for injection/infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:
within standard care and according to SmPCs

Investigational medicinal product name	Clarithromycin lactobionate
Investigational medicinal product code	SUB20333
Other name	
Pharmaceutical forms	Film-coated tablet, Powder for solution for injection/infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:
within standard care and according to SmPCs

Investigational medicinal product name	Clindamycin
Investigational medicinal product code	SUB01344MIG
Other name	CLINDAMYCIN PHOSPHATE

Pharmaceutical forms	Powder for solution for injection/infusion, Tablet
Routes of administration	Intravenous use, Oral use
Dosage and administration details: within standard care and according to SmPCs	
Investigational medicinal product name	DAPTOMYCIN
Investigational medicinal product code	103060-53-3
Other name	SUB06910MIG
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: within standard care and according to SmPCs	
Investigational medicinal product name	ERTAPENEM SODIUM
Investigational medicinal product code	153773-82-1
Other name	SUB16424MIG
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: within standard care and according to SmPCs	
Investigational medicinal product name	FLUCLOXACILLIN SODIUM
Investigational medicinal product code	1847-24-1
Other name	SUB02207MIG
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: within standard care and according to SmPCs	
Investigational medicinal product name	GENTAMICIN SULFATE
Investigational medicinal product code	1405-41-0
Other name	SUB02327MIG
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: within standard care and according to SmPCs	
Investigational medicinal product name	Imipenem Monohydrate
Investigational medicinal product code	74431-23-5
Other name	SUB21472
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: within standard care and according to SmPCs	
Investigational medicinal product name	Cilastatin Sodium
Investigational medicinal product code	SUB01295MIG
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use
Dosage and administration details: within standard care and according to SmPCs	
Investigational medicinal product name	Linezolid
Investigational medicinal product code	SUB08520MIG
Other name	
Pharmaceutical forms	Solution for injection/infusion, Film-coated tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details: within standard care and according to SmPCs	
Investigational medicinal product name	Meropenem Trihydrate
Investigational medicinal product code	SUB21617
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: within standard care and according to SmPCs	
Investigational medicinal product name	METRONIDAZOLE
Investigational medicinal product code	SUB08922MIG
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use, Oral use
Dosage and administration details: subject received 5mg/ml	
Investigational medicinal product name	Piperacillin
Investigational medicinal product code	SUB03840MIG
Other name	PIPERACILLIN SODIUM
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: within standard care and according to SmPCs	
Investigational medicinal product name	Tazobactam
Investigational medicinal product code	SUB04682MIG
Other name	TAZOBACTAM SODIUM
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: within standard care and according to SmPCs	
Investigational medicinal product name	Tobramycin
Investigational medicinal product code	SUB11134MIG
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: within standard care and according to SmPCs	
Investigational medicinal product name	TOBRAMYCIN SULFATE
Investigational medicinal product code	79645-27-5
Other name	SUB04896MIG
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: within standard care and according to SmPCs	
Investigational medicinal product name	TRIMETHOPRIM
Investigational medicinal product code	23256-42-0
Other name	SUB04972MIG
Pharmaceutical forms	Tablet, Concentrate for solution for infusion
Routes of administration	Intravenous use, Oral use
Dosage and administration details: within standard care and according to SmPCs	

Investigational medicinal product name	SULFAMETHOXAZOLE
Investigational medicinal product code	723-46-6
Other name	SUB10711MIG
Pharmaceutical forms	Concentrate for solution for infusion, Concentrate for solution for injection/infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

within standard care and according to SmPCs

Investigational medicinal product name	Vancomycin
Investigational medicinal product code	SUB05077MIG
Other name	VANCOMYCIN HYDROCHLORIDE
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

within standard care and according to SmPCs

Investigational medicinal product name	TIGECYCLINE
Investigational medicinal product code	220620-09-7
Other name	SUB16467MIG
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

within standard care and according to SmPCs

Investigational medicinal product name	Tigecycline
Investigational medicinal product code	
Other name	Tygacil
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

within standard care according to SmPCs

Arm title	control-group

Arm description:

Inpatients invasive or intermittent invasive ventilation via tracheostomy tube either no antibiotic therapy for a longer period (≥90 days),a brochoscopy was performed using a local anesthesia of the bronchi (Lidocain) and concomitant medication administered for sedation (Midazolam/ Propofol) during brochoscopy outside of routine clinical practice.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	AMIII-group	control-group
Started	8	4
Completed	8	4

Baseline characteristics

End points

End points reporting groups

Reporting group title	AMIII-group

Reporting group description:

Inpatients with invasive or intermittent invasive ventilation via tracheostomy tube with completed course of 7-10 days of antibiotic therapy with antimicrobial activity against Gram-negative, Gram-positive and anaerobic bacteria according to SmPC and to marketing authorization. Treatment ended ≥ 5x elimination half-time of the trade product prior AND not more than 72hrs prior to inclusion. Brochoscopy was performed using a local anesthesia of the bronchi (Lidocain) and concomitant medication administered for sedation (Midazolam/ Propofol) during brochoscopy outside of routine clinical practice.

Reporting group title	control-group

Reporting group description:

Inpatients invasive or intermittent invasive ventilation via tracheostomy tube either no antibiotic therapy for a longer period (≥90 days),a brochoscopy was performed using a local anesthesia of the bronchi (Lidocain) and concomitant medication administered for sedation (Midazolam/ Propofol) during brochoscopy outside of routine clinical practice.

Primary: change IGA (BALF)

End point title	change IGA (BALF)[1]

End point description:

pulmonary IgA as measured in broncheoalveolar lavage fluid (BALF)

End point type	Primary

End point timeframe:

on day 0-2

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The steering committee of the trial voted against an analysis of primary and secondary endpoints other than safety endpoints, because of the expected low accuracy of results. Due to the low number of recruited patients (n=12, with 8 patients being in the AMIII-arm), the results of the primary endpoint level of IgA in the broncheoalveolar fluid are expected to be influenced more by interindividual differences than effects of antibiotic therapy and therefore, a specific analysis would not lead to.

End point values	AMIII-group	control-group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	4		
Units: mg/dl				
arithmetic mean (standard error)	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: relative frequency of SAE/AE- day 1-3	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19

Reporting groups	
Reporting group title	AMIII-group
Reporting group description: -	
Reporting group title	Control-group
Reporting group description: -	

Serious adverse events	AMIII-group	Control-group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	AMIII-group	Control-group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	3 / 4 (75.00%)	
Investigations			
Increase of tracheal secretion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	2	
Hypotension			
subjects affected / exposed	4 / 8 (50.00%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			

Tremur			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Dyspnea			
subjects affected / exposed	2 / 8 (25.00%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Hypoxia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Productive cough			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
other: local infection at tracheostoma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2019	update protocol Version 1.2 (23/01/2019) and ICF V1.2
18 December 2019	update Protocol V1.2 (2019/01/23) to Protocol V1.3 : - Change in inclusion criteria from - Antibiotic therapy at inclusion for 24-72h≥ 5x half-life of the drug used and completed - New Sample collection from gastric juice in patients with a gastric tube - add drug of antibiotic therapy (Tigecyclin i.v.)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the ongoing pandemic caused by the SARS-CoV-2 virus and its repercussion in the health sector, no patients could be included in the trial since march 2020. Delay in recruitment led to relevant risks concerning feasibility and business plan of

Notes: