SYNOPSIS OF CLINICAL STUDY REPORT

Version and date of report: Version 1.1/29.05.2020

Study Title:

Randomized double blind placebo-controlled study to demonstrate that antibiotics are not needed in moderate acute exacerbations of COPD– The ABACOPD Study

Protocol code number: 002/2012

EudraCT number: 2012-003234-16

Name and Adress of Sponsor:

Hannover Medical School

represented by Hannover Clinical Trial Center GmbH

Carl-Neuberg-Str. 1

30625 Hannover – Germany

Study Title:

Randomized double blind placebo-controlled study to demonstrate that antibiotics are not needed in moderate acute exacerbations of COPD– The ABACOPD Study

Short title:	The ABACOPD Study
EudraCT number:	2012-003234-16
Protocol code number:	002/2012
Investigational product:	Sultamicillin/Placebo
Indication studied:	Acute moderate exacerbations of COPD (AE-COPD)
Study design:	Randomized, placebo-controlled, multi-center, double-blinded, parallel-group, phase IV clinical trial
Development phase of study:	Phase IV
Study initiation date:	07.06.2013
Date of early study termination [if any]:	05.06.2019
Study completion date:	23.04.2019
Name and affiliation of representative head of the clinical study according to German drug law (LKP), coordinating investigator or principal investigator	LKP/Prof. Dr. Tobias Welte
Sponsor:	Hannover Medical School represented by Hannover Clinical Trial Center GmbH
Good Clinical Practice (GCP) Statement:	This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. Essential documents will be retained in accordance with ICH GCP.

Version and date of report: 1.1/29.05.2020

SIGNATURES

Study title: **The ABACOPD Study**

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Sponsor/Prof. Dr. Heiko von der Leyen	Date
LKP (or Principal investigator or Coordinating investigator)/Prof. Dr. Tobias Welte	Date

Title of study:

Randomized double blind placebo-controlled study to demonstrate that antibiotics are not needed in moderate acute exacerbations of COPD – The ABACOPD Study

EudraCT-No.: 2012-003234-16

Protocol Code No.: 002/2012

Name of Finished Product:

Unacid® PD oral, 375 mg, Filmtabletten

Name of Active Substance:

Sultamicillin

Information about study protocol versions:

Protocol version 1.0,11 FEB 2013

Protocol version 1.1, 14 FEB 2013

Subsequent substantial amendment:

Protocol version 1.2, 18 FEB 2013

Protocol version 1.3, 10 APR 2013

Final protocol version 1.4, 01 JUL 2015

Reasons for changes:

Changes in inclusion and exclusion criteria

Changes of study sites

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Study sponsor:

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Publication (reference):

none

Studied period (years):	**Phase of development:**
date of first enrolment: 07.06.2013	Phase IV

date of last completed: 23.04.2019 temporary halt: no temporary halt Premature termination:05.06.2019	

Objectives:

Primary Objective:

To demonstrate that there is no relevant increase in the "failure-rate" for patients with acute moderate exacerbations of COPD (AE-COPD) treated with placebo instead of antibiotic treatment both on top of standard of care.

Secondary Objectives:

- To evaluate long-term consequences of Placebo treatment
  - Relapse rate at late follow-up 1 (A patient is classified as relapse if new antibiotic therapy for AE-COPD is required within the first six months after TOC)
  - Time to relapse
- To assess patient's clinical improvement relative to treatment
  - Clinical cure rate at the EOT visit
  - Clinical cure rate at the TOC visit (both determined by patient-centered outcomes)
- To assess additional efficacy endpoints and health outcome evaluations following 5 days treatment with either placebo or oral sultamicillin with either treatment used as a supplement to the standard of care for patients with acute exacerbations of COPD:
  - Changes in COPD Assessment Test (CAT)
  - Changes in Exacerbations of Chronic Pulmonary Disease Tool-Patient reported outcome (EXACT_PRO)
  - Changes in relevant systemic biomarkers and their association to mortality
  - Additional antibiotic therapy
  - Time to next exacerbation
  - Number of exacerbations during follow up
  - Per-subject relapse rate at the LFU visit in the subset of subjects in the CE population who were clinically cured at the TOC visit
  - Changes in length of stay in hospital for hospitalized patients
  - All cause mortality
  - Safety endpoints

Methodology:

Randomized, placebo-controlled, multi-center, double-blinded, parallel-group, phase IV clinical trial

Number of patients (planned and analysed):

Planned:

To be allocated to trial: n=980 (n=490 each treatment group)

To be analysed: n=980 in total (n=490 per treatment group)

Analysed:

Randomised: total n=295 (Sultamicillin group n=150, Placebo group n=145)

Patient 828-086-493 was randomized to Placebo, but did not receive the allocated treatment due to discontinuation before start of treatment/before first intake of the study medication. This patient is excluded from all analyses (ITT, PP and safety population).

Analysis populations:

In the primary analysis intention-to-treat (ITT) population, patients who received at least one dose of study medication are included and analysed as randomized.

In the primary analysis population (ITT): n=294 (Sultamicillin group n=150, Placebo group n=144)

In the per protocol (PP) population, only patients with evaluable overall treatment status (success or failure) are analysed.

In the PP population : n=261 (Sultamicillin group n=131, Placebo group n=130)

In the Complete Case population, only patients with evaluable treatment status for every single visit until assessment of the endpoint are analysed.

In the Complete Case population n=253 (Sultamicillin group n=126, Placebo group n=127)

In the study protocol, a Clinically Evaluable (CE) population was defined for secondary analyses. However, for statistical analyses CE population could not be considered due to data limitations. In this study, the safety and ITT population are identical.

In the safety population (equal to ITT): n=294 (Sultamicillin group n=150, Placebo group n=144)

Diagnosis and main criteria for inclusion and exclusion:

Patients older or equal than 40 years of age, with a smoking history of 10 pack years or more, diagnosed with COPD stages I-IV as defined by the Global initiative for chronic Obstructive Lung disease (GOLD) presenting with moderate acute exacerbation of COPD defined by a sustained worsening of the patient's condition were included in the clinical trial.

Inclusion:

1. Adults, either sex, older or equal than 40 years of age
2. For female patients, the following conditions are to be met:
    - has been postmenopausal for at least 1 year, or
    - is surgically incapable of bearing children, or
    - is of childbearing potential, and the following conditions are met:
        - has a negative pregnancy test (urine- or serum-based) immediately before study entry (i.e., before the start of treatment or any other study procedure that could potentially harm the fetus), and one or more of following criteria
        - must agree to abstinence or use an accepted method of contraception. The subject must agree to continue with the same method throughout the study.
        - having only female sexual partners
        - sexual relationship with sterile male partners only
3. Patients diagnosed with COPD stages I-IV as defined by the Global initiative for chronic Obstructive Lung disease (GOLD).

and

4. Doctor's diagnosis of acute (onset < 7 days) moderate exacerbation of COPD defined by a sustained worsening of the patient's condition (including at least 2 of the following symptoms: increased dyspnea, increased sputum production, sputum purulence and increased cough),

from the stable state and beyond normal day-today variations, necessitating a change in regular medication in patient with underlying COPD, needing additional medical assistance.
5. Absence of community acquired pneumonia or lower respiratory tract infection with a clear indication for antibiotic treatment as determined by Procalcitonin level < 0.25 ng/mL and/or absence of pulmonary infiltrates on routine chest x-ray.
6. Smoking history of at least 10 packyears or more.
7. Patients must sign and date an informed consent prior to any study procedures.

Exclusion:

1. Severe exacerbation: defined by need for ventilatory support (indicated by severe dyspnea with failure to respond to emergency treatment and/or persistent hypoxemia (PaO2 <50 mm Hg despite O2 administration and / or respiratory acidosis (pH <7.35 and PaCO2>45mmHg)) or mental confusion or circulatory insufficiency (need of vasopressors)
2. Fever (>38.5°C) (more than 4 days)
3. Known impaired hepatic or renal function
4. Active or suspected tuberculosis infection of the respiratory tract
5. Acute exacerbation of asthma
6. Suspected or known hypersensitivity to, or suspected serious adverse reaction to sultamicillin; suspected or known hypersensitivity to penicillins or cephalosporins
7. Immunosuppression or Immunosuppressive therapy (cytostatic chemotherapy within last 28 days or neutropenia (neutrophils < 1000/µ)l; systemic corticosteroids (≥20 mg prednisolon equivalent/day > 14 days; HIV-infection; immunosuppression after organ- or bone marrow transplant)- Patients with metastatic or hematological malignancy, splenectomized patients or patients with known hyposplenia or asplenia
8. Oral/parenteral antibiotic use within 30 days prior to randomization (a singular administration of antibiotics prior to randomization is allowed)
9. In-patient treatment within the last 30 days (because of actual respiratory infections as primary or secondary diagnosis)
10. An antibiotic is clearly indicated for treatment of a known infection
11. Known MRSA colonization or infection
12. Patients with known bronchiectasis
13. Patients with known bacterial airway colonization (>3 positive sputum cultures in the previous year)
14. Progressively fatal disease, or life expectancy ≤6 months
15. Mononucleosis
16. Lymphatic leukemia
17. Severe gastro-intestinal disorders with vomiting and diarrhea
18. Women who are breast-feeding
19. Patients who have received treatment with any other investigational drug within 1 month prior to study entry, or have such treatment planned for the study period during treatment and follow up phase.
20. Patients with mental conditions rendering them unable to understand the nature, scope, and possible consequences of the study.

Study treatment intervention

Randomized investigational medicinal product (IMP) treatment was:

Arm 1: 1500mg/d Sultamicillin (375mg/capsule, two capsules twice a day)

Arm 2: Placebo (two capsules, twice a day)

Test product, dose and mode of administration, batch number:

Sultamicillin, 375 mg, tablets (Tablets were encapsulated in capsules)

Active substance: Sultamicillin

Oral administration, 2 capsules twice a day

Dosage per capsule: 375 mg

Duration of treatment: 5 days

Batch number:

F71311, B71311, D70702, C61412, D61810, C61810, E61008, B62701, C62701, A61901, C51410, A51310, C50307, C50805, A50805, A50902, B41112, D40412, D42606, C42606, E43005, D32211, B32111, C32111, A31806, B31806, C31806, E31704, D31704, C31704

Reference therapy, dose and mode of administration, batch number:

Placebo, capsules

Oral administration, 2 capsules twice a day

Duration of treatment: 5 days

Batch number:

E71311, A71311, B70702, B61412, A61810, B61810, D61008, A62701, D50912, C50912, A51510, G50610, A50307, C51905, B50602, E40312, A40212, B42506, A42506, D43005, B32211, B31211, A31211, C31706, D31706, E31706, E31504, D31504, C31504

Changes to the conduct of the study

The recruitment was stopped prematurely by the sponsor in accordance with the principal investigator because of difficulties to recruit patients within a reasonable time frame. The most common reasons for non-inclusion regarding inclusion and exclusion criteria were: (i) antibiotic therapy within the last 30 days before randomization, (ii) inpatient hospitalization within the last 30 days and (iii) the presence of community-acquired pneumonia (CAP). In addition, the health status of potential patients treated in the clinic due to their exacerbation was not sufficient, so that an enrollment could not be carried out. Neither safety nor IMP issues contributed to this decision.

In the current study protocol version 1.4 (dated 01.07.2015), approximately 980 patients have been planned to be recruited within 18 months. As the recruitment was strongly delayed the Data Safety Monitoring Board (DSMB) of the ABACOPD Study generated an un-blinded, detailed interim analysis in June 2016 and came to the conclusion that approximately 300 patients need to be recruited to answer clinically relevant questions. Finally, 295 patients were enrolled and it was decided to terminate the study prematurely.

Endpoints/Outcomes

Primary endpoint

Treatment failure rate at day 30

A patient is classified as treatment failure if additional antibiotic therapy is required during treatment period or until test of cure visit (ToC, day 30).

Key Secondary endpoints

- Relapse rate at late follow-up after 6 months and 1 year
  A patient is classified as relapse if new antibiotic therapy for AE COPD is required within the first 6 (follow-up 1) or 12 months (follow-up 2) after ToC
- Clinical failure rate at the EoT visit

Safety variables

- Adverse events
- Serious adverse events
- Laboratory tests

Statistical methods

Efficacy and primary endpoint

Patients are classified as clinical success or failure. A treatment failure is defined as the requirement to administer additional antibiotic therapy during the treatment period or until ToC-visit (day 30). Per treatment group the number of treatment failures was counted. Cochran-Mantel-Haenszel (MH) estimates for the difference in failure rates (Placebo – Sultamicillin) were estimated with stratification for center. The null hypothesis is that there is a relevant increase in the failure rate if AE-COPD is treated with placebo instead of a standard antibiotic regimen. The null hypothesis is rejected, if the upper boundary of the two-sided Wald 95%-confidence interval for difference of the failure-rates with placebo minus active treatment does not exceed a non-inferiority margin of 10% and, in consequence, the one-sided type-I error was set to 2.5%. The primary analysis was conducted in the ITT population. The ITT population included all randomized patients who received at least one dose of study medication.
The most conservative strategy to replace missing values was pre-planned. In order to maximize the difference between treatment groups in a situation, where the irrelevance of the difference is to be demonstrated, missing values in the placebo group were counted as failures and missing values in the active treatment group were counted as treatment success.
Sensitivity analyses for the primary endpoint were conducted in (i) the ITT population with missing values counted as failures, both, in the placebo and the active treatment group, (ii) the PP population including only patients with evaluable overall treatment status (success or failure), and (iii) Complete Case population including only patients with evaluable treatment status for every single visit until ToC (day 30) are analysed.
Subgroup analyses for the primary endpoint were conducted in ITT subpopulations of age (dichotomized at median), sex, GOLD stage (I/II, III and IV), smoker status and occurrence of exacerbations in the previous 12 months where missing values are equally counted as failures in both treatment groups.
The secondary analysis of failure rates after 6 days (EoT) was conducted in the ITT population, PP population and Complete Case population. A patient is classified as relapse if new antibiotic therapy for AE-COPD is required within the first 6 months (follow-up 1) or 12 months (follow-up 2) after ToC, respectively. Secondary analysis of relapse rate at follow-up 1 and 2 only included patients who were assessed for treatment status until ToC (Complete Case population). Further secondary analyses were omitted due to data limitations.

Safety

The safety analysis was conducted in the safety analysis set including all patients, who received at least one dose of the study drugs. Consequently, one patient was excluded from the safety analysis because study participation was stopped during the baseline visit prior to study drug administration. In this study, the ITT and the safety populations are identical.

AEs and SAEs are reported with absolute and relative frequencies per treatment group. Additionally, absolute and relative frequencies of the CTC grades and relation to the study drug of AEs and SAEs were compared between treatment groups. All SAEs that occured between the first application of the IMP and within 28 days after the last application of the IMP were reported to the sponsor since a relation of the SAE to the IMP can be ruled out therafter. Thus, the reporting of SAEs that occurred after 28 days of the last application of the IMP was not mandatory and deviates from the reporting of AEs that were classified as serious AE by the investigator. However, in the safety analysis all serious AEs were considered as SAEs. SAE listings include only SAEs reported to the sponsor. Results of laboratory tests are summarized for baseline, endpoint, and for change from baseline to endpoint using descriptive statistics (mean, median, standard error, minimum, and maximum).

Primary analysis population characteristics

In the ITT population a total of 294 patients (Sultamicillin group: n=150; Placebo group: n=144) are analysed. For a detailed descriptive analysis of the population characteristics see Table 1 in the appendix.

	Treatment			
Characteristic	*A_(Sultamicillin) n=150*	*B_(Placebo) N=144*	*Total N=294*	*p-value*
Demographic Data				
Sex (male) – n/N (%)	91/150 (60.7)	91/144 (63.2)	182/294 (61.9)	0.656
Age - yr	67.13 (9.08)	65.82 (9.81)	66.49 (9.45)	0.234
Vital Signs				
Height - cm	169.69 (9.01)	169.70 (9.35)	169.70 (9.16)	0.994
Weight - kg	76.29 (16.24)	74.81 (20.62)	75.56 (18.50)	0.498
BMI	26.44 (5.10)	25.79 (6.08)	26.12 (5.60)	0.323
History of COPD				
GOLD				0.308
GOLD I – n/N (%)	8/150 (5.3)	9/144 (6.3)	17/294 (5.8)	
GOLD II – n/N (%)	49/150 (32.7)	33/144 (23.1)	82/294 (28.0)	
GOLD III – n/N (%)	51/150 (34.0)	59/144 (41.3)	110/294 (37.5)	
GOLD IV – n/N (%)	42/150 (28.0)	42/144 (29.4)	84/294 (28.7)	
Exacerbations within previous 12 months (yes) – n/N (%)	92 (61.3)	86 (59.7)	178 (60.5)	0.778
Current Smoker (yes) – n/N (%)	88/150 (58.7)	83/144 (57.6)	171/294 (58.2)	0.858
Spirometry				
FEV 1 - l	1.28 (0.59)	1.20 (0.53)	1.24 (0.56)	0.348
FEV 1 - %	47.95 (17.89)	44.07 (16.16)	46.00 (17.11)	0.108
FVC - l	2.30 (0.94)	2.29 (0.81)	2.29 (0.88)	0.929
FVC - %	66.37 (24.19)	61.55 (19.28)	64.00 (21.98)	0.127
Concomitant therapies				
Bronchodilatators (yes) – n/N (%)	143/144 (99.3)	137/138 (99.3)	280/282 (99.3)	1.000*
Corticosteroids (yes) – n/N (%)	81/144 (56.3)	72/138 (52.2)	153/282 (54.3)	0.492

* p-value derived from Fisher's exact test

Displayed numbers represent mean values (and corresponding standard deviation) unless otherwise stated. P-values derived from Chi²-Test unless otherwise stated.

Efficacy results

The failure rate after 30 days (ToC) in the Sultamicillin group is 23/150=15.3% and 36/144=25.0% in the Placebo group. The Mantel-Haenszel-Estimate (stratified for center) for the risk difference of failures (Placebo – Sultamicillin) in the ITT population with the most conservative strategy to replace missing values is 0.0997 with 95% confidence interval [0.007; 0.1923]. Thus, non-inferiority of placebo to sultamicillin could not be demonstrated since the 95% confidence interval includes the non-inferiority margin of 0.1. In this analysis the failure rate with placebo is significantly higher. Detailed results of the primary analysis are given in Table 3 (effect estimates) in the appendix.

Rates and risk difference of failures (ToC, day 30) – ITT (according to study protocol) stratified for center (Mantel-Haenszel-Estimation)

Population	*Sultamicillin: n/N (%)*	*Placebo: n/N (%)*	*Mantel-Haenszel-Estimate of risk difference (Placebo-Sultamicillin)[95%CI]*
ITT (according to study protocol)	23/150 (15.33%)	36/144 (25.00%)	0.0997 [0.007; 0.1923]

An analysis of the number of drop-outs per treatment group in the ITT population (Table 4) provides no evidence for differential dropout between a treatment with standard antibiotic regimen or placebo at ToC (19/150=13% vs. 14/144=10%; p=0.424) and during the active treatment phase until EoT (8/150=5% vs. 9/144=6%; p=0.736). No differences in reasons for premature study termination of dropouts could be identified. Reasons for premature study termination are provided in Table 5 (ToC) and Table 6 (EoT). In total, 28 baseline characteristics in drop-out patients including demographic data, vital signs, history of COPD, concomitant therapies and spirometrical parameters were analysed. No evidence of remarkable differences between treatment groups was found. However, analysis of baseline characteristics for drop-outs in the ITT population (Table 7) showed that there is a significant difference in BMI (Placebo – Sultamicillin: -5.56; p =0.0131).

A first sensitivity analysis based on the ITT population counting missing values as treatment failures irrespective of treatment group, shows a MH risk difference estimate of -0.0227 with a 95% confidence interval [-0.1211; 0.0757]. A second sensitivity analysis applying the primary analysis in the PP population, shows a MH risk difference estimate of -0.0066 with a 95% confidence interval [-0.1005; 0.0874]. A third sensitivity analysis applying the primary analysis in a Complete Case population, shows a MH risk difference estimate of 0.0100 with a 95% confidence interval [-0.0786; 0.0986].

Rates and risk difference of failures (ToC, day 30) – ITT (missing values = failure), PP, Complete Cases stratified for center (Mantel-Haenszel-Estimation)

Population	*Sultamicillin: n/N (%)*	*Placebo: n/N (%)*	*Mantel-Haenszel-Estimate of risk difference (Placebo-Sultamicillin)[95%CI]*
ITT (missing values = failure)	42/150 (28%)	36/144 (25%)	-0.0227 [-0.1211; 0.0757]
PP (without dropout)	23/131 (17.56%)	22/130 (16.92%)	-0.0066 [-0.1005; 0.0874]
Complete Case Analysis	18/126 (14.29%)	19/127 (14.96%)	0.01 [-0.0786; 0.0986]

In consequence, with the exception of the primary analysis, planned to ensure that all participants are completely observed in order to foster the primary objective of this trial, all sensitivity analyses

were able to demonstrate non-inferiority even with the reduced number of patients included into the trial (see Appendix).

Subgroup analyses were conducted in ITT population where missing values are counted as failures irrespective of the treatment group. Subgroup analysis revealed no significant differences in subpopulations of age (dichotomized at median), sex, smoker status, and occurrence of exacerbations within the previous 12 months, and are consistent with the results of the primary analysis. In patients with mild AE-COPD (GOLD I/II) the MH estimate and the corresponding 95% CI for the treatment effect favours sultamicillin and non-inferiority of placebo-treatment is shown. In contrast, the point estimates for moderate and severe AE-COPD (GOLD III and IV) in the ITT population where missing values are treated as failures in both treatment groups are in favour of placebo. However, statistically significant superiority/non-inferiority of placebo in GOLD III and IV patients could not be demonstrated. Results of subgroup analysis are shown in Table 9 in the appendix.

Rates and risk difference of failures (ToC, day 30) – ITT (missing values = failure) stratified for center (Mantel-Haenszel-Estimation)

Subgroup	*Sultamicillin: n/N (%)*	*Placebo: n/N (%)*	*Mantel-Haenszel-Estimate of risk difference (Placebo-Sultamicillin)[95%CI]*
Age - <=67y	17/72 (23.61%)	17/78 (21.79%)	0.0038 [-0.1375; 0.1451]
Age - >67y	25/78 (32.05%)	19/66 (28.79%)	-0.0218 [-0.1746; 0.1311]
Sex - male	14/91 (15.38%)	25/91 (27.47%)	0.0945 [-0.0245; 0.2135]
Sex - female	9/59 (15.25%)	11/53 (20.75%)	0.0459 [-0.1135; 0.2053]
Current smoker - yes	18/62 (29.03%)	16/61 (26.23%)	-0.0024 [-0.1782; 0.1734]
Current smoker - no	24/88 (27.27%)	20/83 (24.1%)	-0.0514 [-0.1805; 0.0777]
Exacerbations in the previous 12 months - yes	26/92 (28.26%)	24/86 (27.91%)	0.0016 [-0.1335; 0.1367]
Exacerbations in the previous 12 months - no	16/58 (27.59%)	12/58 (20.69%)	-0.0517 [-0.2062; 0.1028]
GOLD status - I/II	17/57 (29.82%)	6/42 (14.29%)	-0.2386 [-0.3988; -0.0783]
GOLD status - III	12/51 (23.53%)	14/59 (23.73%)	0.0023 [-0.1581; 0.1628]
GOLD status - IV	13/42 (30.95%)	15/42 (35.71%)	0.0944 [-0.1323; 0.3211]

Secondary analyses were conducted in the Complete Case population. No difference in relapse rates between standard antibiotic treatment and placebo could be found (15.3 % vs. 16.3 %; p=0.836) 6 months after ToC. Relapse rate in the placebo group was slightly higher compared to standard treatment with sultamicillin 1 year after ToC. However, no statistical significance could be reached (sultamigmcillin vs. placebo: 24.8 % vs: 34.5 %; p=0.140). No further secondary analyses were conducted due to data limitations.

Safety results

The safety analyses revealed a slightly better risk profile for Placebo compared to Sultamicillin. In total, 300 AEs occurred (Sultamicillin group: 162, Placebo group: 138). 140/294=48% patients in the safety population had at least one AE. Safety analysis show a higher rate of patients with at least one AE in the Sultamicillin group (80/150=53%) compared to Placebo group (60/144=42%) with p-value 0.0453. However, no differences between Sultamicillin group and Placebo group could be

found when AEs were analysed for each CTC grade seperately. A difference could be found comparing AEs that were considered by the investigator to be related to the study drug (Sultamicillin group: 25/150=17%, Placebo group: 6/144=4%) with a p-value 0.0005. In contrast, the sponsor's assessment of the reported SAEs did not find any relation of an SAE to the study drug. 36/294=12% patients experienced gastrointestinal disorders (Sultamicillin group: 29/150=5%; Placebo group: 7/144=4%), 19/294=6% patients experienced infections and infestations (Sultamicillin group: 12/150=7%; Placebo group: 7/144=5%), and 12/294=6% patients experienced renal and urinary disorders (Sultamicillin group: 10/150=6%; Placebo group: 2/144=1%). Diarrhea was revealed to be the most prominent AE. 24/150=15% patients in the Sultamicillin group experienced diarrhea at least once compared to only 4/144=3% patients in the Placebo group. In 25/294=12% patients (Sultamicillin group: 20/150=12%; Placebo group: 15/144=11%) abnormal laboratory parameters could be found.
In total, 126 SAEs occurred in the safety population (Sultamicillin group: 64, Placebo group: 62). 78/294=27% patients experienced at least one SAE (Sultamicillin group: 41/150=27%, Placebo group: 37/144=26%) with no significant difference between treatment groups (p=0.7503). 20/294=7% patients experienced at least one life-threatening AE (CTC grade 4). 20/294=7% patients died during the conduct of the study without significant differences between treatment groups. SAEs could be attributed to the expected risks associated with severe condition of COPD as outlined in the study protocol.

AEs

	Treatment			
	A_(Sultamicillin) N=150	B_(Placebo) N=144	Total N=294	p-value[1]
Total number of AEs	162	138	300	
Total number of SAEs	64	62	126	
Number of patients with at least one ...				
... AE	80 (53.3%)	60 (41.7%)	140 (47.6%)	0.0453
... SAE	41 (27.3%)	37 (25.7%)	78 (26.5%)	0.7503
... AE CTC grade 5: death	10 (6.7%)	10 (6.9%)	20 (6.8%)	0.9247
... AE CTC grade 4: life threatening	4 (2.7%)	3 (2.1%)	7 (2.4%)	0.7429
... AE CTC grade 3: severe	31 (20.7%)	37 (25.7%)	68 (23.1%)	0.3068
... AE CTC grade 2: moderate	38 (25.3%)	28 (19.4%)	66 (22.4%)	0.2264
... AE CTC grade 1: mild	29 (19.3%)	17 (11.8%)	46 (15.6%)	0.0757
... AE related to study drug[2]	25 (16.7%)	6 (4.2%)	31 (10.5%)	0.0005

[1] p-values were calculated with the use of Chi-Square test.

[2] assessment by study investigator

SAE count deviates from the reported SAEs to the sponsor since SAE reporting was not mandatory after 28 days of the last application of the IMP.

SAEs (reported to the sponsor)

	Treatment			
	A_(Sultamicillin) N=150	B_(Placebo) N=144	Total N=294	p-value[1]
Total number of AEs	42	48	90	
Total number of deaths	9	7	16	
Number of patients with at least one ...				
... SAE	33 (22.0%)	29 (20.1%)	62 (21.1%)	0.6958
... death	9 (6.0%)	7 (4.9%)	16 (5.4%)	0.6670
... relation to study medication	0 (0.0%)	0 (0.0%)	0 (0.0%)	-

[1] **p-values were calculated with the use of Chi-Square test**

[2] **assessment by the sponsor**

SAE and death counts deviate from AE analysis since SAE reporting was not mandatory after 28 days of the last application of the IMP.

A summary of the AE categorized by CTC grade analysed by treatment group, the number of patients with AEs and number of events is given in the appendix (Table 12 and 14). A summary of the reported SAEs and number of events by MedDRA SOC and PT terms is also provided (Table 13 and 15). All AEs and reported SAEs are also listed there in Table 19 and 20. Results of the analysis of laboratory tests are provided in Table 16, 17 and 18.

Conclusion

The study did not reach the recruitment goal and was stopped after 295/940=31% of the planned sample size. The recruitment was stopped prematurely by the sponsor in accordance with the principal investigator because of the difficulties to achieve the planned numbers of patients within a reasonable time frame. Neither safety nor IMP issues caused the premature termination of the study.

The primary analysis for the ITT population (Table 3) did count missing values in the Sultamicillin-group as success and missing values in the placebo-group as failures. This analysis showed that the upper boundary of the 95% CI exceeded the non-inferiority margin of 10% (0.0997 [0.007; 0.1923]). Thus, the null hypothesis cannot be rejected that treatment with placebo compared to standard antibiotic regimen causes a relevant increase of treatment failure in patients with AE-COPD.

In contrast, three sensitivity analyses (counting missing values in the ITT population as treatment failures irrespective of treatment group, PP population with evaluable overall treatment status and Complete Case population with evaluable treatment status for each visit until ToC) were able to demonstrate non-inferiority of placebo treatment to standard antibiotic regimen with sultamicillin.

A detailed assessment of subgroups revealed differences between the stages of severity of AE-COPD (GOLD status). An advantage of additional antibiotic treatment could not be shown in patients with mild or moderate AE-COPD (GOLD I/II). In contrast, patients with severe AE-COPD (GOLD III and IV) still benefit from standard antibiotic treatment. Thus, decision making of AE-COPD treatment with antibiotics should consider the severity of AE-COPD (GOLD status).

The overall safety profile showed a slightly higher risk profile for standard antibiotic treatment regimen with 300 AEs and 126 SAEs in total. Occurrence of diarrhea was the most remarkable difference in AEs between treatment groups (Sultamicillin group: 24=15% patients vs. Placebo group: 4=3% patients). However, diarrhea is a well-known adverse effect of Sultamicillin affecting ≥10% of patients. No remarkable difference in SAE profile between treatment groups could be found.

Date of report: May 15, 2020

Disclaimer

CAPNETZ has been responsible for data management and monitoring. The validated data transfer of the final data was performed on 18.10.2019. A careful assessment of plausibility has been conducted by the members of the department of Biostatistics and findings were discussed jointly with Joelle Naim/Waldemar Kröner (CAPNETZ STIFTUNG) and resolved in the analyses data sets.