ANTIBIOTIC THERAPY IN VIRAL AIRWAY INFECTIONS (ATHENIAN):
AN OPEN LABELED RANDOMIZED CONTROLLED PRAGMATIC TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF DISCONTINUING ANTIBIOTIC THERAPY IN ADULT PATIENTS INFECTED WITH RESPIRATORY VIRUSES

Protocol Identification Number: Ahus-ATHENIAN
EudraCT Number: 2021-004248-11
ClinicalTrials.gov Identifier: NCT05045612

SPONSOR: **Akershus University Hospital**
Head of Department / Associate Professor Jan Erik Berdal
Department of Infectious Diseases
Akershus University Hospital
Sykehusveien 25
1478 Lørenskog, Norway
Tel: +47 48 20 58 17
E-mail: jan.erik.berdal@medisin.uio.no

PROTOCOL VERSION NO. 1.3 – 02.03.22

CONTACT DETAILS

Sponsor: **Head of Department / Associate Professor Jan Erik Berdal, MD PhD**
Department of Infectious Diseases, Division of Medicine
Akershus University Hospital
Sykehusveien 25
1478 Lørenskog, Norway
Tel: +47 48 20 58 17
E-mail: jan.erik.berdal@medisin.uio.no

Principal Investigator: **Associate Professor Magnus Lyngbakken, MD PhD**
Department of Infectious Diseases, Division of Medicine
Akershus University Hospital
Sykehusveien 25
1478 Lørenskog, Norway
Tel: +47 93 40 88 37
E-mail: magnus.lyngbakken@medisin.uio.no

Investigator: **Professor Olav Dalgard, MD PhD**
Department of Infectious Diseases, Division of Medicine
Akershus University Hospital
Sykehusveien 25
1478 Lørenskog, Norway
Tel: +47 92 61 68 00
E-mail: odalgard@uio.no

Investigator: **PhD fellow Magrit Jarlsdatter Hovind, MD**
Department of Infectious Diseases, Division of Medicine
Akershus University Hospital
Sykehusveien 25
1478 Lørenskog, Norway
Tel: +47 97 54 06 81
E-mail: m.j.hovind@medisin.uio.no

Investigator: **Associate Professor Truls Leegaard, MD PhD**
Department of Microbiology and Infection Control
Akershus University Hospital
Sykehusveien 25
1478 Lørenskog, Norway
Tel: +47 90 64 62 65
E-mail: Truls.Michael.Leegaard@ahus.no

Investigator: **Associate Professor Jørgen Vildershøj Bjørnholt, MD PhD**
Department of Microbiology
University of Oslo, OUS HF Rikshospitalet
Postboks 4950 Nydalen
0424 Oslo
Tel: +47 90 21 39 59
E-mail: j.v.bjornholt@medisin.uio.no

Data Monitoring Committee: **Postdoctoral Fellow Aleksander Rygh Holten, MD PhD**
Department of Infectious Diseases
University of Oslo, OUS HF Ullevål
Postboks 4956 Nydalen
0424 Oslo
Tel: +47 99 27 57 84
E-mail: a.r.holten@medisin.uio.no

Associate Professor Dag Henrik Reikvam, MD PhD
Department of Infectious Diseases
University of Oslo, OUS HF Ullevål
Postboks 4956 Nydalen
0424 Oslo
Tel: +47 94 85 89 39
E-mail: d.h.reikvam@medisin.uio.no

Monitor: **Mariann Glenna Davidsen**
Division of Research and Innovation
Akershus University Hospital
Sykehusveien 25
1478 Lørenskog, Norway
Tel: +47 67 96 87 04
E-mail: Mariann.Glenna.Davidsen@ahus.no

Stine Lien Pedersen
Division of Research and Innovation
Akershus University Hospital
Sykehusveien 25
1478 Lørenskog, Norway
Tel: +47 90 75 30 52
E-mail: Stine.Lien.Pedersen@ahus.no

Statistician: **Jurate Saltyte Benth, PhD**
Health Services Research Unit
Akershus University Hospital
Sykehusveien 25
1478 Lørenskog, Norway
Tel: +47 48 22 44 31
E-mail: j.s.benth@medisin.uio.no

SIGNATURE PAGE

Title   Antibiotic THErapy iN vIral Airway iNfections (ATHENIAN): An open labelled randomized controlled pragmatic trial to evaluate the efficacy and safety of discontinuing antibiotic therapy in adult patients infected with respiratory viruses

Protocol ID: ATHENIAN

EudraCT no: 2021-004248-11

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Name	Title	Role	Signature	Date
Jan Erik Berdal	Head of Department/ Associate Professor	Sponsor's representative		
Magnus Nakrem Lyngbakken	Associate Professor	Principal investigator		

SIGNATURE PAGE SITE INVESTIGATORS

Title	Antibiotic THErapy iN vIral Airway iNfections (ATHENIAN): An open labelled randomized controlled pragmatic trial to evaluate the efficacy and safety of discontinuing antibiotic therapy in adult patients infected with respiratory viruses
Protocol ID:	ATHENIAN
EudraCT no:	2021-004248-11

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Name	Title	Signature	Date

PROTOCOL SYNOPSIS

Antibiotic THErapy iN vIral Airway iNfections (ATHENIAN): An open labelled randomized controlled pragmatic trial to evaluate the efficacy and safety of discontinuing antibiotic therapy in adult patients infected with respiratory viruses

Sponsor	Akershus University Hospital HF
Phase and study type	Phase 4, non-inferiority treatment trial
Investigational Medical Product (IMP) (including active comparator and placebo) :	Antibiotic therapy No active or placebo control
Centers:	Initial single center with possible extension to other Norwegian sites pending results and funding. Extension will be according to separate submissions to ethics committee and other regulatory bodies from new centers.
Study Period:	Estimated date of first patient enrolled: 01.12.21 Anticipated recruitment period: 36 months End of study (last patient's last visit): 30.11.24 Estimated study termination: 30.11.29 Time-frame of study data retention: 30.11.44
Treatment Duration:	At the discretion of the treating physician in the control arm of the study
Follow-up:	At five and 30 days

Objectives	Overall objective: In patients with positive airway sample for respiratory viruses, assess whether discontinuation of antibiotic therapy is safe and non-inferior to continuation of antibiotic therapy Specific objectives: In patients with positive airway sample for respiratory viruses, assess whether discontinuation of antibiotic therapy is non-inferior to continuation of antibiotic therapy with regard to 1. Early clinical response 2. In-hospital mortality and mortality after 30 days 3. Duration of hospital admission 4. Days of therapy with antibiotics 5. Rescue antibiotic therapy during hospital admission 6. New antibiotic therapy up to 30 days after discharge 7. Hospital readmission up to 30 days after discharge
Endpoints:	Primary endpoint: • Early clinical response assessed at 120 hours after randomization, defined as survival with symptom improvement without receipt of rescue antibacterial therapy Secondary endpoints: • In-hospital mortality • Mortality at 30 days • Duration of hospital admission • Days of therapy with antibiotics • Rescue antibiotic therapy during hospital admission • New antibiotic therapy for presumed airway infection up to 30 days after discharge • Hospital readmissions up to 30 days after discharge
Study Design:	Two-arm, open label, single center, pragmatic study with possible extension to other Norwegian sites.
Main Inclusion Criteria:	1. Hospitalized 2. Adults 18 year or older 3. Moderately severe disease (CRB65 ≤ 2 at time of inclusion) 4. Nasopharyngeal swab positive for influenza virus, parainfluenza virus, respiratory syncytial virus (RSV) or human metapneumovirus (hMPV) 5. On antibiotic therapy as instituted by the receiving physician from the emergency department 6. Signed informed consent must be obtained and documented according to ICH GCP, and national/local regulations.
Main Exclusion Criteria	1. Requiring ICU admission at screening 2. Requiring high-flow oxygen therapy or non-invasive ventilation at screening 3. Signs of severe pneumonia (abscesses, massive pleural effusion, a well-defined lobar infiltrate on chest X-ray strongly suggestive of bacterial etiology) 4. Not immunocompetent (i.e. on active chemotherapy, corticosteroid therapy equaling ≥ 20 mg prednisolone daily for ≥ 4 weeks, chronic immunosuppression due to solid organ transplant) 5. SARS-CoV-2 positive

	6. Bacteremia
	7. Urine antigen test positive for legionella
	8. Any other infection necessitating antibiotic treatment
	9. Antibiotic use for assumed airway infection within the last 24 hours before admission to hospital
Sample Size:	380 patients (1:1 randomized to intervention and control), considering screening failure and loss to follow-up, we will aim to include at least 400 patients
Efficacy Assessments:	Early clinical response assessed at 120 hours after randomization, defined as survival with symptom improvement without receipt of rescue antibacterial therapy
Safety Assessments:	Serious Adverse Events (SAE) and Suspected Unexpected Serious Adverse Reactions (SUSAR).

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
AE	Adverse Event
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
DAE	Discontinuation due to Adverse Event
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Council for Harmonization
IMP	Investigational Medicinal Product (includes active comparator and placebo)
ITT	Intention to treat
PP	Per-protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure

1 INTRODUCTION

1.1 Background – Disease

Patients with lower respiratory tract infections constitute a heterogeneous group of patients with substantial short- and long-term mortality, and community acquired pneumonia (CAP) is a leading cause of morbidity and mortality worldwide. The etiology of CAP is often not possible to determine even in stringent scientific studies. The most commonly identified agents are typical bacteria (e.g. S. pneumoniae and H influenzae), atypical bacteria (e.g. Legionella species and Mycoplasma pneumoniae), or respiratory viruses (e.g. influenza viruses and respiratory syncytial virus) *(1)*. In a large epidemiological study conducted by the Centers for Disease Control and Prevention, despite the extensive diagnostic workup performed, no pathogen was detected in 62 per cent of the cases. A viral pathogen was detected as single pathogen in 22 per cent, whereas solely bacterial pathogens were detected in 11 per cent and coinfection virus-bacteria were detected in 3 per cent of the cases *(2)*. Among the viral pathogens detected, human rhinovirus was the most commonly detected followed by influenza virus. Common symptoms of CAP include fever, cough, dyspnea, and pleuritic chest pain, but clinical signs do not accurately reflect the underlying microbiological pathology. In the case of convincing signs and symptoms of CAP, antibiotic therapy is generally started immediately after admission, as delays in appropriate antibiotic treatment that exceed four hours have been associated with increased mortality *(3)*. Considering the vastly diverse microbiological etiologies of CAP, frequently including a principal viral cause, antibacterial treatment is often futile and will only contribute to progressive antimicrobial resistance.

Overuse of antibiotics is a main driver of antibiotic resistance. Misuse of antibiotics is particularly common in respiratory tract infections, where a large proportion is caused by respiratory viruses *(2)*. In the hospital setting, widespread availability of nucleic acid amplification tests (NAAT) for respiratory tract specimens allows rapid viral detection, offering the possibility of withholding or stopping antibiotic therapy when respiratory viruses are believed to be causative agents. In the 2012 to 2013 winter season, the majority of patients admitted to Akershus University Hospital with RSV (82.7% n=133), H3N2 (73.3% n=176) and H1N1 (68.2% n=132) flu virus were treated with antibiotics. Data on the proportion of these patients who continued antibiotics after hospital discharge is unknown, but the prescription pattern likely represents antibiotic overtreatment.

In an acutely ill patient with CAP, detection of respiratory viruses may represent infection involving the lower respiratory tract, but could also be colonization, persistent shedding after a prior infection or infection restricted to the upper respiratory tract *(4)*. No clear consensus has been reached about whether patients with CAP and respiratory viruses detected in the respiratory tract need to be treated with antibiotics, but antibiotic treatment for all hospitalized patients with CAP is commonly recommended due to the near impossibility of excluding bacterial co-infection. However, a general recommendation to treat all hospitalized CAP patients with antibiotics likely leads to significant antibiotic overtreatment *(5)*. The wide availability of NAAT enables us to define individuals with CAP who can be managed without antibiotics.

1.2 Background - Therapeutic Information

Antibiotic therapy has revolutionized modern medicine and made treatment of potentially life threatening bacterial infections possible. However, antibacterial therapeutics have no effect on viruses, and merely subject the patient to side effects besides contributing to increasing antimicrobial resistance. Specific antiviral therapy is limited, especially for respiratory viruses, and supportive care is usually the treatment of choice in established viral respiratory infections.

1.3 Rationale for the Study and Purpose

In patients with positive airway sample for respiratory viruses, we hypothesize that discontinuation of antibiotic therapy is safe and non-inferior to continuation of antibiotic therapy. More specifically, we hypothesize that the early clinical response assessed at 120 hours after randomization, defined as survival with symptom improvement without receipt of rescue antibacterial therapy, will be similar between patients who discontinue and continue antibiotic therapy. Furthermore, we hypothesize that discontinuation of antibiotic therapy is associated with similar mortality rates, duration of hospital admission, readmission rates and reduced number of days of therapy with antibiotics. Antimicrobial resistance is one of the most urgent health threats of our time, and Norwegian hospitals were required but failed to reduce the use of broad-spectrum antibiotics with 30% by the end of 2020. In this context, novel initiatives aiming at reducing use of antibiotics are direly needed.

2 STUDY OBJECTIVES AND RELATED ENDPOINTS

The **primary aim** is to assess whether discontinuation of antibiotic therapy in patients with positive airway sample for respiratory viruses is safe and associated with early clinical response assessed at 120 hours after randomization that is comparable to patients who continue antibiotic therapy.

The **secondary aims** are to assess whether discontinuation of antibiotic therapy in patients with positive airway sample for respiratory viruses is associated comparable (1) mortality rates, (2) duration of hospital admission, (3) days of therapy with antibiotics, (4) rate of rescue antibiotic therapy during hospital admission, (5) frequency of new antibiotic therapy after discharge, and (6) hospital readmissions.

Specific objectives

- In patients with positive airway sample for respiratory viruses, assess the impact of discontinuing antibiotic therapy on early clinical response quantified as survival with symptom improvement without receipt of rescue antibacterial therapy. Early clinical response is defined as improvement of one or more levels relative to baseline in two or more symptoms of the investigator's assessment of symptoms of community-acquired bacterial pneumonia and no worsening of one or more levels in other symptoms (**Table 1**).
- In patients with positive airway sample for respiratory viruses, assess the impact of discontinuing antibiotic therapy on in-hospital mortality
- In patients with positive airway sample for respiratory viruses, assess the impact of discontinuing antibiotic therapy on 30 day mortality
- In patients with positive airway sample for respiratory viruses, assess the impact of discontinuing antibiotic therapy on duration of hospital admission

- In patients with positive airway sample for respiratory viruses, assess the impact of discontinuing antibiotic therapy on days of therapy with antibiotics
- In patients with positive airway sample for respiratory viruses, assess the impact of discontinuing antibiotic therapy on rescue antibiotic therapy
- In patients with positive airway sample for respiratory viruses, assess the impact of discontinuing antibiotic therapy on new prescriptions of antibiotics for airway infections up to 30 days after hospital discharge
- In patients with positive airway sample for respiratory viruses, assess the impact of discontinuing antibiotic therapy on hospital readmissions up to 30 days after hospital discharge

Table 1. Symptom severity assessment

Absent	Mild	Moderate	Severe
COUGH?			
No cough or resolution of cough to pre-CAP baseline	Cough present but it does not interfere with subject's usual daily activities	Cough present, frequent and it does interfere with some of the subject's usual daily activities	Cough is present throughout the day and night; it limits most of the subjects' usual daily activities and sleep patterns
PLEURITIC CHEST PAIN?			
No chest pain or resolution of chest pain to pre-CAP baseline	Chest pain present occasionally with deep breathing but it does not interfere with subject's usual daily activities	Chest pain is present with normal breaths and it does interfere with the subject's usual daily activities	Chest pain is present at rest and/or with shallow breathing; it limits most of the subject's usual daily activities
SHORTNESS OF BREATH?			
No shortness of breath or resolution of shortness of breath to pre-CAP baseline	Shortness of breath with strenuous activities only but it does not interfere with subject's usual daily activities	Shortness of breath with usual activities and it does interfere with the subject's usual daily activities	Shortness of breath with minimal exertion or at rest; it limits most of the subject's usual daily activities
PHLEGM/SPUTUM PRODUCTION?			
No coughing up of phlegm/sputum or resolution of coughing up phlegm/sputum to pre-CAP baseline	Subject coughs up a small amount of phlegm/sputum	Subject coughs up a moderate amount of phlegm/sputum	Subject coughs up a large amount of phlegm/sputum
From Stets et al. N Engl J Med. 2019;380:517-527. *(6)*			

2.1 Primary Endpoint

- Early clinical response at 120 hours after randomization, quantified as survival with symptom improvement without receipt of rescue antibacterial therapy.

2.2 Secondary Endpoints

- Duration of hospital admission
- In-hospital mortality
- 30 day mortality
- Days of therapy with antibiotics
- In-hospital rescue antibiotic therapy

- New antibiotic therapy for assumed airway infection within 30 days after discharge
- Hospital readmissions up to 30 days after discharge

3   OVERALL STUDY DESIGN

The study is a two-arm, open label, pragmatic randomized controlled non-inferiority stop trial designed to assess the safety and efficacy of discontinuing antibiotic therapy in patients with positive airway sample for respiratory viruses. Pragmatic clinical trials (PCT) are characterized by 3 attributes: (1) focus on informing decision-makers (e.g. patients, politicians, administrators) on optimal clinical medicine practice, as opposed to elucidating a biological or social process; (2) intent to enroll a population representative to the decision in practice and for whom the decision is relevant; and (3) either an intent to streamline procedures and data collection in the trial or to measure a broad range of outcomes. By utilizing resources already paid for by the hospitals (physicians and nurses in daily clinical practice), pragmatic clinical trials can include a larger number of patients at a short time duration and at a lower cost than studies utilizing traditional randomized controlled trial (RCT) designs with an external study organization (e.g. study nurses, study physicians). A pragmatic approach will enable swift initiation of randomization and treatment. We will especially use data from the data warehouse at Akershus University Hospital for eligible patient identification (i.e. *electronic surveillance*) and for automatic data extraction to the study specific database. The study will examine the effects of discontinuing treatment and the study will accordingly not be placebo-controlled.

In the initial phase of the study, patients will be included from a single center (Akershus University Hospital). The study will have interim efficacy and safety analyses after the inclusion of 40 patients or after the first winter season (March 2022), whichever comes first. Subsequent interim analyses will be performed after 100 and 200 completed patients. Extraordinary interim meeting will also conducted if deemed necessary by the Sponsor. This approach will enable frequent assessment of the primary outcome measure and safety measures. See Section 10 Statistical methods and data analysis for further details.

All patients at Akershus University Hospital with suspicion of acute respiratory tract infections are examined with a nasopharyngeal swab, with subsequent microbiological examination, including specific polymerase chain reaction (PCR) for respiratory viruses. Laboratory reports from the Department of Microbiology are surveilled real-time for positive samples in the local data warehouse, which will allow for immediate screening and randomization in all eligible subjects. **Figure 1** gives a schematic overview of the study.
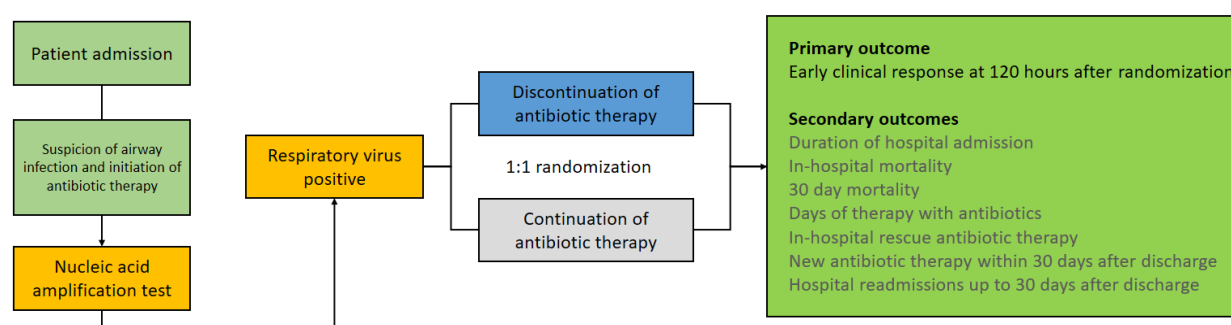

Figure 1. Trial design

Study Period of initial study phase:	Estimated date of first patient enrolled: 01.12.21
	Anticipated recruitment period: 36 months
	Estimated date of last patient completed: 30.11.23
	Estimated study termination: 30.11.28

Treatment Duration:	Patients randomized to continuation of antibiotic therapy will be treated according to the discretion of the treating physician, commonly five days of antibiotic therapy if suspicion of pneumonia
Follow-up:	Symptom severity assessment at 120 hours after randomization
	Mortality assessment during admission and after 30 days

4 STUDY POPULATION

4.1 Selection of Study Population

Participants will be recruited from the entirety of the inpatients at the participating hospitals. Electronic real-time surveillance of laboratory reports from the Department of Microbiology will be examined regularly, with maximum interval 24 hours, for patients positive for respiratory viruses.

4.2 Number of Patients

We aim to include a total of 380 patients randomized in a 1:1 fashion to intervention (stop antibiotic therapy) or control (continue antibiotic therapy at the discretion of the treating physician). Interim analyses are planned after 40, 100, and 200 included patients. See Section 10 Statistical methods and data analysis for further details on the analysis populations.

4.3 Inclusion Criteria

All of the following conditions must apply to the prospective patient at screening prior to inclusion:
1. Hospitalized
2. Adults 18 year or older
3. Moderately severe disease (CRB65 ≤ 2 at time of inclusion; **Figure 2**)
4. Nasopharyngeal swab positive for influenza virus, parainfluenza virus, respiratory syncytial virus (RSV) or human metapneumovirus (hMPV)
5. On antibiotic therapy as instituted by the receiving physician from the emergency department
6. Signed informed consent must be obtained and documented according to ICH GCP, and national/local regulations.

CRB65 severity score:
1 point for each feature present:

• **C**onfusion
• **R**espiratory rate ≥ 30/min
• **B**lood pressure (SBP < 90 or DBP ≤ 60mmHg)
• Age ≥ **65** years

Treat according to clinical judgement and CRB65 severity score

0	1-2	3-4
Low severity	Moderate severity	High severity
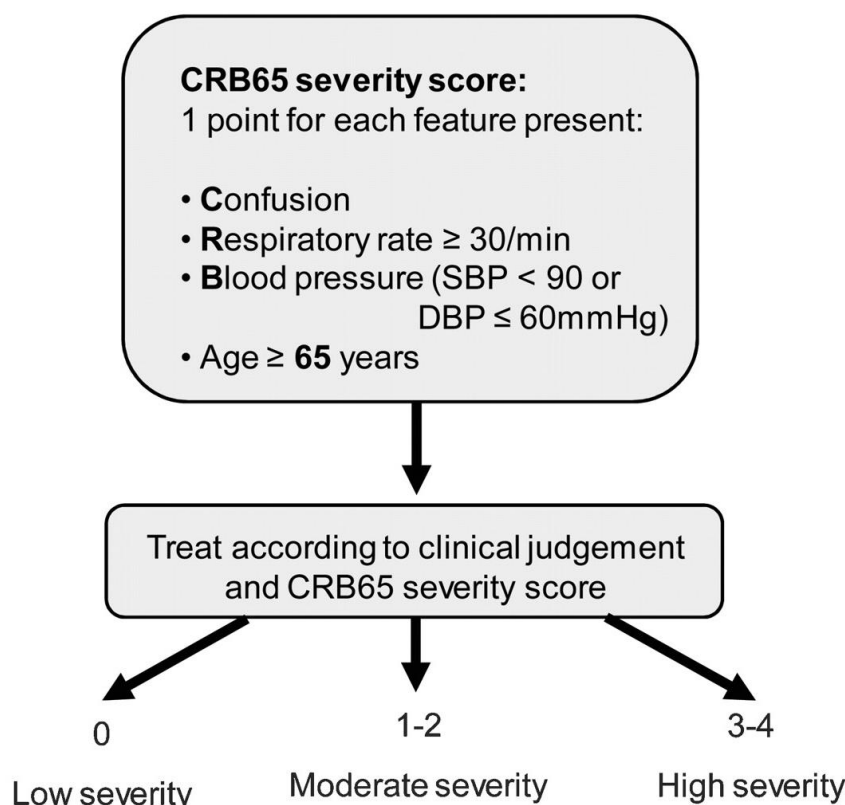
4.4   Exclusion Criteria

Patients will be excluded from participation in the study if they meet any of the following criteria:

1.   Requiring ICU admission at screening
2.   Requiring high-flow oxygen therapy or non-invasive ventilation at screening
3.   Signs of severe pneumonia (abscesses, massive pleural effusion, a well-defined lobar infiltrate on chest X-ray strongly suggestive of bacterial etiology)
4.   Not immunocompetent (i.e. on active chemotherapy, corticosteroid therapy equaling ≥ 20 mg prednisolone daily for ≥ 4 weeks, chronic immunosuppression due to solid organ transplant)
5.   SARS-CoV-2 positive
6.   Bacteremia
7.   Urine antigen test positive for legionella
8.   Any other infection necessitating antibiotic treatment
9.   Antibiotic use for assumed airway infection within the last 24 hours before admission to hospital

5   TREATMENT

Antibiotic therapy has limited effect in infection due to respiratory viruses. Early in the ongoing SARS-CoV-2 pandemic, antibiotic therapy was frequently prescribed to patients admitted with covid-19 due to fear to bacterial coinfections. Coinfection are however infrequent in patients hospitalized with covid-19, and current guidelines do not recommend empiric antibiotic therapy in patients with moderate disease not in need of ICU admission *(8)*. The wide availability of NAAT for rapid viral detection together with radiographic CAP has the potential to define patients who can be managed without antibiotics.

The active intervention in this study is to stop antibiotic therapy in patients with positive airway sample for respiratory viruses. Patients randomized to the control group will continue antibiotic therapy at the discretion of the treating physician. Apart from this, local standard-of-care will apply to all study patients.

5.1   Drug Identity, Dosage and Administration

At enrollment, all patients will be under antibiotic treatment as initiated by the receiving physician in the emergency department. All included patients randomized to intervention will discontinue antibiotic therapy, and all patients randomized to the control group will continue antibiotic therapy at the discretion of the treating physician.

All drug treatment will be provided by the trial sponsor (Akershus University Hospital) as part of clinical routine.

5.2   Duration of Therapy

Duration of therapy for study patients randomized to the control group is at the discretion of the treating physician, study participants randomized to the intervention group will discontinue antibiotic therapy at randomization.

5.3   Concomitant Medication

All concomitant medication used by the patient will be recorded at admission and retrieved from the hospital electronic prescribing system.

5.4   Subject Compliance

All study medication will be administered by health care personnel during hospital admission. Study patients discharged with per oral antibiotic therapy will not be followed up with regard to compliance.

5.5 Drug Accountability

All study medication will be administered by health care personnel during hospital admission, who are accountable for all study drugs.

5.6 Subject Numbering

Each subject is identified in the study by a unique subject number that is assigned when subject signs the Informed Consent Form. Once assigned the subject number cannot be reused for any other subject.

6 RISKS AND BENEFITS

As described previously, antimicrobial resistance is one of the most urgent health threats of our time and overuse of antibiotics is a main driver of antibiotic resistance. In this context, novel initiatives aiming at reducing use of antibiotics are direly needed. This study holds strong potential to influence established clinical practice and contribute to novel approaches in the management of lower airway infections.

A personal benefit for the participant is a closer follow-up than the clinical routine with the assessment 120 hours after randomization. The participants may also find the opportunity to contribute to research meaningful. A reduction in antibiotic-resistant microbes will benefit the future patients and the participant themselves when they need antibiotics for an infection caused by a bacteria. Participants in the intervention group will have reduced risk of antibiotic-related side effects, such as infection caused by C. difficile.

In all antibiotic stewardship programs, antibiotic de-escalation and discontinuation inevitably carry a risk to the individual for the benefit of the community at large, as the non-existence of a condition (bacterial infection) cannot be proven. For the participant there is a potential risk of undertreatment of a bacterial co-infection despite the detection of respiratory virus. The risk will be minimized by including only low-to-moderate risk patients, offering close monitoring and deferring discontinuation decisions to after a short observation period where one to three doses of antibiotics are given pending results of NAAT for viruses. A pragmatic study design allows rescue antibiotic therapy at the discretion of the treating physician and participants will be encouraged to seek health care in case of deterioration after discharge. The possible benefits on individual, national and international scale greatly outweighs individual risk.

7 STUDY PROCEDURES

As described in Section 3, the current study will utilize a pragmatic approach. In this regard, we will utilize resources already paid for by the hospitals, and all study procedures will be performed at the discretion of the treating physician, including laboratory testing, medical imaging and other procedures deemed clinically necessary (**Table 2**).

Table 2. Study flow chart								
			Time after randomization					
	Admission	Randomization	24 h	48 h	72 h	96 h	120h	30 d
Nasopharyngeal test	X							
Inclusion/exclusion evaluation		X						
Informed consent		X						
Physical examination	[1]X		[1]X	[1]X	[1]X	[1]X	[1]X	
Blood samples	[2]X		[2]X	[2]X	[2]X	[2]X	[2]X	
SAE and SUSAR[3]			[2]X	[2]X	[2]X	[2]X	[2]X	
Record of concurrent medication[4]		X						
Mortality			X	X	X	X	X	X

Symptom severity assessment		X					[5]X	

[1]Clinical examination at the discretion of the admitting physician (full clinical examination including heart, lungs, abdomen, extremities), as well as medical history, substance use, allergies, current medication, etc.
[2]At the discretion of the treating physician
[3]If discharged before end of treatment, assessment of SAE will be performed by phone directly to the patient at 120 hours
[4]Current medication at admission and antimicrobial therapy initiated at admission
[5]By phone if discharged

7.1 Criteria for Patient Discontinuation

Patients may be discontinued from the study any time. Specific reasons for discontinuing a patient for this study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment.
- Incorrect enrolment i.e. the patient does not meet the required inclusion/exclusion criteria for the study

7.2 Procedures for Discontinuation

7.2.1 Patient Discontinuation

The reason for discontinuation will be recorded, if the patient chooses to disclose it. Management of patients who withdraw or are withdrawn from the study will have to be individualized and will be discussed with the Principal Investigator. All patients randomized will be included in the study population.

7.2.2 Trial Discontinuation

The whole trial may be discontinued at the discretion of the sponsor in the event of any of the following:
1. Occurrence of SAEs unknown to date in respect of their nature, severity and duration that may negatively affect the benefit/risk of the trial.
2. Medical or ethical reasons affecting the continued performance of the trial
3. Difficulties in the recruitment of patients
4. The sponsor and principal investigator(s) will inform all investigators, the relevant Competent Authorities and Ethics Committees of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the Competent Authorities and Ethics Committees will be informed within 15 days.

7.3 Laboratory Tests

On admission, a standard panel of laboratory test will be performed on all patients (covering hematology, electrolytes, liver- and renal function, standard serology, inflammatory markers), and these will be performed locally in accordance with hospital/laboratory standard procedures. Nasopharyngeal sampling, blood cultures and urine antigen tests will be performed at the discretion of the receiving physician in the emergency department.

7.4 Clinical variables

Collection of clinical variables will start at admission and for the entirety of the hospital stay. Data will be collected from the hospital electronic record system, including electronic patient records, laboratory and medical imaging systems, and prescribing systems. The data warehouse at Akershus University Hospital will be utilized for automatic data extraction to the study specific database. All clinical variables will be registered in the study eCRF system, including clinical endpoints.

Data retrieved from hospital electronic record system	
Date of birth	

Sex	
Ethnicity	
Admission date	
Discharge date	
Date of symptom onset	
Admission signs and symptoms	Fever Chills Sore throat Myalgia Cough Sputum production Chest pain Shortness of breath
Imaging on admission (chest X-ray, CT, etc)	Infiltrates Pleural effusion Ground glass opacities
Co-morbidities	Cardiovascular disease Chronic obstructive pulmonary disease Chronic kidney disease Autoimmune disease Diabetes mellitus Cognitive impairment/dementia Cancer
Substance use	Tobacco and alcohol consumption
Clinical biochemistry on admission	At the discretion of the treating physician
Results from microbiology	Nasopharyngeal specimen Blood culture results Legionella urine antigen tests
Anthropometrics	Height (cm) Weight (kg)
Vital signs on admission	Respiratory rate Oxygen saturation Supplemental oxygen Temperature Blood pressure Heart rate Level of consciousness (alert, verbal, pain, unresponsive) NEWS score
Medical therapy/medication	Current medication at admission Antimicrobial therapy initiated at admission Antimicrobial therapy during admission
Clinical outcomes	Early clinical response (combination of all of the following) • Survival • Improvement of one or more levels relative to baseline in two or more symptoms of the investigator's assessment of symptoms of community-acquired bacterial pneumonia and no worsening of one or more levels in other symptoms • No rescue antibiotic therapy

	Mortality (in-hospital and after 30 days)
	Duration of hospital admission
	Days of therapy with antibiotics, including antibiotic therapy during admission and per oral antibiotics after discharge
	Rescue antibiotic therapy during admission
	New antibiotic therapy prescribed for presumed airway infection within 30 days after discharge
	Hospital readmissions up to 30 days after discharge
Safety monitoring and reporting	Serious adverse events
	Suspected unexpected serious adverse reactions

8   ASSESSMENTS

8.1   Assessment of Efficacy / Response

Early clinical response at 120 hours after randomization is the primary efficacy measure.

8.2   Safety and Tolerability Assessments

Safety will be monitored by the assessments described below. For details on collection and reporting, refer to Section 8.

9   SAFETY MONITORING AND REPORTING

9.1   Adverse Events

An AE is any untoward medical occurrence in a patient in relation to administration of a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
The term AE is used to include both serious and non-serious AEs.

In the current study, the control group will continue antibiotic therapy as prescribed by the treating physician (i.e. "standard of care"). Common side effects of antibiotic therapy reported in the SPC (section «Bivirkninger») of the IMPs are considered expected effects in the control group and will not be recorded as AE.

Traditional Adverse Event reporting, i.e. reporting side effects to the sponsor is not within the scope of this study for several reasons. The study is a stop trial investigating the safety and efficacy of discontinuing possibly futile treatment (antibiotic therapy for viral infection). Complications caused by the lack treatment does not constitute Adverse Event in this regard. Further, antibiotic therapy currently used at Akershus University Hospital is approved by the Norwegian Medical Agency, and have established side effect profiles.

9.2   Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:
- Results in death

- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above,

Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should be considered as serious.

9.3   Suspected Unexpected Serious Adverse Reactions (SUSAR)

The Sponsor's Medical Officer will review all SAEs reported as related to the trial drug and evaluate whether the event is expected according to the Reference Safety Information (RSI). The SPC of the current drug is used as Reference Safety Information in this trial. SUSARs will be reported to the Competent Authority according to national regulation. SUSARs will be reported to the Norwegian Medicines Agency and REK Sør-Øst according to national regulation. The sponsor will ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible and in no case later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

9.4   Safety and reporting

The Data Monitoring Committee (DMC) will overview the outcomes throughout the study. SAE and SUSAR will be surveyed and reported as described above.

9.5   Data Monitoring Committee (DMC)

A data monitoring committee (DMC) will be established to monitor the safety and efficacy of the study treatment and will consist of one statistician and two physicians with experience from virology/infectious disease and clinical studies. All members will be independent from the sponsor and will not be investigators or collaborators in the current study. The DMC will review all SAEs. The study investigators may call on the DMC to review specific SAEs. The DMC will conduct its tasks according to the EMA guideline *(9)*. A DMC charter based on the NORCRIN template *(10)* will be signed and included in the Trial Master File.

10   DATA MANAGEMENT AND MONITORING

10.1   Electronic Case Report Forms (eCRF)

The Clinical Data Management System (CDMS) used for the electronic case report form (eCRF) in this study is RedCap. The designated investigator staff will enter the data required by the protocol into the eCRF. The Investigator is responsible for assuring that data entered into the eCRF is complete, accurate, and that entry is performed in a timely manner. The signature of the investigator will attest the accuracy of the data on each eCRF. If any assessments are omitted, the reason for such omissions will be noted on the eCRFs. Corrections, with the reason for the corrections will also be recorded. After database lock, the investigator will receive a digital copy of the subject data for archiving at the investigational site.

10.2   Source Data

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

The medical records for each patient should contain information that is important for the patient's safety and continued care, and to fulfil the requirement that critical study data should be verifiable. To achieve this, the medical records of each patient should clearly describe at least:

- That the patient is participating in the study, e.g. by including the enrolment number and the study code or other study identification;
- Date when Informed Consent was obtained from the patient and statement that patient received a copy of the signed and dated Informed Consent;
- Results of all assessments confirming a patient's eligibility for the study;
- Diseases (past and current; both the disease studied and others, as relevant);
- Results of assessments performed during the study;
- Serious Adverse Events (if any) including causality assessments;
- Date of, and reason for, withdrawal from study;

Ethnicity will be recorded directly into the eCRF, meaning that eCRF is source data and not the hospital records.

10.3 Study Monitoring

The investigator will be visited on a regular basis by the Clinical Study Monitor, who will check the following:
- Informed consent process
- Reporting of adverse events and all other safety data
- Adherence to protocol
- Maintenance of required regulatory documents
- Facilities and equipment if applicable
- Data completion on the CRFs including source data verification

The monitor will review the relevant CRFs for accuracy and completeness and will ask the site staff to adjust any discrepancies as required.

Sponsor's representatives (e.g. monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study will be required.

10.4 Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period permitted by each hospital. The study documentation (CRFs, Site File etc) shall be retained and stored during the study and for 15 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

10.5 Database management

Data management will be performed by the data management unit at the Clinical Trials Unit, Akershus University Hospital. The Data management procedures will be performed in accordance with the department's SOPs and ICH guidelines. The data management process will be described in the study specific Data Handling Plan and the study specific Data Handling Report after database closure.

Data entered into the eCRF will be validated as defined in the Data Validation Plan. Validation includes, but is not limited to, validity checks (e.g. range checks), consistency checks and customized checks (logical checks between variables to ensure that study data are accurately reported) for eCRF data and external data (e.g. laboratory data). A majority of edit checks will be triggered during data entry and will therefore facilitate efficient 'point of entry' data cleaning.

Data management personnel will perform both manual eCRF review and review of additional electronic edit checks to ensure that the data are complete, consistent and reasonable. The electronic edit checks will run continually throughout the course of the study and the issues will be reviewed manually online to determine what action needs to be taken.

Manual queries may be added to the system by clinical data management or study monitor. Clinical data managers and study monitors are able to remotely and proactively monitor the patient eCRFs to improve data quality.

All updates to queried data will be made by authorized study center personnel only and all modifications to the database will be recorded in an audit trail. Once the queries have been resolved, eCRFs will be signed by electronic signature. Any changes to signed eCRFs will be approved and resigned by the Investigator.

Medical history will be coded from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA).Once the full set of eCRFs have been completed and locked, the Sponsor will authorize database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then be made only by written agreement.

The data will be stored in a dedicated and secured area at Akershus University Hospital. Data will be stored in a de-identified manner, where each study participant is recognizable by his/her unique trial subject number. The data will be stored until 15 years following the last patient's final study visit.

11   STATISTICAL METHODS

11.1   Determination of Sample Size

The clinical course of viral airway infections is heterogeneous and depend on patient demographics and comorbidities, as well as causative viral agent. In patients with influenza, clinical improvement is expected at around day 3 to 7 *(11, 12)*. The proportion of study patients with early clinical improvement from baseline to 120 hours will be used as the basis for determination of sample size. Early clinical improvement does not equate to complete resolution of symptoms, and the in-hospital mortality rate of moderately ill patients admitted with viral airway infections is very low. Accordingly, we assume an early clinical improvement of 90% in both treatment groups, with a non-inferiority margin of 10%. Under these assumptions using a 2.5% one-sided significance level and 90% power, we would need to include a total of 380 patients (190 randomized to the intervention group and 190 randomized to the control group). To account for screening failures and loss to follow-up, we aim to include up to 400 patients in the current study. The first interim analysis will be at 40 included patients or after the first winter season of the study (March), whichever comes first. Subsequent interim analyses will be performed after 100 and 200 completed patients. Extraordinary interim meeting will also conducted if deemed necessary by the Sponsor. This approach will enable frequent assessment of the primary outcome measure and safety measures.

11.2   Randomization

11.2.1   Allocation - sequence generation

Eligible patients will be allocated in a 1:1 ratio, using a computer randomization procedure. The allocation sequence will be prepared by an independent statistician.

11.2.2   Allocation - procedure to randomize a patient

The computer-generated randomized allocation sequence will be imported into the eCRF system and made available to site personnel responsible for the participant enrolment. Randomization allocation will automatically be visible when enrolling a new eligible patient. This is an open-label study and no steps to conceal allocation are necessary.

The study statistician will be blinded to the randomization allocation for the writing of the statistical analysis plan (SAP). The authorizations bound to role of the study statistician in the eCRF when reading or downloading data will ensure that the statistician will not see the treatment allocation until database lock.

11.2.3 Blinding and emergency unblinding

This is an open-label study. However, the statistician responsible for analysis of the data will be blinded to the treatment allocation for the writing of the SAP.

11.3 Population for Analysis

The following populations will be considered for the analyses:

- Intention to treat (ITT) population: All randomized participants will be included in the main ITT analyses, regardless of protocol adherence.
- Per-protocol population (PP): Includes all patients in the ITT population having completed the study treatment without major protocol violations. Criteria for inclusion in the PP population will be specified in the SAP and the final criteria will be defined prior to database lock
- Safety population: Includes all subjects with any safety information after baseline.
- Total population: All enrolled participants independent of study arm will be used for additional analyses in the total population.

The primary population is the ITT population.

11.4 Planned analyses

Interim analyses are planned after 40, 100, and 200 completed patients.

Each statistical analysis is planned when

- The planned number of patients have been included
- All included patients have either finalized their last assessment discharge or has/is withdrawn/lost to follow-up according to protocol procedures
- All data have been entered, verified and validated according to the data management plan

Prior to each statistical analysis, the data in the database will be exported and the exported data will be locked for further altering of data. A SAP will provide details on the planned statistical analyses. The SAP will be finalized, signed and dated prior to first interim analysis. The statistical interim analysis will be performed by an unblinded Data Monitoring Committee (DMC) statistician based on program code from the trial statistician. The trial statistician will remain blinded to treatment when finalizing the SAP prior to first interim analysis and throughout the trial until final database lock. The unblinded statistician performing the analysis will only provide the study group with information on whether the trial should be stopped or continued. Details of the DMC and their procedures will be given in a separate DMC charter.

11.5 Statistical Analysis

11.5.1 Primary analysis

The primary outcome is early clinical response defined as a combination of all of the following:

1. Survival
2. Improvement of one or more levels relative to baseline in two or more symptoms of the investigator's assessment of symptoms of community-acquired bacterial pneumonia and no worsening of one or more levels in other symptoms
3. No rescue antibiotic therapy

The primary outcome will be analyzed on the ITT population using a logistic regression model and direct comparison of proportions.

11.5.2 Secondary analyses

1. Mortality (in-hospital and after 30 days)
2. Duration of hospital admission
3. Antibiotic therapy prescribed after discharge

4. Days of therapy with antibiotics, including antibiotic therapy during admission and per oral antibiotics after discharge
5. Rescue antibiotic therapy during admission
6. New antibiotic prescription for presumed airway infection within 30 days after discharge
7. Hospital readmissions up to 30 days after discharge

Between group comparisons will be performed for the primary variable on the per-protocol population in addition to secondary efficacy endpoints on both efficacy populations (ITT and PP populations).

The between-group comparisons for secondary variables will be tested as for the primary variable where applicable and additional analyses will be performed based on the following methods (but not limited to):
- Continuous variables will be subject to linear regression models or appropriate non-parametric alternatives.
- Time-to-event endpoints and durations will be analyzed using the Kaplan-Meier method and comparisons between the two groups will be performed using the log rank test or Cox regression analyses.
- Binary response variables will be analyzed using logistic regression

Unless otherwise specified, all statistical hypotheses will be tested as the primary variable, i.e. with an assessment of non-inferiority of the estimated difference between the groups. All efficacy analyses will be presented with the results from the hypothesis testing (by p-value) in addition to estimates and 95% confidence limits of the treatment effect.

In case of inconsistency between the SAP and the statistical chapter of the study protocol (Chapter 11), the SAP will have precedence.

11.5.3 Safety analyses
The safety analyses population will include all patients. Safety analyses will be descriptive and presented as summary tables by treatment group.

11.5.4 Descriptive statistics
Descriptive statistics will be presented with number and percentages for categorical variables, and means, standard deviation, and range for continuous variables. In case of clearly skewed continuous variables, they will be presented with median, interquartile range (25th and 75th percentiles) and range. Demographics and baseline characteristics will be presented with descriptive statistics without any hypothesis testing.

11.5.5 Missing data
If missing data is regarded as having a significant effect on the conclusions of the trial, sensitivity analyses with different methods for handling missing data will be included. Such methods may include complete case analyses, last observation carried forward, worst case/best case imputation and multiple imputation techniques.

11.5.6 Subgroup analyses
The primary analysis results will be assessed separately according to the following subgroups:
- Type of respiratory virus detected (influenza, parainfluenza virus, RSV, or hMPV)
- Patients with and without radiographic evidence of pneumonia (lobar infiltrates, bronchopneumonia, etc) .

12   STUDY MANAGEMENT

12.1   Investigator Delegation Procedure

The principal investigator is responsible for making and updating a "delegation of tasks" document listing all the involved co-workers and their role in the project. He will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

12.2   Protocol Adherence

Investigators ascertain that they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR). Criteria of protocol adherence will be defined in the SAP prior to database lock.

12.3   Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to and approved by the Competent Authority and the Ethics Committee according to EU and national regulations.

12.4   Audit and Inspections

Authorized representatives of a Competent Authority and Ethics Committee will visit the center to perform inspections, including source data verification. Likewise, the representatives from sponsor may visit the center to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

13   ETHICAL AND REGULATORY REQUIREMENTS

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

13.1   Ethics Committee Approval

The study protocol, including the patient information and informed consent form to be used, must be approved by the regional ethics committee before enrolment of any patients into the study.

13.2   Other Regulatory Approvals

The protocol will be submitted and approved by the applicable competent authorities before commencement of the study. Amendments to the protocol will be submitted to the competent authorities according to local regulations.
The protocol will be registered in www.clinicaltrials.gov before inclusion of the first patient.
Application to the Norwegian Medicines Agency will be approved before inclusion of the first patient.
Collection, storage and analyses of all data and sensitive information will be conducted according to current General Data Protection Regulation (GDPR) and in accordance with approval from the local Data Protection Official.

13.3   Informed Consent Procedure

The investigator is responsible for giving the patients full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she/he wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent.

A copy of the patient information and consent will be given to the patients. The signed and dated patient consent forms will be filed in the Investigator Site File binder. In cases where the patient does not speak Norwegian or English, a professional translator will be used.

13.4 Subject Identification

The investigator is responsible for keeping a list of all included patients including patient's date of birth and personal number, full names and last known addresses. The patients will be identified in the CRFs by patient number.

14 TRIAL SPONSORSHIP AND FINANCING

The study is sponsored by Akershus University Hospital.

15 TRIAL INSURANCE

The Principal Investigator has insurance coverage for this study through membership of the Drug Liability Association (see http://www.laf.no for more details).

16 PUBLICATION POLICY

Upon study completion and finalization of the study report, the results of this study will either be submitted for publication and/or posted in a publicly assessable database of clinical study results. All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors.

17 LIST OF APPENDICES

18 REFERENCES

1. Holter JC, et al. BMC Infect Dis 2015;15:64.
2. Jain S, et al. N Engl J Med 2015;373:415-27.
3. Seymour CW, et al. N Engl J Med 2017;376:2235-44.
4. Ruuskanen O, et al. Lancet 2011;377:1264-75.
5. Niederman MS. CHEST 2010;138:767-9.
6. Stets R, et al. N Engl J Med 2019;380:517-27.
7. Lim WS, et al. Thorax 2009;64 Suppl 3:iii1-55.
8. Centers for Disease Control and Prevention. Co-infection and antimicrobial stewardship. https://www.idsociety.org/covid-19-real-time-learning-network/disease-manifestations--complications/co-infection-and-Antimicrobial-Stewardship/
9. European Medicines Agency. Guideline on data monitoring committees. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf
10. NorCRIN. Klinisk utprøving av legemidler. https://www.norcrin.no/prosedyrer-kliniske-studier/klinisk-utproving-av-legemidler/
11. Centers for Disease Control and Prevention. Clinical signs and symptoms of influenza. https://www.cdc.gov/flu/professionals/acip/clinical.htm
12. Jefferson T, et al. Cochrane Database Syst Rev 2014:CD008965.