A randomized controlled non-inferiority trial of placebo versus macrolide antibiotics for *Mycoplasma pneumoniae* infection in children with community-acquired pneumonia

MYTHIC Study

Clinical Study Protocol

Study type:	Clinical trial with Investigational Medicinal Product (IMP)
Study categorization:	Risk category B
Study registration:	Planned: kofam.ch, clinicaltrials.gov SNSF ID: 207286
Study identifier:	MYTHIC Study
Sponsor:	Prof. Dr. med. Christoph Berger Division of Infectious Diseases and Hospital Epidemiology University Children's Hospital Zurich, Switzerland Steinwiesstrasse 75, CH-8032 Zürich Phone: +41 44 266 78 40; Fax: +41 44 266 80 72; Email: christoph.berger@kispi.uzh.ch
Coordinating principal investigator:	PD Dr. Dr. med. Patrick M. Meyer Sauteur Division of Infectious Diseases and Hospital Epidemiology University Children's Hospital Zurich, Switzerland Steinwiesstrasse 75, CH-8032 Zürich Phone: +41 44 266 78 96; Fax: +41 44 266 80 72 Email: patrick.meyersauteur@kispi.uzh.ch
Investigational Product:	Azithromycin (Azithromycin Pfizer® powder for oral suspension 200mg/5mL, Pfizer) and matching placebo
Protocol version and date:	Version 1.3 (24/04/2024)

Signature pages

Study number	SNSF ID: 207286
Study title	A randomized controlled non-inferiority trial of placebo versus macrolide antibiotics for *Mycoplasma pneumoniae* infection in children with community-acquired pneumonia (MYTHIC Study)

The sponsor, principal investigator, and trial statistician have approved the protocol version 1.3 (24/04/2024), and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki [1], the ICH-GCP guidelines [2], and the local legally applicable requirements.

Sponsor:

Prof. Dr. med. Christoph Berger

Zürich, 24.04.2024 — Christoph Berger

Place/Date — Signature

Coordinating principal investigator:

PD Dr. Dr. med. Patrick M. Meyer Sauteur, MD PhD

Zürich, 24.04.2024

Place/Date — Signature

Trial statistician:

Dr. ETH Stefanie von Felten

Zürich, 24.04.2024 — Stefanie von Felten

Place/Date — Signature

Local principal investigator at study site: **Zurich**

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki [1], the ICH-GCP guidelines [2], and the local legally applicable requirements.

Site	University Children's Hospital Zurich, Switzerland
Address	Universitäts-Kinderspital Zürich - Eleonorenstiftung Steinwiesstrasse 75 CH-8032 Zürich
Local principal investigator	PD Dr. med. Michelle Seiler

Zürich, 24.4.24

Place/Date

Signature

Local principal investigator at study site: **Triemli**

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki [1], the ICH-GCP guidelines [2], and the local legally applicable requirements.

Site	Department of Pediatrics, Triemli Hospital Zurich, Switzerland
Address	Kinderklinik Stadtspital Zürich Triemli Birmensdorferstrasse 497 CH-8063 Zürich
Local principal investigator	Prof. Dr. med. Maren Tomaske

Zürich, 29.04.2024

Place/Date

Signature

Local principal investigator at study site: **Winterthur**

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki [1], the ICH-GCP guidelines [2], and the local legally applicable requirements.

Site	Department of Pediatrics, Cantonal Hospital Winterthur, Switzerland
Address	Klinik für Kinder- und Jugendliche Kantonsspital Winterthur Brauerstrasse 15 Postfach CH-8401 Winterthur
Local principal investigator	Dr. med. Andreas Jung

Kantonsspital Winterthur
Dr. med. Andreas Jung
Leitender Arzt päd. Pneumologie
Zentrum Kinder- und Jugendmedizin
CH-8401 Winterthur

24.04.24

Place/Date

Signature

Local principal investigator at study site: **Basel**

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki [1], the ICH-GCP guidelines [2], and the local legally applicable requirements.

Site	University of Basel Children's Hospital, Switzerland
Address	Universitäts-Kinderspital beider Basel (UKBB) Spitalstrasse 33 CH-4056 Basel
Local principal investigator	PD Dr. Dr. med. Julia Anna Bielicki

Basel, 30.4.2024

Place/Date

Signature

Local principal investigator at study site: **St. Gallen**

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki [1], the ICH-GCP guidelines [2], and the local legally applicable requirements.

Site	Children's Hospital of Eastern Switzerland St. Gallen
Address	Ostschweizer Kinderspital Claudiusstrasse 6 CH-9006 St. Gallen
Local principal investigator	Dr. med. Anita Niederer-Loher

St. Gallen, 29.04.2024

Place/Date

Signature

Local principal investigator at study site: **Chur**

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki [1], the ICH-GCP guidelines [2], and the local legally applicable requirements.

Site	Department of Pediatrics, Cantonal Hospital Graubuenden, Switzerland
Address	Kantonsspital Graubünden Departement Kinder- und Jugendmedizin Loëstrasse 170 CH-7000 Chur
Local principal investigator	Dr. med. Beate Deubzer

Kantonsspital Graubünden
Dr. med. Beate Deubzer
Oberärztin
Kinder- und Jugendmedizin

Chur, 25.04.24
Place/Date

Beate Deubzer
Signature

Local principal investigator at study site: **Lucerne**

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki [1], the ICH-GCP guidelines [2], and the local legally applicable requirements.

Site	Children's Hospital of Central Switzerland, Switzerland
Address	Kinderspital Zentralschweiz Kinder- und Jugendnotfallzentrum Spitalstrasse CH-6000 Luzern 16
Local principal investigator	Dr. med. Alex Donas

Luzern 24.4.2024

Place/Date

Signature

Local principal investigator at study site: **Aarau**

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki [1], the ICH-GCP guidelines [2], and the local legally applicable requirements.

Site	Children's Hospital Aarau, Switzerland
Address	Kantonsspital Aarau Kinderspital Haus 9 Tellstrasse 25 CH-5001 Aarau
Local principal investigator	Prof. Dr. med. Henrik Köhler

Aarau 24.04.24

Place/Date

Signature

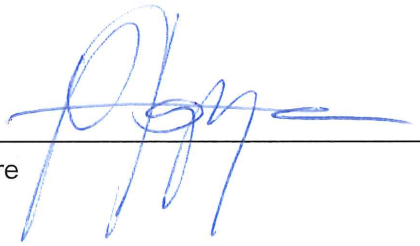
Local principal investigator at study site: **Bern**

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki [1], the ICH-GCP guidelines [2], and the local legally applicable requirements.

Site	University Children's Hospital Bern, Switzerland
Address	Kinderklinik Inselspital Universitätsspital Bern Freiburgstrasse CH-3010 Bern
Local principal investigator	PD Dr. med. Philipp Agyeman

BERN 24.04.2024

Place/Date



Signature

Local principal investigator at study site: **Geneva**

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki [1], the ICH-GCP guidelines [2], and the local legally applicable requirements.

Site	Children's Hospital of Geneva, University Hospitals of Geneva, Switzerland
Address	Hôpital des enfants Hôpitaux Universitaires Genève Rue Willy-Donzé 6 CH-1205 Genève
Local principal investigator	Dr. med. Noémie Wagner

Geneva, 26.04.24 — Place/Date

N Wagner — Signature

Local principal investigator at study site: **Lausanne**

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki [1], the ICH-GCP guidelines [2], and the local legally applicable requirements.

Site	Department of Pediatrics, Department Mother-Woman-Child, Lausanne University Hospital, Switzerland
Address	Hôpital de l'enfance de Lausanne Département femme-mère-enfant Centre hospitalier universitaire vaudois (CHUV) Rue du Bugnon 21 CH-1011 Lausanne
Local principal investigator	Dr. med. Ludivine Coulon

Lausanne / 01.05.2024

Place/Date

Signature

Local principal investigator at study site: **Fribourg**

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki [1], the ICH-GCP guidelines [2], and the local legally applicable requirements.

Site	Department of Pediatrics, Fribourg Hospital, Switzerland
Address	Pädiatrie HFR Freiburg – Kantonsspital Postfach CH-1708 Freiburg
Local principal investigator	PD Dr. Dr. med. Petra Zimmermann

Fribourg, 01/05/2024

Place/Date Signature

Local principal investigator at study site: **Bellinzona**

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki [1], the ICH-GCP guidelines [2], and the local legally applicable requirements.

Site	Institute of Pediatrics of Southern Switzerland, EOC, Bellinzona, Switzerland
Address	Istituto Pediatrico della Svizzera Italiana Ospedale San Giovanni Via Athos Gallino 12 CH-6500 Bellinzona
Local principal investigator	Dr. med. Lisa Kottanattu

Bellinzona, 25.04.2024

Place/Date

Signature

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STUDY SYNOPSIS

Sponsor:	Prof. Dr. med. Christoph Berger Division of Infectious Diseases and Hospital Epidemiology University Children's Hospital Zurich Steinwiesstrasse 75, CH-8032 Zurich, Switzerland
Coordinating principal investigator:	PD Dr. Dr. med. Patrick M. Meyer Sauteur Division of Infectious Diseases and Hospital Epidemiology University Children's Hospital Zurich Steinwiesstrasse 75, CH-8032 Zurich, Switzerland
Study title:	A randomized controlled non-inferiority trial of placebo versus macrolide antibiotics for *Mycoplasma pneumoniae* infection in children with community-acquired pneumonia (MYTHIC Study)
Short title / study ID:	MYTHIC Study / SNSF ID: 207286
Protocol version and date:	Version 1.3 (24/04/2024)
Trial registration:	Planned: kofam.ch, clinicaltrials.gov
Study category and rationale:	Risk category B: • Azithromycin Pfizer® powder for oral suspension 200mg/5mL is authorized in Switzerland (3-day regimen), but the use in this study deviates from the Swissmedic approved prescribing information with regard to the dosage (5-day regimen). • The study is controlled with a matching placebo. In contrast to Azithromycin Pfizer® powder for oral suspension 200mg/5mL, the matching placebo differs in composition which may impact on the quality of the investigational medicinal product (IMP). • The study is double-blinded and manufacturing procedures (labelling and packaging) are thus necessary to guarantee blinding.
Clinical phase:	Phase IV trial
Background:	*Mycoplasma pneumoniae* (*Mp*) is the most commonly detected bacterial pathogen of community-acquired pneumonia (CAP) in hospitalized school-aged children. Macrolides are the first-line treatment for this infection. However, it is unclear if macrolides are effective for *Mp* CAP. The extensive global macrolide use has led to alarming *Mp* resistance rates. Efficacy data and targeted prescription of macrolides are needed to reduce the emergence of antimicrobial resistance (AMR).
Rationale:	Our observation of a substantial proportion of *Mp* CAP patients fully recovering without antibiotic treatment supports the hypothesis of an immune-mediated pathogenesis of *Mp* infection. Therefore, we expect no clinically relevant effect of macrolides compared to placebo in children with *Mp* CAP. However, children are treated with macrolides without an accurate diagnosis for *Mp*. No single current diagnostic test, neither polymerase chain reaction (PCR) from upper respiratory tract (URT) samples nor serology, can accurately discriminate *Mp* infection from carriage. Importantly, a considerable number of macrolide-treated children may have self-limiting *Mp* CAP or may be *Mp* carriers suffering from CAP caused by other pathogens. We have shown that an *Mp*-specific antibody-secreting cell (ASC) enzyme-linked immunospot (ELISpot) assay differentiated between *Mp* infection and carriage. Improved diagnosis with this new test may help evaluating the effect of macrolides on the outcome of CAP patients with true *Mp* infection.
Objectives:	The overall aim of this trial is to produce efficacy data for macrolide treatment in children with *Mp* CAP by evaluating outcomes that are of high importance for patients, such as duration of clinical disease (efficacy) and progression of disease (safety). Co-primary objectives are to show in children aged 3-17 years with *Mp* CAP that treatment with placebo is non-inferior to treatment with macrolides regarding: 1.1: Time to normalization of all vital signs (VS) (efficacy), including body temperature (T), respiratory rate (RR), heart rate (HR), and saturation of peripheral oxygen (SpO_2).

	1.2: CAP-related change in patient care status (safety), such as (re-)admission or ICU transfer. Secondary objectives include the evaluation of: 2.1: Overall clinical outcome based on benefits and harms (desirability of outcome ranking [DOOR] and response adjusted for duration of antibiotic risk [RADAR] approach). 2.2: Time to normalization of CAP-related symptoms (i.e., cough, shortness of breath, wheeze, chest pain, sore throat, nasal congestion or runny nose, headache, muscle aches or pains, nausea or vomiting, diarrhea, reduced general condition, decreased appetite, not sleeping well, reduced activity). 2.3: Quality of life (QoL) assessment of the patient's family. 2.4: Time to return to daily routine, defined as return to childcare/school/work of patients and their families. 2.5: Development of *Mp*-associated extrapulmonary manifestations. Additional objectives include the evaluation of: 3.1: Length of hospital stay (LOS). 3.2: Unscheduled medical visits. 3.3: (Re-)treatment with antibiotics and total antibiotic exposure. 3.4: Side effects/adverse events (AEs)/serious AEs (SAEs) of IMP. 3.5: Antimicrobial/anti-inflammatory effects. Other additional objectives independent of study intervention include the evaluation of: 4.1: Parent's perception of informational video about the study. Exploratory subgroup analyses will assess the interaction between subgroup variables and treatment. The subgroup variables will include age, sex, patient care status, prodromal symptom duration, IgM ASC ELISpot-confirmed *Mp* infection, and radiological evidence of CAP.
Outcomes:	Co-primary outcomes: 1.1: Time (days) to normalization of all VS for at least 24h (efficacy), defined as T <38.0°C, RR and HR within age-specific reference ranges, and SpO_2 on room air ≥93%. 1.2: CAP-related change in patient care status within 28 days (safety), such as (re-)admission or ICU transfer. Secondary outcomes: 2.1: Overall clinical outcome based on benefits and harms (DOOR/RADAR approach) according to documentation of clinical response (normalization of all VS) and solicited AEs 1x/24h at the end of treatment (day 5) and each FUP visit. 2.2: Time (days) to normalization of CAP-related symptoms. 2.3: QoL assessment of the patient's family with a standardized and validated QoL questionnaire until day 28. 2.4: Time (days) to return to daily routine, defined as return to childcare/school/work of patients and their families. 2.5: Development of *Mp*-associated extrapulmonary manifestations within 28 days after randomization based on clinical examination and/or parent report. Additional outcomes: 3.1: LOS (days) in hospitalized patients after index hospitalization. 3.2: Number of unscheduled medical visits (apart from the study) until day 28. 3.3: Proportion of patients (re-)treated with antibiotics for any reason until 28 days and total antibiotic exposure in days up to 28 days. 3.4: Side effects/AEs/SAEs of IMP. 3.5: Microbiological indicators (proportion of patients who cleared *Mp* in the URT within 28 days, proportion of patients in which *Mp* became resistant to macrolides within 28 days, proportion of patients with change in co-detecting pathogens in the URT at day 3 and 28) and inflammatory indicators (biomarker and cytokine profiling at day 3 and 28).

	Other additional outcomes independent of study intervention: 4.1: Degree of usefulness of informational video about the study on a five-point Likert scale.
Study design:	This is a randomized, double-blind, placebo-controlled, multicenter, non-inferiority trial in 13 Swiss pediatric centers with two parallel groups (one active, one control). Previously healthy children aged 3-17 years presenting to the emergency department (ED) with clinically diagnosed CAP will be screened with a highly sensitive, commercially available *Mp* IgM LFA using a capillary blood sample where the results will be available within 10min. Additionally, a nasopharyngeal swab (NPS) specimen for *Mp* PCR (as reference test) on screened patients will be collected. Patients with a positive *Mp* LFA will be included and a venous blood sample for *Mp* IgM ASC ELISpot assay (as confirmatory test for distinguishing between carriage and infection) will be collected. *Mp* CAP patients will be randomized 1:1 to receive a 5-day-treatment (1 daily dose) of macrolide (Azithromycin Pfizer®; 10mg/kg/day on day 1 and 5mg/kg/day on days 2-5) or placebo (control group).
Inclusion / exclusion criteria:	Inclusion criteria: *Inclusion criteria for screening phase:* • Children aged 3-17 years (from 3rd up to 18th birthday) presenting to the ED who will be managed ambulatory or will be admitted to general ward. • Clinical diagnosis of CAP: 1) Diagnosis defined as the treating physician's documented diagnosis of CAP; AND 2) Fever ≥38.0°C (measured by any method [i.e., ear, axillary, rectal, or forehead site] in the ED or via parent report observed in the last 24h); AND 3) Tachypnea (defined as RR above age-specific reference value) during the assessment in ED (triage or clinical examination). • Written screening consent for participation in screening phase signed by parents/legal guardians and the patient if ≥14 years of age. *Additional inclusion criteria for intervention phase:* • Positive *Mp* screening test result with the *Mp* IgM LFA (grade 2 or 3). • Written informed consent for participation in intervention phase signed by parents or legal guardians and the patient if ≥14 years of age. Exclusion criteria: *Exclusion criteria for screening phase:* • None. *Exclusion criteria for intervention phase:* • Contraindication to azithromycin: Documented allergy to azithromycin; cardiovascular disease, *including bradycardia, arrhythmias, and/or QT-interval prolongation**; myasthenia gravis. **Co-medication with arrhythmogenic or QT-interval-prolonging drug (www.qtdrugs.org) is no exclusion criteria but will be discussed with the local investigators and/or trial management team (TMT).* • Underlying comorbidities: Cystic fibrosis or other chronic lung disorders (excluding asthma), primary or secondary immunodeficiency, sickle-cell anemia, or severe cerebral palsy. • History of recurrent pneumonia (two or more episodes) or severe pneumonia (ICU admission or complications of CAP such as lung abscess, effusion, and empyema) in lifetime. • Antibiotic treatment against *Mp* within the previous 7 days, including macrolides, tetracyclines, or fluoroquinolones. • Referral to ICU directly from the ED. • Inability to take oral medication.

	• Parents are unlikely to reliably complete follow up (FUP) visits and questionnaires (e.g., due to language barriers or living far from the study site).
Measurements and procedures:	The ED staff (triage nurse or treating physician) will inform the local investigators (study physician or study nurse) about an eligible patient with diagnosis of CAP (pre-screening). The local investigators will check inclusion criteria for the screening phase, initiate the contact, and inform the patient and caregivers about this trial. After the written screening consent is obtained the screening to assess inclusion and exclusion criteria will be performed. The *Mp* IgM LFA results will be available within 10min and will be communicated to the treating physician. In case of a positive *Mp* IgM LFA result, written informed consent for intervention phase participation will be obtained by the local investigators and the patient will be enrolled into the trial. Before randomization, a venous blood sample for *Mp* IgM ASC ELISpot assay will be collected and VS will be measured. The patient will be randomized 1:1 either to azithromycin (active group: 1 daily dose for 5 days, 10mg/kg/day on day 1 and 5mg/kg/day on days 2-5) or matching placebo (control group: 5 days of placebo) within a maximum of 6h after ED admission. VS will be recorded every 8h for hospitalized patients or 3x/24h for ambulatory patients by themselves via patient self-documentation with secuTrial® or study diary until 3 consecutive normal measurements of all VS within 24h are documented (co-primary outcome). FUP in-hospital visits will be performed at day 3 and 28 (close-out visit), including a clinical assessment as well as NPS and capillary blood sampling. Additional FUP phone call visits will take place at day 7, 14, and 21 to ensure data collection and query additional symptoms and adverse events.
Study product / intervention:	Azithromycin Pfizer® powder for oral suspension will be used in the active comparator arm. Patients in MYTHIC will be randomized 1:1 either to azithromycin (active group: 1 daily dose for 5 days, 10mg/kg/day on day 1 and 5mg/kg/day on days 2-5) or matching placebo (control group: 5 days of placebo). The doses used in MYTHIC differ from the Swissmedic-approved prescribing information (3-day regimen), but are in accordance with the FDA-approved prescribing information for CAP (5-day regimen) to achieve globally accepted study results.
Control intervention:	Children in the control arm will be receiving oral placebo matched to the product described above and supplied by the ZüriPharm AG (former Kantonsapotheke Zürich), Zurich, Switzerland.
Number of participants with rationale:	Under the assumptions outlined below, 376 patients will be recruited for the intervention phase of the trial. Based on previous studies, we assume that 66.7% of the patients agree to screening (and study participation) and that 15% of screened patients will have a positive *Mp* IgM LFA result, resulting in 10% of screened patients available for recruiting into the intervention phase of the study (0.67×0.15=0.10). Thus, we expect that the number of patients to screen is 3,760.
Study duration:	Total duration: 60 months Recruitment period: 48 months
Study schedule:	07/2024 First-Participant-In (planned) 06/2028 Last-Participant-Out (planned)
Investigators:	Coordinating principal investigator: **PD Dr. Dr. med. Patrick M. Meyer Sauteur** Local principal investigators: 1. PD Dr. med. Michelle Seiler (University Children's Hospital Zurich) 2. Prof. Dr. med. Maren Tomaske (Triemli Hospital Zurich) 3. Dr. med. Andreas Jung (Cantonal Hospital Winterthur) 4. PD Dr. Dr. med. Julia Anna Bielicki (University of Basel Children's Hospital) 5. Dr. med. Anita Niederer-Loher (Children's Hospital of Eastern Switzerland St. Gallen) 6. Dr. med. Beate Deubzer (Cantonal Hospital Graubuenden)

	7. Dr. med. Alex Donas (Children's Hospital of Central Switzerland) 8. Prof. Dr. med. Henrik Köhler (Children's Hospital Aarau) 9. PD Dr. med. Philipp Agyeman (University Children's Hospital Bern) 10. Dr. med. Noémie Wagner (Children's Hospital of Geneva) 11. Dr. med. Ludivine Coulon (Lausanne University Hospital) 12. PD Dr. Dr. med. Petra Zimmermann (Fribourg Hospital) 13. Dr. med. Lisa Kottanattu (Institute of Pediatrics of Southern Switzerland, EOC)
Study centers:	Multi-center study with 13 participating Swiss centers: 1) Universitäts-Kinderspital Zürich - Eleonorenstiftung, Steinwiesstrasse 75, CH-8032 Zürich 2) Kinderklinik Stadtspital Zürich Triemli, Birmensdorferstrasse 497, CH-8063 Zürich 3) Klinik für Kinder- und Jugendliche, Kantonsspital Winterthur, Brauerstrasse 15, Postfach, CH-8401 Winterthur 4) Universitäts-Kinderspital beider Basel (UKBB), Spitalstrasse 33, CH-4056 Basel 5) Ostschweizer Kinderspital, Claudiusstrasse 6, CH-9006 St. Gallen 6) Kantonsspital Graubünden, Departement Kinder- und Jugendmedizin, Loëstrasse 170, CH-7000 Chur 7) Kinderspital Zentralschweiz, Kinder- und Jugendnotfallzentrum, Spitalstrasse, CH-6000 Luzern 16 8) Kantonsspital Aarau, Kinderspital, Haus 9, Tellstrasse 25, CH-5001 Aarau 9) Kinderklinik, Inselspital, Universitätsspital Bern, Freiburgstrasse, CH-3010 Bern 10) Hôpital des enfants, Hôpitaux Universitaires Genève, Rue Willy-Donzé 6, CH-1205 Genève 11) Hôpital de l'enfance de Lausanne, Département femme-mère-enfant, Centre hospitalier universitaire vaudois (CHUV), Rue du Bugnon 21, CH-1011 Lausanne 12) Pädiatrie, HFR Freiburg – Kantonsspital, Postfach, CH-1708 Freiburg 13) Istituto Pediatrico della Svizzera Italiana, Ospedale San Giovanni, Via Ospedale 1, CH-6500 Bellinzona
Statistical considerations:	Multiplicity with two co-primary endpoints was handled using the "at least one" success criterion: We estimated the sample size for both co-primary endpoints for a one-sided significance level of 1.25% and a power of 80%, and use the larger of the two sample sizes for the trial. This assures a minimum power of 80% to reject at least one null hypothesis. The co-primary endpoint time to normalization of all VS is considered as a time-to-event endpoint. The sample size was estimated assuming an overall event rate of 99% and a hazard ratio of 1 for placebo vs. macrolide (a hazard ratio <1 would indicate longer duration with placebo than with macrolide). The sample size was estimated to show the non-inferiority of placebo vs. macrolide in *Mp* PCR-positive patients using a non-inferiority margin of 0.7 for the hazard ratio. Considering a drop-out rate of 14.5%, 354 patients should be recruited for the intervention phase of this study (302 evaluable patients). For the co-primary endpoint CAP-related change in patient care status (binary) we expect an absolute risk of 5% in both trial arms and thus an absolute risk difference (ARD, $risk_{macrolide} - risk_{placebo}$) of 0 between the two arms. An ARD <0 would indicate a higher risk with placebo than macrolide. The sample size was estimated to show the non-inferiority of placebo vs. macrolide in *Mp* PCR-positive patients, using a non-inferiority margin of -7.5% for the ARD. Considering a drop-out rate of 14.5%, 376 patients should be recruited for the intervention phase of this study (322 evaluable patients).
GCP statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ICH-GCP, as well as all national legal and regulatory requirements.

ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
AMR	Antimicrobial resistance
AR	Adverse reaction
ARD	Absolute risk difference
ASC	Antibody-secreting cell
ASR	Annual safety report
BASEC	Business Administration System for Ethical Committees (https://submissions.swissethics.ch/en/)
BTS	British Thoracic Society
CA	Competent authority (e.g., Swissmedic)
CAP	Community-acquired pneumonia
CEC	Competent ethics committee
CI	Confidence interval
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin, in Italian: OSRUm)*
CTCAE	Common terminology criteria for adverse events
CTC Zurich	Clinical Trials Center Zurich
CXR	Chest radiograph
DOOR	Desirability of outcome ranking
DSUR	Development safety update report
eCRF	Electronic case report form
ED	Emergency department
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunospot
FAS	Full analysis dataset
FOPH	Federal Office of Public Health
FUP	Follow-up
GCP	Good clinical practice
Ho	Null hypothesis
HR	Heart rate (or hazard ratio in section 11)
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
HRO	Ordinance on human research with the exception of clinical trials
IB	Investigator's brochure
ICU	Intensive care unit
IDMC	Independent data monitoring committee
IDSA	Infectious Diseases Society of America
IMP	Investigational medicinal product
IIT	Investigator-initiated trial
ITT	Intention-to-treat
LFA	Lateral flow assay
LOS	Length of hospital stay
LRTI	Lower respiratory tract infection
Mp	*Mycoplasma pneumoniae*
MRMP	Macrolide-resistant *Mycoplasma pneumoniae*
NPS	Nasopharyngeal swab
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PIDS	Pediatric Infectious Diseases Society
POC	Point-of-care
PPS	Per protocol set
QoL	Quality of life
RADAR	Response adjusted for duration of antibiotic risk
RCT	Randomized controlled trial
RR	Respiratory rate
RTI	Respiratory tract infection
SAE	Serious adverse event

SAR	Serious adverse reaction
SCTO	Swiss Clinical Trial Organization
SDV	Source data verification
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SPC	Summary of product characteristics
SpO_2	Saturation of peripheral oxygen
SUSAR	Suspected unexpected serious adverse reaction
T	Body temperature
TMF	Trial master file
TMT	Trial management team
TSC	Trial steering committee
UAR	Unexpected adverse reaction
URT	Upper respiratory tract
VS	Vital signs

SUMMARY OF THE REVISION HISTORY IN CASE OF AMENDMENTS

Version Nr, Version Date	Chapter	Description of change	Reason for the change
-	-	-	-

STUDY SCHEDULE

Patient timeline:

Procedure	Pre-screening	Screening	Enrollment (within 6h after admission to ED)	**Randomization (within 10h after admission to ED)**	Treatment phase					Follow-up				**Close-out**
Time point	$-t_1$	$-t_1$	$-t_1$	**t_0**	**t_1**	t_2	t_{3+}	t_4	t_5	t_{6+}	t_{7+}	t_{8+}	t_{9+}	**t_{final}**
Days in trial	**1**	**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6-28** (until normalization)	**7**	**14**	**21**	**28**
Time window (range) if patient at home (days in trial)							3-5				±1 (6-8)	±2 (12-16)	±3 (18-24)	±4 (24-32)
Clinic (C), phone (P), home (H)	**C**	**C**	**C**	**C**	**C**	C/H	**C**	C/H	C/H	C/H	P	P	P	**C**
Trial participation														
Screening phase:														
Eligibility check (screening)	X													
CAP diagnosis	X													
Written screening consent	X													
Capillary blood[a]: **LFA**		X												
NPS: **multiplex PCR**			X[b]				X							X
Intervention phase:														
Eligibility check (intervention)			X											
Written informed consent			X											
Venous blood[c]: **ASC ELISpot**			X[c]											
IMP allocation (minimization)				X										
IMP dispensing[d]				X										
IMP administration[e]					**X**	**X**	**X**	**X**	**X**					
Clinical assessment														
Medical history				X										
Physical examination				X			X							X
VS (T, RR, HR, SpO_2)			**X**		**X**[f,g]	**X**[f,g]	**X**[f,g]	**X**[f,g]	**X**[f,g]	**X**[f,g]	(X)[f,g]	(X)[f,g]	(X)[f,g]	X
Symptom review, including adverse events (AEs)				X		X[g]	X	X[g]	X[g]	X[g]	X	X	X	X
Concomitant care review				X		X[g]	X	X[g]	X[g]	X[g]	X	X	X	X
QoL assessment							X				X	X	X	X
Other study specific appointments														
Hand out trial box				X										
Return of trial box														X
Laboratory and radiological assessment														
Capillary blood[a]: biomarkers (hematology and biochemistry assessment)			X				X							X
Blood: ELISA[h]			X											
Chest radiograph (CXR)			(X)[i]											
Other assessments														
Study film perception														X

Gray background color indicates clinical visit (ED or hospital); red background color indicates IMP administration period. Abbreviations: ASC, antibody-secreting cell; CAP, community-acquired pneumonia; CXR, chest radiograph; ELISA, enzyme-linked immunosorbent assay; ELISpot, enzyme-linked immunospot; HR, heart rate; LFA, lateral flow assay; NPS, nasopharyngeal swab; PCR, polymerase chain reaction; RR, respiratory rate; SpO_2, saturation of peripheral oxygen; T, body temperature; VS. vital signs.

[a] Directly venous blood sampling for *Mp* IgM LFA and/or biomarkers if IV line or venous blood sample required for clinical reasons (which is often the case in CAP presenting or admitted to the hospital).

[b] A majority of children admitted with a diagnosis of CAP currently have a (multiplex) PCR from NPS for SARS-CoV-2 and other viruses as part of the routine diagnostic work-up and/or for patient cohorting (the placement of patients exposed to or infected with the same laboratory-confirmed pathogen in the same inpatient room). If a NPS is performed for clinical reasons, remaining sample will be stored locally (and transferred later in batches to the MYTHIC Biobank at University Children's Hospital Zurich) so that no more than one swab will be performed on patients on day 1. If a PCR for *Mp* (single- or multiplex) is performed for clinical reasons, false-positive tested participants with the *Mp* IgM LFA screening test will be followed also until the close-out visit on day 28.

[c] Venous blood sampling is required and often routinely available (because an IV line and/or venous blood sampling is performed for clinical reasons in many CAP patients presenting to the hospital), but it is not a necessary inclusion criterion (to avoid exclusion because of refusal to draw blood for the study).

[d] IMP will be labelled with center-specific patient ID.

[e] IMP administration by study nurses or care-givers (including nurses, treating physicians) with relevant trial training or by the parent on day 2-5 if ambulatory managed.

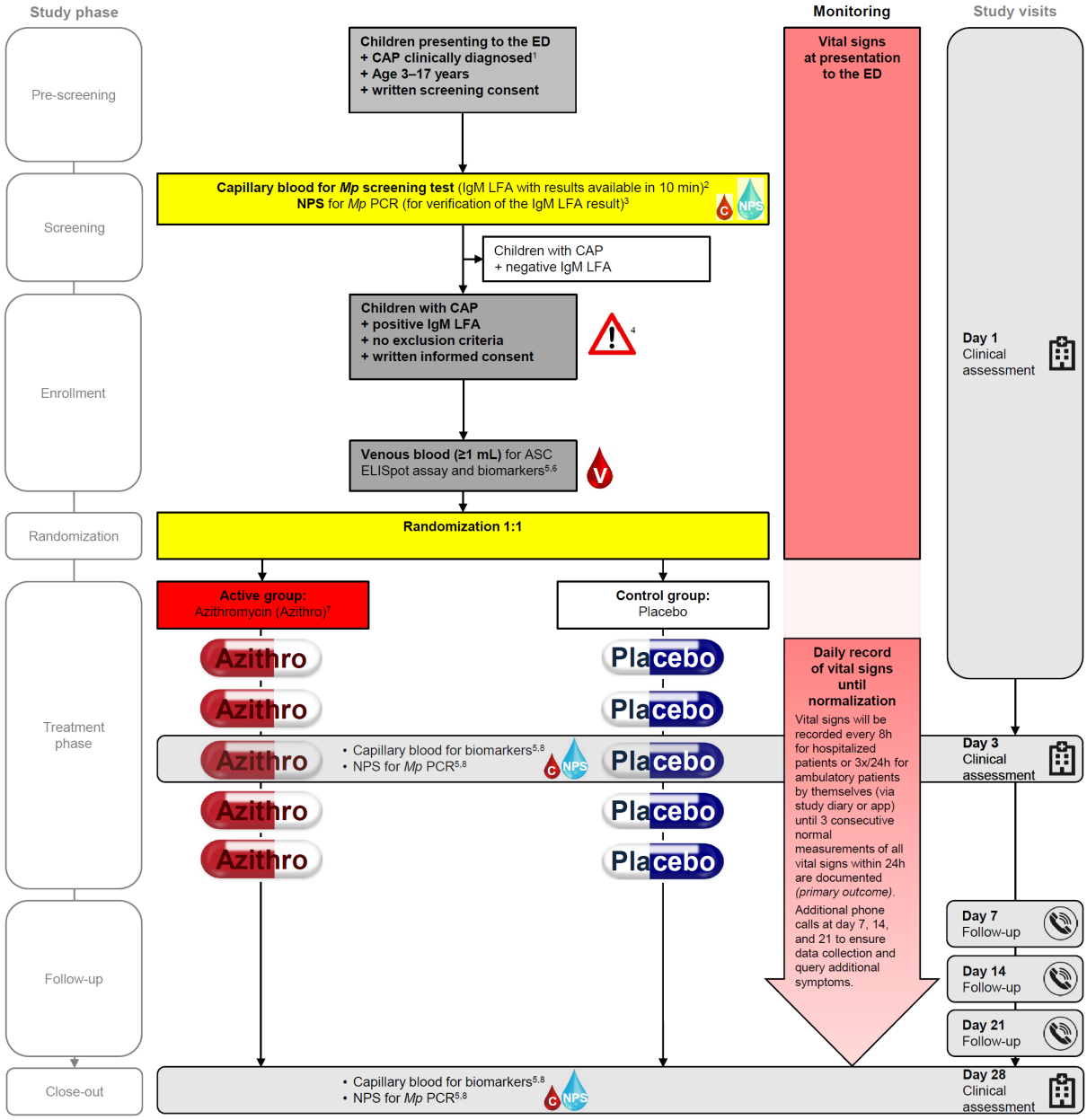
[f] Measured every 8h for hospitalized patients or 3x/24h for ambulatory patients, until 3 consecutive normal measurements of all VS within 24h are documented.

[g] Documentation via patient self-documentation with secuTrial® or study diary in ambulatory patients.

[h] If venous blood is available also *Mp* IgM ELISA will be performed but results not used to guide study procedures and statistical analyses.

[i] CXR is no inclusion criteria but desirable to confirm the clinical diagnosis and often routinely performed in cases with CAP presenting to the hospital.

Study flow:



1 CXR is no inclusion criteria but desirable to confirm the clinical diagnosis and often routinely performed in cases with CAP presenting to the hospital.

2 Directly venous blood sampling for *Mp* IgM LFA, *Mp* IgM ASC ELISpot assay, and biomarkers if IV line or venous blood sample required for clinical reasons (which is often the case in CAP presenting to the hospital).

3 A majority of children admitted with a diagnosis of CAP currently have a (multiplex) PCR from NPS for SARS-CoV-2 and other viruses as part of the routine diagnostic work-up and/or for patient cohorting. If a NPS is performed for clinical reasons, remaining sample will be stored locally (and transferred later in batches to the MYTHIC Biobank at University Children's Hospital Zurich) so that no more than one swab will be performed on patients on day 1. If a PCR for *Mp* (single- or multiplex) is performed for clinical reasons, false-positive tested participants with the *Mp* IgM LFA screening test will be followed also until the close-out visit on day 28.

4 Decision about additional treatment with bacterial cell wall synthesis inhibitors (such as amoxicillin) to avoid potential non-treatment of co-infecting bacterial pathogens in study patients will be made by the treating physician and will not be influenced by local investigators. Importantly, the lack of a cell wall makes *Mp* resistant to bacterial cell wall synthesis inhibitors and those antibiotics do not exhibit anti-inflammatory effects.

5 Test results not available until study closure.

6 Venous blood sampling is required and often routinely available (because an IV line and/or venous blood sampling is performed for clinical reasons in many CAP patients presenting to the hospital), but it is not a necessary inclusion criterion (to avoid exclusion because of refusal to draw blood for the study).

7 Azithromycin Pfizer®, 1 daily dose for 5 days, 10mg/kg/day on day 1 and 5mg/kg/day on days 2-5.

8 Capillary blood and NPS will be again collected to evaluate the anti-inflammatory effect (by biomarkers) and anti-microbial effect (by multiplex PCR) of azithromycin.

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor

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1.5 Monitoring institution and data management

Clinical Trials Center (CTC) Zurich, University Hospital Zurich, Switzerland
Universitätsspital Zürich, Rämistrasse 100, CH-8091 Zürich

1.6 Safety monitoring

The responsibility of the **independent data monitoring committee (IDMC)** will be to safeguard the interests of trial participants, assess the safety of the interventions during the trial, and contribute to monitoring the overall conduct of the clinical trial. The IDMC is independent of, but reports to, the trial management team (TMT). Details of IDMC functioning and procedures will be provided by the sponsor and coordinating principal investigator in the IDMC Charter agreed and signed by all IDMC members.

1.7 Any other relevant committee, person, organization, institution

1.7.1 Trial management team (TMT)

A **TMT** will be formed comprising the sponsor, coordinating principal investigator, the statistician, and the trial manager. The TMT will be responsible for the day-to-day running and management of the trial. Details of the TMT functioning will be provided by the sponsor and coordinating principal investigator in trial-internal working instructions.

1.7.2 Pharmacy

ZüriPharm AG (former Kantonsapotheke Zürich), Zurich, Switzerland
Südstrasse 3, CH-8952 Schlieren
Phone: +41 43 258 54 12
Email: Clinicaltrials@zueripharm.ch

2. ETHICAL AND REGULATORY ASPECTS

Before the study will be conducted, the protocol, the proposed patient information, and consent form, as well as other study-specific documents will be submitted to the competent ethics committee (CEC) of Zurich (Kantonale Ethikkommission Zürich), other relevant CECs in Switzerland, and Swissmedic. Any amendment to the protocol will be approved by these institutions.

The decision of the CEC and Swissmedic concerning the conduct of the study will be made in writing to the sponsor before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities will be implemented.

2.1 Study registration

This study will be register in the following registries:

– Swiss National Clinical Trials Portal (SNCPT): https://www.kofam.ch/en

– ClinicalTrials.gov: https://clinicaltrials.gov

2.2 Categorization of study

The MYTHIC Study is a risk category B trial. Azithromycin Pfizer® powder for oral suspension 200mg/5mL is authorized in Switzerland for the treatment of CAP in children (3-day regimen), but the administration in this study differs from the prescribing information with regard to the dosage (5-day regimen). The 5-day regimen is the standard treatment according to the FDA-approved prescribing information and internationally recognized guidelines (section 3.4). The effectiveness of the 3-day regimen has not been established in pediatric patients with CAP [3]. The study is controlled with a matching placebo. In contrast to Azithromycin Pfizer® powder for oral suspension 200mg/5mL, the matching placebo differs in the composition with a constituent other than the active substance (denatonium benzoate as replacement for azithromycin), which may impact on the quality of the investigational medicinal product (IMP). The study is double-blinded and manufacturing procedures (labelling and packaging) are thus necessary to guarantee blinding. Quality and manufacturing of IMP must be reviewed by Swissmedic.

2.3 Competent ethics committee (CEC)

The responsible investigator at each site ensures that approval from an appropriately constituted CEC is obtained for MYTHIC.

Reporting duties and allowed time frame (all changes in the research activity and all unanticipated problems involving risks to humans, including in case of planned or premature study end and the final report) and changes made to the protocol will not be made without prior sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study will be reported within 15 days. The regular end of the study will be reported to the CEC within 90 days, the final study report will be submitted within one year after study end. Amendments are reported according to section 2.10.

2.4 Swissmedic

The sponsor will obtain approval from Swissmedic before the start of the clinical trial. Duties and allowed time frame will be reported to Swissmedic, including the reporting duties in case of planned or premature study end and the final report. Reporting duties and timelines are the same as for CEC, except of non-substantial amendments that shall be reported as soon as possible. Amendments are reported according to section 2.10.

2.5 Ethical conduct of the study

The study will be carried out in accordance to the protocol and with principles enunciated in the current

version of the Declaration of Helsinki, the guidelines of good clinical practice (GCP) issued by ICH, and Swiss law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety reports (ASR) and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

There are no potential conflicts of interest to disclose.

2.7 Patient information and informed consent

Informed consent will be obtained by a nominated deputy as recorded on the Sponsor's Delegation of Responsibilities Log. All individuals taking informed consent will have received study-specific training and have received or are enrolled in GCP training. They will explain to each patient verbally (patients aged 3-10 years) and in writing (patients aged 11-17 years) and to the legal representative (referred to as "parent") the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail.

The parent (and patient) will receive the following forms:

Screening consent: A consent form for research projects with persons (ordinance on human research with the exception of clinical trials [HRO], chapter 2) providing sufficient information about the study to make a decision about **screening the patient with the IgM lateral flow assay (LFA) and collecting a NPS sample**.

Informed consent: A short (summary), an informational video, and a detailed patient information sheet, as well as a consent form describing the study and providing sufficient information to make an informed decision about **participation of the patient in the study and further use of their samples and coded data for future research projects**.

The parent (and patient) will be informed that participation in the study is entirely voluntary, that the patient is under no obligation to enter the trial, and that the parent (and patient) may withdraw from the study at any time without having to give a reason and that withdrawal of consent will not affect subsequent medical assistance and treatment of the patient. Furthermore, the parent (and patient) will be informed that they will be contacted, if health-relevant results from further use projects with biological material become known, and that they have the right to waive this information.

For the screening consent, the parent (and patient) will be approached at the ED. For the informed consent, the parent (and patient) will be approached at the ED (for ambulatory patients) or as closely as possible to hospital admission (for hospitalized patients) within maximum 6h after ED admission. This corresponds to randomization within 10h from presentation to the ED and will therefore provide time for parent (and patient) to read and consider all documentation before signing and dating the informed consent form. Informed consent will only be obtained within this time frame if the parent (and patient) feels that further deliberation will not lead to a change in their decision, and provided the person seeking consent is satisfied that the parent (and patient) has fully retained, understood, and deliberated on the information given. In the case of unmarried parents, the father will only be able to provide consent if he is named on the child's birth certificate.

The parent (and patient) will be informed that medical records may be examined by authorized individuals other than their treating physician.

The applicable patient information sheets and consent forms will be submitted to the CEC to be reviewed and approved. The formal consent of the parent (and patient), using the approved informed consent form, will be obtained before the participant is submitted to any study-specific procedures. They will be given a copy of the signed document. The screening consent and informed consent form will be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and

disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorized representatives of the sponsor, a competent authority (e.g., Swissmedic), or a CEC may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

The sponsor may terminate the study prematurely because of:

- ethical concerns,
- when the safety of the participants is doubtful or at risk, or
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise.

2.10 Protocol amendments

Suggestions for a protocol amendment can be made to the TMT by any group member and by all investigators. Should these impact trial specific procedures, additional on-site or web-based training will be provided to all investigators. Substantial amendments are only implemented after approval of the CEC and Swissmedic, respectively.

Under emergency circumstances, deviations from the protocol to protect the rights, safety, and well-being of human subjects may proceed without prior approval of the sponsor and the CEC/Swissmedic. Such deviations shall be documented and reported to the sponsor and the CEC/Swissmedic as soon as possible.

All non-substantial amendments are communicated to Swissmedic as soon as possible if applicable and to the CEC within the ASR.

3. BACKGROUND AND RATIONALE

3.1 Background and rationale

The WHO has designated antimicrobial resistance (AMR) as a significant threat to modern medicine [4]. If left unaddressed the WHO states that AMR will lead to an era in which common infections such as pneumonia lead to increased rates of death. Pneumonia is one of the most common serious bacterial infections in children and causes substantial morbidity and mortality [5]. It is the leading cause of death among children <5 years in low- and middle-income settings [6] and a leading cause of hospitalization in high-income settings [7-9]. Although the etiology is often unknown in a child, lower respiratory tract infection (LRTI), such as pneumonia, is the primary diagnosis for prescribing antibiotics in children [10]. Pneumonia accounts for more treatment days with antibiotics in children's hospitals in the U.S. than any other condition [11]. Therefore, pneumonia is an important target for antimicrobial stewardship efforts and cost-effectiveness considerations [10, 12, 13].

CAP is defined as a clinical diagnosis of pneumonia caused by a community-acquired infection in a previously healthy child [8]. Current guidelines recommend the beta-lactam antibiotic amoxicillin as first-line treatment for CAP in children [8, 9]. While beta-lactams are highly effective against most common bacterial pneumonia pathogens, including *Streptococcus pneumoniae* (*Sp*), they do not possess activity against atypical bacteria, such as *Mp*. The lack of a cell wall makes *Mp* resistant to bacterial cell wall synthesis inhibitors such as beta-lactams. Before the COVID-19 pandemic, *Mp* was the most frequently detected bacterial pathogen in hospitalized U.S. children with CAP (8% of all detected pathogens), followed by *Sp* (4%) [7]. Based on previous CAP etiology studies, *Mp* was responsible for 8-28% of childhood CAP [7, 14-17]. *Mp* is detected most frequently in school-aged children with CAP [17-20], with rates of 18% (5-9 years [21]), 19% (5-17 years [7]), and 29% (3-17 years [22]), respectively. Macrolides are antibiotics with *in vitro* activity against both *Mp* and *Sp*. For children with CAP, macrolides are prescribed at higher rate than incidence data suggests [23, 24]. The extensive worldwide use of macrolides has led to alarming resistance rates among *Sp* [25] and *Mp* [26]. Reported macrolide-resistant *Mp* (MRMP) prevalence is particularly high in Asia with >90% in some regions and it ranges from 1-26% across European countries (reviewed in [27]). In Switzerland, we observed an increase in MRMP rates from 2% during 2011-2013 [28]) to 9% in 2014-2017 [29]).

Macrolide antibiotics inhibit protein synthesis by binding to the 23S rRNA component of the large subunit (50S) of the bacterial ribosome [26]. In addition to the antimicrobial activity, macrolides may have anti-inflammatory properties [30], which could also play a role in *Mp* CAP where host cell-mediated immunity is suggested to be involved in the pathogenesis of disease. Macrolides are effective against *Mp in vitro* [26], and they are recommended for suspected *Mp* infection by the most globally recognized guidelines on pediatric CAP published by the British Thoracic Society (BTS) [8] and the Pediatric Infectious Diseases Society/Infectious Diseases Society of America (PIDS/IDSA) [9]. However, these guidelines graded this recommendation as weak based on the lack of evidence on the *in vivo* efficacy of macrolides in *Mp* CAP children [8, 9]. Two recent meta-analyses examined macrolide treatment for *Mp* CAP in children. A Cochrane review [31] evaluated 7 randomized controlled trials (RCTs) on the effectiveness of antibiotic treatment for *Mp* LRTI in children. However, the diagnostic criteria, the type and duration of treatment, inclusion criteria, and outcome measures differed significantly, making it impossible to draw any specific conclusions. A systematic review [32] including 17 randomized and non-randomized studies corroborated these results by showing insufficient evidence to support or refute the use of macrolides for *Mp* LRTI. Also this review reported significant limitations of included studies such as substantial bias and subjective outcomes, inability to correct for timing of intervention, and most importantly, difficulty interpreting testing modalities [32]. Even so, another recent CAP study did not demonstrate benefits of empirical macrolide therapy in those with *Mp* infection [13].

A major challenge of previous studies on the effectiveness of macrolides in *Mp* CAP was the treatment of children for *Mp* without an accurate diagnosis. Currently, no diagnostic test, neither PCR from URT samples nor IgM serology, can accurately discriminate *Mp* infection from carriage [33]. *Mp* carriage in the URT is found in up to 56% of healthy children [19, 34]. Importantly, a considerable number of macrolide-treated children may have self-limiting *Mp* CAP or may be *Mp* carriers suffering from CAP caused by other pathogens [35]. We have shown that a *Mp*-specific ASC ELISpot assay differentiated between *Mp* infection and carriage [34]. *Mp*-specific IgM ASCs were detectable in children with *Mp* CAP but *not* in *Mp* carriers suffering from CAP caused by other pathogens or asymptomatic *Mp* carriers. *Mp*-specific ASCs are short-lived and associated with clinical disease, in contrast to pharyngeal *Mp* DNA and serum antibodies that persist for months [22]. The potential of the *Mp* IgM ASC ELISpot assay in diagnosing *Mp* CAP has also very recently been demonstrated by another group [36]. Improved diagnosis with this new test may help to evaluate the effect of macrolides on the outcome of CAP patients with true *Mp* infection in this study, as illustrated below (section 6.1, Table 5, "Diagnostic

approach and test result constellations").

Altogether, these findings further support the need for future RCTs assessing the effect of antibiotics for *Mp* CAP. The PIDS/IDSA guideline states that macrolide effectiveness for *Mp* is a specific area needing additional research [9].

3.2 Investigational product (treatment) and indication

Azithromycin Pfizer® powder for oral suspension 200mg/5mL will be used as the active treatment in this study. This medicinal product is authorized in Switzerland for the use in children from the age of 6 months. The authorization holder is Pfizer AG, Zurich, Switzerland (Swissmedic No. 61257). After reconstitution with water, the suspension contains 40mg of the active substance azithromycin (ATC-Code: J01FA10) per 1mL.

Azithromycin is a macrolide antibiotic, which has an oral bioavailability of 38% and a long plasma half-life of approximately 68 hours (Pfizer AG, Zurich, Switzerland). According to the prescribing information, the indications for Azithromycin Pfizer® are upper and LRTI, including CAP, acute otitis media, skin and soft tissue infections, nongonococcal urethritis and cervicitis, as well as prophylaxis against *Mycobacterium avium* complex infection in HIV-infected patients (Swissmedic).

3.3 Clinical evidence to date

The antibiotics with the best minimum inhibitory concentration values against *Mp* include macrolides, tetracyclines, and fluoroquinolones [26]. Macrolide antibiotics (i.e., azithromycin, clarithromycin, and erythromycin) have a more favorable side effect profile and are therefore the first-line antibiotics for *Mp* infections in children [8, 9]. Azithromycin is the most frequently used macrolide antibiotic worldwide because of its improved tolerability (over erythromycin) and a much longer half-life that enables a 5-day treatment (compared to a 7-10-day treatment with clarithromycin) [19]. Azithromycin can be administered orally, is available in a child-friendly formulation, and has also a much better taste compared to the strong bitter intensity of clarithromycin [37], which is essential for an IMP in terms of compliance.

Azithromycin is safe and well tolerated [38]. Side effects/adverse events (AEs) associated with azithromycin are mainly related to gastrointestinal symptoms such as diarrhea, vomiting, abdominal pain, and nausea [39]. In adults, azithromycin can elicit arrhythmias as a potential consequence of QT-interval prolongation, particularly in patients with preexisting cardiovascular risk factors [40]. Given the low concentrations resulting from oral dosing of macrolides, the incidence of arrhythmias in adults in response to macrolides in absence of additional risk factors is very low (<1:100,000) [41]. The risk of cardiac toxicity in children is unknown [39]. Nevertheless, underlying cardiovascular disease is preventively listed as exclusion criteria in MYTHIC (section 7.1).

3.4 Rationale for the dosage, route, regimen

Azithromycin is recommended by the FDA-approved prescribing information [3] and internationally recognized guidelines, such as the BTS and PIDS/IDSA guidelines [8, 9, 42], as follows: once daily for 5 days (10mg/kg/day on day 1 and 5mg/kg/day on days 2-5) [9, 42]. Swissmedic recommends once daily for 3 days (10mg/kg/day once daily) for atypical CAP. The total treatment dose is equal for both the recommended 5-day (BTS/PIDS/IDSA) and 3-day (Swissmedic) regimen (30mg/kg per treatment course). However, the effectiveness of the 3-day regimen has not been established in pediatric patients with CAP [3].

To confirm our hypothesis that treatment with placebo is non-inferior to azithromycin treatment and to avoid criticism that this effect may be due to a reduced treatment period of a 3-day regimen, we propose to use a 5-day regimen according to international guidelines. This globally accepted 5-day regimen also allows to achieve worldwide accepted and comparable study results.

All participating centers have experience in prescribing and administering azithromycin to children for respiratory tract infections (RTIs). The acceptability of this product is therefore very high.

3.5 Explanation for choice of comparator (or placebo)

A placebo control is necessary to prove our hypothesis that treatment with placebo is non-inferior to azithromycin treatment. With the double-blind design, we ensure blinding of care-givers (including nurses, treating physicians), the patient and parent, the investigators, and outcome assessors. The inclusion of a placebo will mitigate the bias associated with conduct of an open trial. The ZüriPharm AG, Zurich, Switzerland will be providing the placebo product for MYTHIC.

We do not feel withholding azithromycin treatment from patients in the control arm poses any risk of serious harm based on the following considerations:

Mild and self-limiting disease

In our previous observational study, one-third of CAP patients with confirmed *Mp* infection by the IgM ASC ELISpot assay were not treated with an antibiotic *in vitro* active against *Mp* (i.e., no antibiotic treatment or treatment with beta-lactam antibiotics). Nevertheless, all of these children fully recovered [43]. Further, we did not find in this cohort statistically significant differences in fever duration following CAP diagnosis, LOS, or recovery at FUP between *Mp*-positive patients who did and did not receive antibiotics against *Mp* [43]. Also bacterial load and persistence in the URT did not differ between *Mp*-positive patients treated with macrolides and those treated with no antibiotic against *Mp* [22]. Only 32% of *Mp* CAP patients were hospitalized, which reflects the mild disease course in most cases [17, 18, 20]. **Such a mild and self-limiting disease course in the absence of antibiotic treatment has frequently been reported since the first descriptions of *Mp* disease [17, 20, 44, 45]. Also, fulminant *Mp* CAP is very uncommon and deaths associated with *Mp* infections are extremely rarely reported [18, 20].**

Immune-mediated pathogenesis

The previously described observations [43] about a self-limiting disease in a substantial proportion of *Mp* CAP patients supports the hypothesis of an immune-mediated pathogenesis of *Mp* infection. It has already been observed in human volunteers in the 1960s that reinfection or challenge after vaccination with inactivated or live attenuated *Mp* strains led to exacerbation of *Mp* [46, 47]. This finding suggests that the immune response triggered by *Mp* contributes to the severity of *Mp* CAP [18]. These findings were corroborated by observations in animal models assuming that T helper 1 (Th1) cells contribute to inflammatory lesions in mycoplasma pneumonia [18, 48, 49]. Also clinical studies in children and adults show a correlation between the interferon-γ response and the disease severity in *Mp* CAP [50-53]. **Based on these findings, which suggest that host cell-mediated immunity is involved in the pathogenesis of *Mp* CAP, we expect *no* clinically relevant effect of macrolides in children with *Mp* CAP.**

All participating centers consented to *not* administering macrolides as treatment for a *Mp* CAP as part of this trial (i.e., by administering placebo). To guarantee the safety and health of patients within this trial, we have incorporated strict criteria for discontinuing or modifying the treatment (section 6.3 Table 6, and section 7.4). Hospitalized patients and ambulatory patients will closely be monitored by measuring VS at in-hospital visits and at home. Detailed patient information will be gathered during FUP to ensure safety in a hospitalized and in an ambulatory setting (section 9.2). Finally, the possibility of contacting the TMT and/or study physician is guaranteed around the clock.

3.6 Risks and benefits

Risks

Active comparator arm:

Azithromycin is frequently prescribed for RTIs in children, particularly in the ambulatory setting (section 3.1). As outlined in section 3.3, AEs caused by drug toxicity are extremely rare when azithromycin is administered in regular doses recommended by Swissmedic and for a maximum of 5 days. They are mainly related to gastrointestinal symptoms [39]. According to the FDA-approved prescribing information [3], the most frequent AEs attributed to 5-day azithromycin treatment were diarrhea/loose stools (5.8%), nausea (1.9%), vomiting (1.9%), abdominal pain (1.9%), and rash (1.6%) (section 5.2., Table 2). A recent RCT evaluating early administration of a 5-day azithromycin treatment on recurrent severe LRTI progression in preschool children reported only mild gastrointestinal symptoms in 3 out of 223 (1.3%) children who received azithromycin [54]. These AEs were mild and did not lead to a study discontinuation. In adults, azithromycin is known to potentially elicit arrhythmias particularly in patients with preexisting cardiovascular risk factors [40]. However, the incidence of arrhythmias as a potential consequence of QT-interval prolongation in response to macrolides in absence of additional risk factors is very low in adults (<1:100,000) [41]. Also, azithromycin administration in children is not associated with QT prolongation [39, 55]. Nevertheless, as a preventive measure and to minimize the risk for AEs, an underlying cardiovascular condition has been defined as an exclusion criterion for MYTHIC (section 7.1).

Control placebo arm:

Based on the assumption of a mild, self-limiting, and immune-mediated disease course of *Mp* CAP, the risk of progression of disease without azithromycin treatment may be minimal (section 3.5). Nevertheless, strict criteria for discontinuing or modifying treatment will guarantee the safety of patients in MYTHIC and are detailed in section 6.3: "**Unblinding Procedures (Code Break)**". Patients are closely monitored by measuring VS at home, at in-hospital visits, and in the ambulatory setting. Detailed patient information during FUP is provided by the patient self-documentation with secuTrial® or study diary (section 9.2). The possibility of contacting the TMT and/or study physician is guaranteed 24 hours a day, 7 days a week. These measures will guarantee safety in MYTHIC.

Benefit

Active comparator arm:

Azithromycin is frequently prescribed for RTIs in children and recommended for CAP by international guidelines [8, 9, 42]. However, macrolide treatment did not yet demonstrate benefit in CAP patients with *Mp* infection [13] (section 3.1).

Control placebo arm:

Withholding azithromycin treatment will reduce antibiotic exposure and the development of AMR (MYTHIC patient) and produce efficacy data that allow targeted prescription of macrolides to reduce the emergence of AMR (future patients).

Additionally, patients in both arms will benefit from close 28-day FUP in terms of monitoring and caring during the course of illness, AEs, and/or progression of disease.

3.7 Justification of choice of study population

CAP is the leading cause of hospitalization in children and adolescents in high-income settings [7-9]. However, the etiology and pathophysiology of CAP differs considerably between adults and children [7, 56, 57]. Therefore, observations from adult CAP studies do not necessarily apply to a pediatric population [6]. In 2017, 1361 children aged 1-14 years have been hospitalized with pneumonia in Switzerland according to the Federal Office of Public Health (FOPH). This represents an incidence of 115 cases per 100,000 individuals in this age group. *Sp* and *Mp* are the two major bacterial causes of pneumonia in hospitalized children [14]. Over the past three decades, *Sp* conjugate vaccines have markedly reduced the incidence of pneumococcal pneumonia so that *Mp* emerged to be the most frequently detected pathogen causing bacterial CAP in hospitalized U.S. children. *Mp* is detected most

frequently in school-aged children with CAP [17-20], with a prevalence of 18% (5-9 years [21]), 19% (5-17 years [7]), and 29% (3-17 years [22]), respectively. The estimation of the *Mp* CAP disease burden would even be higher considering cases not only managed in hospitals but also by primary care physicians. Overall, these numbers demonstrate the on-going burden of childhood CAP, and particularly *Mp* CAP, in the Swiss healthcare landscape. Thus, MYTHIC will recruit children aged 3-17 years with *Mp* CAP (section 7). No competing trials recruiting children with CAP is being conducted in Switzerland from the start of MYTHIC.

Tailored prescription of antibiotic treatment is needed to minimize selection of antibiotic resistant pathogens [39]. Thus, reducing the excessive use of macrolides is an important target [13, 25, 58]. In Switzerland, azithromycin, a macrolide antibiotic, is frequently used for RTIs based on its good taste, excellent tolerability, its short regimen duration, and its once daily dosing (www.swisspeddose.ch). In the U.S., macrolides are the most common antibiotics prescribed during ED visits for childhood pneumonia, and accounted for nearly half of all antibiotics given to children [59]. However, the widespread use of macrolides has led to a global emergence and spread of MRMP [27]. The most recent MRMP prevalence of 9% (2014-2017) shows that macrolide resistance is a relevant issue in Switzerland [29], even more considering past macrolide-resistant *Sp* prevalence of 10-20% (2004-2014) [60]. The targeted prescription of macrolides is therefore a priority in Switzerland. Previous studies failed to successfully demonstrate a treatment effect of macrolides for *Mp* CAP. Therefore, the proposed MYTHIC Study is a unique opportunity to produce the first worldwide available efficacy data for the use of macrolides in childhood *Mp* CAP. By using the novel IgM ASC ELISpot assay, which is so far the only test accurately differentiating between *Mp* carriage and infection, this study will generate reliable efficacy data impacting macrolide administration for childhood *Mp* CAP in Switzerland and worldwide. With these prospects this study will be of particular significance for pediatric antibiotic administration in Switzerland. On a global scale, this study will provide vital information for reducing macrolide resistance in *Mp* and other bacteria causing pediatric CAP. The results of this study will be immediately relevant to the authorities providing guidance on the treatment of childhood CAP in Switzerland and worldwide. Overall, the study results will have a direct impact on the management and antibiotic prescription strategies for childhood respiratory diseases. Finally, these results will potentially lead to a global reduction of the over-prescription of macrolides in pediatric infectious diseases leading to reducing the spread of MRMP.

4. STUDY OBJECTIVES

4.1 Overall objective

The overall objective of MYTHIC is to produce efficacy data allowing targeted prescription of macrolides in pediatric *Mp* CAP (immediate effect) for reducing the emergence of AMR (longer term effect). This will consist of:

- Evaluating the efficacy of macrolide antibiotics vs. placebo on VS abnormalities and symptom duration; and
- Evaluating the safety of macrolide antibiotics vs. placebo in terms of change in patient care status, such as (re-)admission or an ICU transfer.

Furthermore, MYTHIC will investigate the influence of macrolides on bacterial clearance and AMR development (antimicrobial effects), as well as inflammation and host immunity (anti-inflammatory effects) in *Mp* CAP.

4.2 Co-primary objectives

This study aims to show in ambulatory and hospitalized children aged 3-17 years with *Mp* CAP that treatment with placebo is non-inferior to treatment with azithromycin in terms of (1.1) efficacy and (1.2) safety:

1.1: Efficacy: Time to normalization of all VS, including body temperature (T), respiratory rate (RR), heart rate (HR), and saturation of peripheral oxygen (SpO_2).

Hypothesis: The administration of a placebo in pediatric *Mp* CAP will be non-inferior with respect to the duration of VS abnormalities compared to a 5-day azithromycin regimen.

1.2: Safety: CAP-related change in patient care status, such as (re-)admission or ICU transfer, within 28 days after the index episode.

Hypothesis: The administration of a placebo in pediatric *Mp* CAP will be non-inferior with respect to the CAP-related change in patient care status compared to a 5-day azithromycin regimen.

4.3 Secondary objectives

The secondary objectives include the evaluation of:

2.1: Overall clinical outcome based on benefits and harms (desirability of outcome ranking [DOOR] and response adjusted for duration of antibiotic risk [RADAR] approach).

2.2: Time (days) to normalization of CAP-related symptoms (i.e., cough, shortness of breath, wheeze, chest pain, sore throat, nasal congestion or runny nose, headache, muscle aches or pains, nausea or vomiting, diarrhea, reduced general condition, decreased appetite, not sleeping well, reduced activity).

2.3: Quality of life (QoL) assessment of the patient's family.

2.4: Time (days) to return to the patient's daily routine, defined as return to childcare/school/work of patients and their families.

2.5: Development of *Mp*-associated extrapulmonary manifestations.

4.4 Additional objectives

Additional objectives include the evaluation of:

3.1: Length of hospital stay (LOS).

3.2: Unscheduled medical visits.

3.3: (Re-)treatment with antibiotics and total antibiotic exposure.

3.4: Side effects/ AEs/ serious AEs (SAEs) of IMP.

3.5: Antimicrobial/anti-inflammatory effects.

Other additional objectives independent of study intervention include the evaluation of:

4.1: Parent's perception of informational video about the study.

Exploratory subgroup analyses will assess the interaction between subgroup variables and treatment. The subgroup variables will include age, sex, patient care status, prodromal symptom duration, IgM ASC ELISpot-confirmed *Mp* infection, and radiological evidence of CAP.

4.5 Safety objectives

Objectives regarding safety of the placebo treatment are part of the co-primary objectives (1.2, CAP-related change in patient care status), secondary objectives (2.1, overall clinical outcome based on benefits and harms and 2.4, development of *Mp*-associated extrapulmonary manifestations), and additional objectives (unscheduled medical visits, [re-]treatment with antibiotics, side effects/AEs/SAEs of IMP). The MYTHIC Study will collect data on specific expected side effects/ AE of azithromycin in children, in particular parent reported gastrointestinal side effects (section 3.6 and section 5.2., Table 2) and discontinuation or modification of the IMP (section 6.3, Table 6, and section 7.4).

5. STUDY OUTCOMES

5.1 Co-primary outcomes

1.1: **Time (days) to normalization of all VS for at least 24h (efficacy)**
Defined as T <38.0°C, RR and HR within age-specific reference ranges, and SpO_2 on room air ≥93% (Table 1).

Table 1. Reference values for body temperature (T), respiratory rate (RR), heart rate (HR), and saturation of peripheral oxygen (SpO_2) on room air.

Vital sign (VS):	**Body temperature (T)**	**Respiratory rate (RR)**	**Heart rate (HR)**	**Saturation of peripheral oxygen (SpO_2) on room air**
Specific measurement:	Ear thermometer	Clinical assessment or parental report	Pulse oximetry (mobile device for ambulatory patients)	Pulse oximetry (mobile device for ambulatory patients)
Unit:	°C	Breaths/min	Beats/min	%
Reference:	[7]	[61]	[61]	[8]
3 years	<38.0	21-29	86-123	≥93
4-5 years		20-27	81-117	
6-7 years		18-24	74-111	
8-11 years		16-22	67-103	
12-14 years		15-21	62-96	
15-17 years		13-19	58-92	

The specific variables and age-specific reference values will appear in the patient self-documentation in secuTrial® or study diary.

Specific measurement: VS will be measured before randomization (or prior to the administration of antipyretic medication at the ED). These VS measurements will be taken as the index time point for the assessment. VS will be measured after having the patient relax (without running, crying, etc. for at least 5min) every 8h (for hospitalized patients) or 3x/24h (for ambulatory patients) until 3 consecutive normal measurements of *all* VS (T, RR, HR, and SpO_2) within 24h are documented.
Analysis metric: Time to event (days).
Method of aggregation: Hazard/median time to event.
Time point: Time point of the last of 3 consecutive normal measurements of all VS within 24h.

Rationale: The resolution of all VS abnormalities has been proposed as an important primary endpoint for antibiotic trials in childhood pneumonia by the IDSA [62]. In contrast to adults, severe morbidity and mortality from CAP is minimal in children, particularly for *Mp* CAP (section 3.5 and 3.7). Previous trials on macrolides for *Mp* CAP have mainly focused on fever duration as a key endpoint [31, 32]. In the myCAP study, the median body temperature (T) at presentation among myCAP patients was 39.1°C (IQR, 39.0-39.7), and the clinical diagnosis of CAP based on fever and tachypnea could be radiologically confirmed in 98% of the cases [43]. On room air, 17% *Mp* CAP patients had an SpO_2<93% and required additional oxygen supply. The median fever duration for *Mp* CAP children was 2 days. There were no statistically significant differences between patients with or without antibiotic treatment for *Mp* [43]. Lu et al. [63] observed a mean fever duration of 5 days (no statistically significant differences between patients treated with macrolides or placebo). To conclude, this study will use VS measurements taken at the timepoint before randomization as baseline measurements. The VS measurements will be followed up until normalization of VS to reference values. We expect a rate of <1% of patients' VS not normalizing within a 28-day FUP. In agreement with the IDSA considerations [62], an assessment of the time to VS normalization (T, RR, HR, SpO_2) has been selected to be of main interest for MYTHIC.

1.2: **CAP-related change in patient care status within 28 days (safety)**
Defined as any change in patient care status from an ambulatory to hospitalized setting (admission or re-admission), or from a hospitalized on general ward to an ICU setting (ICU transfer).

Specific measurement: Incidence of (re-)admission to hospital or transfer to the ICU.
Analysis metric: Final value.
Method of aggregation: Proportion.
Time point: Within 28 days after randomization.

Rationale: We expect the placebo to be non-inferior to macrolides treatment regarding a CAP-related change in patient care status. This non-inferiority will be assessed by the incidence of (re-)admission to

the hospital or transfer to the ICU (safety). A recent U.S. study showed that re-admission occurred in 5% of children with CAP receiving beta-lactam monotherapy and in 2% receiving beta-lactam plus macrolide combination therapy [13]. In another U.S. CAP study, re-admission was reported in 0.5% of those who received beta-lactam monotherapy and in 0.6% of those who received beta-lactam plus macrolide combination therapy [64]. Detailed information about the proportion of patients with *Mp* infection was not available for both studies. Based on these data we expect a small proportion (≤5%) of patients with a CAP-related change in patient care status.

5.2 Secondary outcomes

A number of secondary and additional outcomes have been defined as relevant endpoints for antibiotic trials in childhood CAP by the IDSA [62].

2.1: **Overall clinical outcome based on benefits and harms (DOOR/RADAR approach)**
According to documentation of clinical response (normalization of all VS) and solicited AEs 1x/24h at the end of treatment (day 5) and each FUP visit.

Specific measurement: Documentation of clinical response (normalization of all VS, section 5.1) and solicited AEs (Table 2) 1x/24h at the end of treatment (day 5) and at each FUP visit.
Analysis metric: Desirability of outcome ranking (DOOR) [65].
Method of aggregation: Probability of better DOOR.
Time point: Day 3 (in-hospital visit), day 5 (end of treatment), day 7, 14, 21 (phone calls), and day 28 (close-out visit).

Rationale: The novel *response adjusted for duration of antibiotic risk* (RADAR) methodology utilizes a superiority design [65]. In RADAR, all trial participants are assigned a DOOR. The DOOR is constructed using a 2-step process: (1) categorization of all patients into an overall clinical outcome (Table 3), and (2) ranking participants in the trial using 2 rules: (2a) when ranking the outcomes of 2 patients with different overall clinical outcomes, the patient with a better overall clinical outcome receives a higher rank; and (2b) when ranking the outcomes of 2 patients with the same overall clinical outcome, the patient treated with placebo receives a higher rank. These DOOR ranks are then compared between the treatment arms with regard to the probability of a better DOOR for a randomly selected patient with placebo vs. azithromycin (i.e., Wilcoxon-Mann-Whitney statistic [66]). The DOOR/RADAR approach is helpful for RCTs to define the optimal therapeutic strategy, since considering exclusively the primary endpoint may not allow researchers to accurately balance a proven benefit with other potential harms (i.e., impaired effectiveness or side effects/AEs).

Table 2: Solicited adverse events (AEs) grading [66, 67].

Symptom	Mild (grade 1)	Moderate (grade 2)	Severe (grade 3)
Diarrhea	Looser than normal stools occurring 3-6 times/day	Looser than normal stools occurring >6 times/day	Bloody diarrhea, or diarrhea that requires medical intervention, laboratory testing, or hospitalization
Vomiting	1 episode/day	2-3 episodes/day	≥4 episodes/day
Abdominal pain	Mild or intermittent and does not interfere with daily activity	Moderate or persistent and interferes with daily activity but did not need a medical visit or absenteeism from daily routine	Prevents daily activity and resulted in medical visit or absenteeism
Allergic reaction (rash and/or pruritus)	Localized rash or pruritus without rash	Diffuse rash (maculopapular or urticarial)	Generalized rash consistent with Stevens-Johnson syndrome, erythema multiforme, or toxic epidermal necrolysis; anaphylaxis; or angioedema
Oral/pharyngeal thrush or nappy rash (Candidiasis)	Mild mucocutaneous candidiasis or diaper dermatitis, with no treatment or topical treatment only	Moderate mucocutaneous candidiasis requiring oral antimicrobial treatment	Severe mucocutaneous candidiasis; requires medical intervention, intravenous treatment, or hospitalization

Table 3: Overall clinical outcome.

Outcome	Adequate clinical response*	Solicited AEs**
1	Yes: normalization of all VS	No
2	Yes: normalization of all VS	Mild (grade 1)
3	Yes: normalization of all VS	Moderate (grade 2)
4	Yes: normalization of all VS	Severe (grade 3)
5	No: no normalization of all VS without additional ED or clinic visit or hospitalization	Any grade
6	No: no normalization of all VS **with additional ED or clinic visit** but without hospitalization	Any grade
7	No: no normalization of all VS **with hospitalization** (admission, re-admission, or ongoing hospitalization)	Any grade
8	Death (any cause)	

* Adequate clinical response defined by the co-primary outcome normalization of all VS (section 5.1).
** Solicited AEs are defined in Table 3.

2.2: **Time (days) to normalization of CAP-related symptoms** (i.e., cough, shortness of breath, wheeze, chest pain, sore throat, nasal congestion or runny nose, headache, muscle aches or pains, nausea or vomiting, diarrhea, reduced general condition, decreased appetite, not sleeping well, reduced activity).

Specific measurement: Documentation of symptoms 1x/24h according to a validated measure for childhood respiratory infections [68, 69] by parent and the child until normalization.
Analysis metric: Time to event (days).
Method of aggregation: Hazard/median time to event.
Time point: Time point of resolution of all CAP-related symptoms.

Rationale: A rapid clinical recovery with no respiratory problems represents a direct patient-relevant outcome. *Mp* CAP patients have been reported to suffer from a prolonged cough after normalization of VS, but the exact duration and influence of macrolides is unclear [19].

2.3: **QoL assessment of the patient's family with a standardized and validated QoL questionnaire until day 28**

Specific measurement: A standardized and validated QoL questionnaire (Appendices, section 17.4 [70]) will be completed by parent.
Analysis metric: Final value (score).
Method of aggregation: Mean.
Time point: Day 3 (in-hospital visit), 7, 14, 21 (phone calls), and day 28 (final in-hospital visit).

Rationale: CAP in children causes a significant burden on both patients and their families, including loss of routine and decrease in QoL [70].

2.4: **Time (days) to return to daily routine, defined as return to childcare/school/work of patients and their families**

Specific measurement: Exact dates will be reported by parent until day 28 after randomization.
Analysis metric: Time to event (days).
Method of aggregation: Hazard/median time to event.
Time point: Time point of return to childcare/school/work of all family members.

Rationale: CAP in children can have considerable socioeconomic impacts on the child and parent by allowing a return to normal activity for the whole family [70].

2.5: **Development of *Mp*-associated extrapulmonary manifestations within 28 days after randomization based on clinical examination and/or parent report**

Specific measurement: Incidence of extrapulmonary manifestations based on clinical examination and/or parent report.
Analysis metric: Final value.
Method of aggregation: Proportion.
Time point: Within 28 days after randomization.

Rationale: Mp can cause extrapulmonary manifestations, which occur in up to 25% of infections and may affect almost every organ [71]. *Mp*-associated extrapulmonary manifestations can be associated with increased morbidity [72].

5.3 Additional outcomes

Additional outcomes are as follows:

3.1: LOS (days) in hospitalized patients after index hospitalization.

3.2: Number of medical visits (apart from the study) until day 28.

3.3: Proportion of patients (re-)treated with antibiotics for any reason until 28 days and total antibiotic exposure in days up to 28 days.

3.4: Side effects/AEs/SAEs of IMP (section 10).

3.5: Microbial and inflammatory indicators:

Microbiological indicators:
- Proportion of patients who cleared *Mp* in the URT within 28 days.
- Proportion of patients in which *Mp* became resistant to macrolides within 28 days.
- Proportion of patients with change in co-detecting pathogens in the URT at day 3 and 28.

Inflammatory indicators:
- Biomarker and cytokine profiling at day 3 and 28.

Other additional outcomes independent of study intervention:

4.1: Degree of usefulness of informational video about the study on a five-point Likert-scale.

5.4 Safety outcomes

The main outcomes regarding safety include the co-primary outcome (1.2, CAP-related change in patient care status), secondary outcomes (2.1, overall clinical outcome based on benefits and harms, and 2.5, development of *Mp*-associated extrapulmonary manifestations), and additional outcomes in section 5.3, such as unscheduled medical visits, (re-)treatment with antibiotics, and side effects/AEs/SAEs of IMP.

6. STUDY DESIGN

6.1 General study design and justification of design

This is an investigator-initiated, randomized, double-blind, placebo-controlled, multicenter, non-inferiority trial with two parallel groups. Previously healthy children aged 3-17 years presenting to the ED with clinically diagnosed CAP will be screened for *Mp* infection.

The Study flow is presented on page 29.

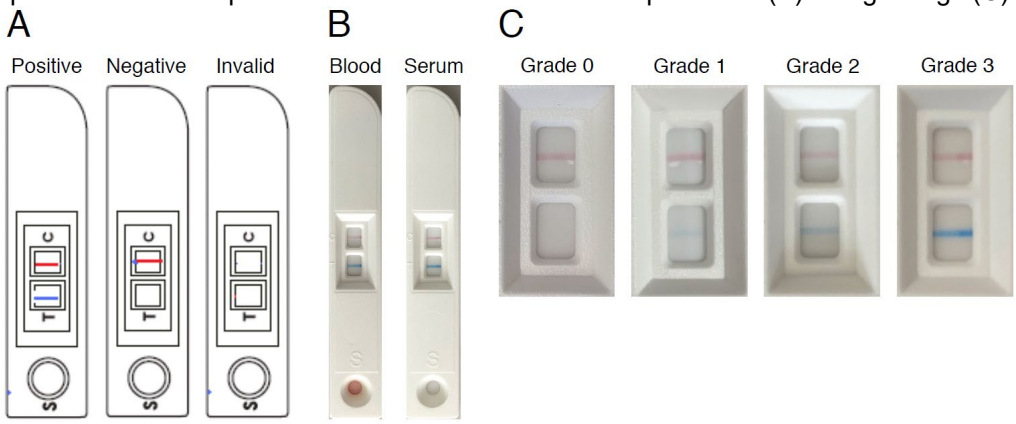
Pre-screening

The ED staff (triage nurse or treating physician) will inform the local investigators (study nurse, study physician, or GCP-trained ED consultant) about an eligible patient aged 3-17 years with clinical diagnosis of CAP. The local investigators will initiate contact and inform the parent (and patient), obtain a written screening consent, and perform the screening for *Mp* infection with the ***Mp* IgM LFA**.

Screening

Mp-specific PCR, IgM enzyme-linked immunosorbent assay (ELISA), and IgM ASC ELISpot assay are too time-consuming to be used as on-site screening tool, and no approved point-of-care (POC) test is available for direct detection of *Mp* [19]. Therefore, many previous RCTs randomized all CAP children to either macrolide or placebo (or beta-lactams) [32]. The evidence derived from these studies is insufficient to draw any conclusions about the efficacy of macrolides for *Mp* infection (section 3.1). Labsystems Diagnostics (Vantaa, Finland; https://www.labsystemsdx.com/) has launched a new POC LFA (Biocard™ *Mycoplasma pneumoniae* IgM) for the detection of *Mp*-specific IgM antibodies from a capillary blood sample, with results available within 10min (Figure 1). The *Mp* IgM LFA is an accurate POC test to diagnose *Mp* infection [73].

Figure 1. Biocard™ *Mp* IgM LFA. (A) Illustrative examples of positive, negative, and invalid test results. (B-C) Representative examples show test results for different specimens (B) and gradings (C) [74].



We evaluated the *Mp* IgM LFA as screening test against *Mp* PCR as reference test for MYTHIC using two CAP cohorts: the myCAP cohort (*n*=94 [74]) and the KIDS-STEP cohort (*n*=66 [75]). Applying the same inclusion criteria as in MYTHIC on both cohorts, a positive *Mp* IgM LFA result defined as moderate to strong blue test line (grade 2 or 3, Figure 1) was *good* at ruling in a *Mp* PCR-positive CAP patient with a positive likelihood ratio (LR+) of >10 (Table 4) [76, 77].

Table 4. Diagnostic performance of the *Mp* IgM LFA compared to *Mp* PCR as reference test.

Cohort, *n*	Characteristics	Reference test **PCR**	Screening test **IgM LFA**		Performance
myCAP study (*n*=94, published in [74]) and KIDS-STEP study (*n*=31, unpublished results) *n*=125 (total)	• CAP clinically diagnosed • Age 3-17 years • Inpatients or outpatients • Previous healthy children		**Positive** (grade 2 or 3)	Negative (grade 0 or 1)	Sensitivity: 86.0% (95% CI 72.7%-93.4%) Specificity: 95.1% (95% CI 88.1%-98.1%) LR+: 17.64 (95% CI 6.73-46.22) LR-: 0.15 (95% CI 0.07-0.31) DOR: 120.25 (95% CI 31.99-452.07)
		Positive	37 (29.6%)	6 (4.8%)	
		Negative	4 (3.2%)	78 (62.4%)	

Abbreviations: CI, confidence interval; DOR, diagnostic odds ratio; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

All screened and enrolled participants will provide a NPS sample (see Study flow), either performed as part of the clinical routine diagnostic work-up or exclusively for the use in this study. All collected NPS samples will be tested with an ***Mp* PCR** as reference test to verify the *Mp* IgM LFA test result. *Mp* IgM LFA false-positive participants will be excluded from the per protocol analyses (Table 5). All NPS samples will be frozen and stored locally (-20°C to -80°C depending on the infrastructure of the center). The stored NPS samples will be transferred to and analyzed by *Mp* PCR at University Children's Hospital Zurich. The results of the *Mp* PCR will not be available before the close-out visit on day 28. In case a *Mp* PCR (single- or multiplex) is performed for clinical reasons, and indicates a false-positive *Mp* IgM LFA, participants will be followed up until the close-out visit on day 28 (Table 5).

Enrollment

The *Mp* IgM LFA results will be available within 10min. In case of a positive *Mp* IgM LFA result, the local investigators will carefully check for eligibility, and obtain written informed consent for participation in the intervention phase of the trial (enrollment).

For enrolled children, a venous blood sample for the ***Mp* IgM ASC ELISpot assay** is required. This venous blood sample is often already routinely available (IV line and/or venous blood sampling is performed for clinical reasons in many CAP patients). However, to avoid exclusion of patients due to refusal to drawing a venous blood sample, this venous blood sample is not required for inclusion into the study. The results of the *Mp* IgM ASC ELISpot assay for the study will not be available before study closure.

The diagnostic approach with additional *Mp* PCR (as reference test) on screened patients and additional *Mp* IgM ASC ELISpot assay (as confirmatory test, section 3.1) on randomized patients will ensure a correct diagnosis and clear guidance on study procedures and statistical analyses according to different test results (Table 5). This diagnostic approach will be the major advantage compared to previous studies evaluating the effect of macrolides in children with *Mp* CAP.

Table 5. Diagnostic approach and test result constellations.

Test:	Method:	Turn-around time:	Specimen:	Expected test results with specific rates based on pilot results using the myCAP cohort [74] and KIDS-STEP cohort (*n*=125, Table 4):				
1. Screening test:	**IgM LFA**	**10min**	**Capillary blood**	**–**		**+ Randomization**		
Expected proportion (%) and number (*n*) based on pilot studies:				67.2% *n*=84/125		32.8% *n*=41/125		
2. Reference test:	**PCR**[2]	**After study closure**	**NPS**	**–**	**+**	**–**	**+**	
Expected proportion (%) and number (*n*) based on pilot studies:				92.9% *n*=78/84	7.1% *n*=6/84	9.8% *n*=4/41	90.2% *n*=37/41	
Interpretation in regard to IgM LFA:				*Negative*	*False-negative*	*False-positive*	***Detection***	
3. Confirmatory test:	**IgM ASC ELISpot**[3]	**after study closure**	**Venous blood**	NA[1]	NA[1]	**–**	**–**	**+**
Expected proportion (%) and number (*n*) based on pilot studies:						9.8% *n*=4/41	14.6% *n*=6/41	75.6% *n*=31/41
Final interpretation:				*Negative*	*False-negative*	*False-positive*	*Carriage and/or persistence*	***Infection***[3]
Study procedure:				No randomization	No randomization	**FUP until final visit on day 28**[2]	**FUP until final visit on day 28**	**FUP until final visit on day 28**
Statistical analysis:				Diagnostic accuracy	Diagnostic accuracy	**Intention-to-treat**	**Per protocol**	**Strict per protocol**

[1] No venous blood sampling because not enrolled.

[2] A majority of children admitted with a diagnosis of CAP currently have a (multiplex) PCR from NPS for SARS-CoV-2 and other viruses as part of the routine diagnostic work-up and/or for patient cohorting (the placement of patients exposed to or infected with the same laboratory-confirmed pathogen in the same inpatient room). If a NPS is performed for clinical reasons, remaining sample will be stored locally (and transferred later in batches to the MYTHIC Biobank at University Children's Hospital Zurich) so that no more than one swab will be performed on patients on day 1. If a PCR for *Mp* (single- or multiplex) is performed for clinical reasons, false-positive tested participants with the *Mp* IgM LFA screening test will be followed also until the close-out visit on day 28.

[3] The *Mp* IgM ASC ELISpot assay may not be available in all patients (refusal to draw blood) and/or peripheral blood mononuclear cell (PBMC) viability can be decreased in very few instances (pre-analytical processing) and result in poor assay performance. If venous blood is available also *Mp* IgM enzyme-linked immunosorbent assay (ELISA) will additionally performed but these results will not be used to guide study procedures and statistical analyses.

Intervention

After the patient was allocated to the IMP, the 1st dose of the IMP will be administered immediately after allocation by study nurses or care-givers (including nurses, treating physicians) with relevant trial training. Relevant doses will be determined according to the weight-banded dosing chart (section 8.2.1, Table 7, rounded to 0.25 mL according to the oral syringe supplied with the IMP). The parent will receive detailed instructions for the administration of the IMP at the ED (for ambulatory patients) or at the ward (for hospitalized patients if discharge occurs before completion of the 5-day treatment). Dose and time point of administration will be shown in the patient self-documentation in secuTrial® or study diary.

FUP

In-hospital FUP study visits will be performed at day 3 and 28, including a clinical assessment as well as NPS and capillary blood sampling. FUP phone calls will take place at day 7, 14, and 21 to ensure data collection and query additional symptoms.

Sample processing

Venous blood samples from enrolled patients will be sent directly to the MYTHIC Biobank at University Children's Hospital Zurich. NPS samples and capillary blood from screened and enrolled patients will be frozen and stored locally and transferred later in batches to the MYTHIC Biobank at University Children's Hospital Zurich.

6.2 Methods of minimizing bias

6.2.1 Randomization

Patients will be allocated 1:1 to either azithromycin for 5 days or matching placebo for 5 days through minimization, which allows balance between treatment groups for several characteristics at all stages of the trial [78].

The following characteristics will be considered:

1) **Age:** 3-9 years vs. 10-17 years [7].
2) **Patient care status:** ambulatory vs. hospitalized.
3) **Duration of respiratory tract symptoms and/or fever before presentation to the ED:** ≤6 days vs. >6 days [43, 79].
4) **Participating center:** 13 centers.

The allocation of a participant to the IMP based on the aforementioned characteristics will be done using the electronic data capture (EDC) system secuTrial®. The first participant will be truly randomly allocated by the system; for each subsequent participant, the treatment allocation that minimizes the imbalance on the selected characteristics between groups at that time will be identified by the system. This allocation will be made with a probability of 0.8 in favor of the intervention that would minimize imbalance between treatment groups. The random element (of 0.2) ensures that allocation is not fully deterministic.

The ZüriPharm AG at the University Hospital Zurich will assemble, blind, label, and distribute the IMP for each site to guarantee all safety regulations. Each kit (IMP, oral syringe, and measuring cup) has a unique medication ID. The medication ID and the associated treatment (active drug and placebo) are linked in a medication list, which is stored in secuTrial® by the study data manager at the CTC Zurich. The medication list in secuTrial® includes medication IDs for medication that is available at each center (e.g., ZH123, LU123) and guarantees enough supply for each treatment arm. The medication list is concealed to all other parties.

Prior to allocation, the local investigators (study physician or study nurse) must enroll the participants who fulfill all inclusion/exclusion criteria via the EDC and enter the respective characteristics. The EDC will then allocate the medication ID to the patient by minimization and release the medication ID to the investigator. Patients will be allocated to the IMP at the ED (for ambulatory patients) or as closely as possible to hospital admission (for hospitalized patients) within a maximum of 6h after ED admission.

Information about eligible patients that will undergo screening (section 7.2) will be collected in a screening log at the local sites by the treating physician or local investigators. Each eligible patient receives a patient ID (documented in the screening log). Patients who will be included and allocated to IMP (medication ID) will be documented in the designation log and entered into the electronic Case Report Form (eCRF) in secuTrial® by the local investigators. Patient ID, medication ID, and date of allocation will be added to the eCRF accessible from the local site. The designation log will be held at each site and in copy at the CTC Zurich.

6.2.2 Blinding procedures

Blinding will be ensured through the use of placebo, which is provided by the ZüriPharm AG and indistinguishable from the active treatment in any way but the active ingredient. ZüriPharm AG and the study data manager (who links medication ID to active drug and placebo in secuTrial®) are unblinded (section 6.2.1). All care-givers (including nurses, treating physicians), the parent (and patient), the investigators, and outcome assessors will be blinded to the allocated treatment. The trial statistician will be blinded when performing the blinded sample size review, but will be unblinded for the final analysis.

The medication ID released by secuTrial® will be entered into a screening log. This screening log will be stored locally in every study center and can be used as back-up for unblinding procedures in case the secuTrial® would not be available for any technical circumstances.

6.2.3 Other methods of minimizing bias

Not applicable.

6.3 Unblinding procedures (code break)

In the MYTHIC, no situations needing emergency unblinding are foreseen. AEs caused by drug toxicity and needing discontinuation of the drug are expected to be extremely rare when administering azithromycin in regular doses and for 5 days. The acute toxicity of a one-off azithromycin overdose is very limited. There is no specific antidote and management is symptomatic. Allergic reactions to any of the ingredients of the formulation can occur. However, these are extremely rare. In situations where an allergic reaction due to trial treatment is suspected, and further regimen doses are due, trial treatment is to be discontinued. The following criteria for discontinuation or modification (Table 6) guarantee safety in MYTHIC without the necessity of unblinding the IMP:

Table 6. Criteria and procedures for discontinuation or modification of the IMP.

Discontinuation criteria:	Modification criteria:
• Any change in the patient's condition that justifies the discontinuation of the IMP (e.g., need for ICU transfer). • Unacceptable toxicity or AE (according to the prescribing information). • Use of a medication with a known major drug interaction with azithromycin. • Withdrawal of informed consent for IMP by patient/parent.	*Ambulatory patients:* • Need for hospital admission. *Hospitalized patients:* • Failure to maintain oxygen saturation ≥90% with FiO2 100%. • Oxygen saturation <90% for >48h. • Clinical features of severe respiratory distress/exhaustion and/or shock/sepsis.
Procedures:	Procedures:
• **Stop IMP**	• **Treatment modification with antibiotics against atypical pathogens*** and/or • **Switch to standard of care****
Important note: Decision about additional treatment with beta-lactams (such as amoxicillin) to avoid potential non-treatment of co-infecting bacterial pathogens (e.g., *Streptococcus pneumoniae*) in study patients will be made by the treating physician and will not be influenced by local investigators or TMT.*/**	

* Treatment alternatives to the IMP (azithromycin as active drug) against atypical pathogens (e.g., *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*) must be discussed between the local investigators and the TMT. These include clarithromycin (as another potent macrolide) or doxycycline in children ≥8 years of age (also as treatment option for infections with MRMP) [9]. In case of clinical suspicion of MRMP infection (e.g., worsening and/or non-responding symptoms), testing and (modifying) treatment for MRMP should be initiated irrespective of the study. The TMT will also support the local team at the participating centers in managing infections with (possible) MRMP.

** Decision about switch to standard of care (defined as treatment-as-usual, usual care, or routine care) will be made by the local team. The IMP should be continued for the total 5-day treatment duration whenever possible.

In case of need for emergency unblinding due to unforeseen circumstances in a study participant, the coordinating principal investigator or TMT must be contacted. They will be available around the clock by phone in case an emergency unblinding is deemed necessary. Unblinding of the respective study participant will occur through the secuTrial® database by a person with an appropriate right.

7. STUDY POPULATION AND INFORMED CONSENT PROCEDURE

7.1 Eligibility criteria

Inclusion criteria:

Inclusion criteria for screening phase:

- **Children aged 3-17 years** (from 3rd up to 18th birthday) presenting to the ED who will be managed ambulatory or will be admitted to general ward.

- **Clinical diagnosis of CAP:**
  1) **Diagnosis defined as the treating physician's documented diagnosis of CAP**; AND
  2) **Fever ≥38.0°C** (measured by any method [i.e., ear, axillary, rectal, or forehead site] in the ED or via parent report observed in the last 24h); AND
  3) **Tachypnea** (RR above the age-specific reference value as defined in section 5.1, Table 1 during the assessment in ED [triage or clinical examination]).

  This trial aims to produce translational results generalizable to a "real-world" setting. In ED settings, the diagnosis of CAP is generally based on clinical criteria [8, 9]. Therefore, inclusion criteria for this study will not be based on radiological or laboratory diagnostics. However, according to our experience from previous studies and feedback from participating centers, we expect ≥90% of children to have a CXR performed as part of their diagnostic routine.

- **Written screening consent for participation in screening phase** signed by parents or legal guardians and the patient if ≥14 years of age.

Additional inclusion criteria for intervention phase:

- **Positive *Mp* screening test result** with the *Mp* IgM LFA (grade 2 or 3) (section 6.1).
- **Written informed consent for participation in intervention phase** signed by parents or legal guardians and the patient if ≥14 years of age.

Exclusion criteria:

Exclusion criteria for screening phase:

- None.

Exclusion criteria for intervention phase:

- Contraindication to azithromycin: Documented allergy to azithromycin; cardiovascular disease, *including bradycardia, arrhythmias, and/or QT-interval prolongation**; myasthenia gravis.

  *Co-medication with arrhythmogenic or QT-interval-prolonging drug (https://crediblemeds.org) is no exclusion criteria but will be discussed with the local investigators and/or TMT.
- Underlying comorbidities: Cystic fibrosis or other chronic lung disorders (excluding asthma), primary or secondary immunodeficiency, sickle-cell anemia, or severe cerebral palsy.
- History of recurrent pneumonia (two or more episodes) or severe pneumonia (ICU admission or complications of CAP such as lung abscess, effusion, and empyema) in lifetime.
- Antibiotic treatment against *Mp* within the previous 7 days, including macrolides, tetracyclines, or fluoroquinolones.
- Referral to ICU directly from the ED (e.g., development of respiratory failure).
- Inability to tolerate oral medication.
- Parents are unlikely to reliably complete FUP visits and questionnaires (e.g., due to language barriers or living far from the study site).

7.2 Recruitment, screening, and informed consent procedure

Patient information material about the MYTHIC Study will be provided to participating centers in form of a short one-page DIN A5 flyer with a QR code to the MYTHIC website that can be placed in the waiting areas of the ED. The MYTHIC website (www.mythic-study.ch) will be created with both public and member-only areas, including a short informational film. Any information material reviewed and endorsed by the relevant CEC will be also deposited in the publicly accessible area of the MYTHIC website.

The ED staff (triage nurse or treating physician) will inform the local investigators (study nurse, study physician, or GCP-trained ED consultant) about an eligible patient with diagnosis of CAP (pre-screening). The local investigators will check inclusion criteria for the **screening phase** and initiate contact. Eligible patients and/or their parent will receive a consent form for research projects with persons (HRO, chapter 2) providing sufficient information about the screening phase of the study to make an informed decision. The local investigators will obtain written screening consent, and perform the screening with the *Mp* IgM LFA from capillary blood and collect a NPS for *Mp* PCR. The *Mp* IgM LFA results will be available within 10min and will be communicated to the treating physician. In case of a positive *Mp* IgM LFA result, written informed consent for **intervention phase** participation will be obtained at the ED (for ambulatory patients) or as closely as possible to hospital admission (for hospitalized patients) within maximum 6h after the ED admission. This corresponds to randomization within 10h from presentation to the ED and will therefore provide time for parent (and patient) to read the consent.

All patients will be assessed against the inclusion and exclusion criteria as listed in section 7.1 for both the written screening consent (screening phase) and written informed consent (intervention phase), and will be considered eligible for enrollment into MYTHIC if they fulfill *all* the inclusion criteria and none of the exclusion criteria. There will be no exceptions to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed prior to randomizing a participant. Eligibility will be reviewed and documented by a local investigator at each participating center before patients are randomized into the study.

Written informed consent to enter into MYTHIC and be randomized must be obtained from the parent (and patient) after explanation of the aims, methods, benefits, and potential hazards of the respective phase of the trial and before any trial-specific procedures are conducted. Written informed consent (intervention phase) may only be obtained once eligibility has been confirmed.

It must be made completely and unambiguously clear that the parent (and patient) is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting the treatment of the patient.

The informed consent process must be documented in the clinical information system, the signed consent forms must be kept by the local principal investigators and documented in the eCRF, and a copy given to the family. The pediatrician/general practitioner of the patient will be informed about participation in MYTHIC with the ED and/or hospital letter (including a separate paragraph with information about the trial, medication ID, and FUP procedures).

Further information on recruitment and screening are described in section 6.1 and shown in the Study flow (page 29).

Families will not be compensated for participating in the MYTHIC Study.

7.3 Assignment to study groups

Randomization is performed through minimization using stratification factors as described in section 6.2.1. After patient enrollment, the local investigators (study physician or study nurse) will enter the data for stratification (age, patient care status, and prodromal symptom duration) into secuTrial®, which will randomize the patient and allocate the medication ID for the patient.

7.4 Criteria for withdrawal / discontinuation of participants

With consenting to the trial, the parent (and patient) is consenting, to trial treatment, trial FUP, and data collection. However, an individual patient may stop treatment early or be stopped early for any of the following reasons (section 6.3, Table 6, **"Discontinuation criteria"**):

- **Any change in the patient's condition that justifies the discontinuation of the IMP (e.g., need for ICU transfer).**
- **Unacceptable toxicity or AE (according to the prescribing information).**

- **Use of a medication with a known major drug interaction with azithromycin.**
- **Withdrawal of consent for the trial by parent.**

As the patient's participation in the trial is entirely voluntary, the parent (and patient) may choose to discontinue the trial participation at any time without penalty or loss of benefits to which they are otherwise entitled. Although the parent (and patient) is not required to give a reason for discontinuing trial treatment, a reasonable effort should be made to establish this reason while fully respecting the patient's rights.

If at all possible, it should be established whether the withdrawal relates only to continued receipt of IMP or whether the family wishes to discontinue FUP. A parent who chooses to discontinue trial treatment should be encouraged to follow the trial procedures and FUP schedule. However, a decision to stop the patient's participation early must be accepted. In this case, the TMT should be informed of this in writing.

Patients who discontinue IMP or stop trial FUP early will not be replaced in the trial (section 8.5).

8. STUDY INTERVENTION

8.1 Identity of investigational products

Children enrolled in MYTHIC will be receiving either oral azithromycin (Azithromycin Pfizer®) or oral matching placebo dosed once daily for 5 consecutive days.

8.1.1 Experimental intervention

Azithromycin Pfizer® powder for oral suspension 200mg/5mL is commercially available from Pfizer AG, Zurich, Switzerland and will be used in the active comparator arm according to a weight-banded dosing chart (Table 7).

8.1.2 Control intervention (comparator treatment)

Patients in the control arm will be receiving oral placebo (section 2.2) matched to the commercially available drug product described in section 8.1.1 and supplied by the ZüriPharm AG, Zurich, Switzerland.

8.1.3 Packaging, labelling and supply (re-supply)

Azithromycin Pfizer® and placebo will be provided as trial supplies to the study centers. The same packaging will be used for all children (2 bottles for 30mL oral suspension per patient). Each bottle will contain either powder with 1200mg azithromycin for 30mL oral suspension (200mg/5mL) or identically looking placebo. All bottles will be labelled in a blinded manner (identical bottles and labels for active comparator and placebo) and each kit (IMP, oral syringe, and measuring cup) will have a unique medication ID. The ZüriPharm AG will be responsible for the labelling, packaging, and supply (re-supply) of IMP. Each center will be provided with a minimum number of bottles at the start of the study. The IMP is pre-packed with a measuring cup for reconstitution and with an oral syringe for administration, and the following information are provided on the IMP label: IMP name (incl. placebo), dose form, strength of the product, “for clinical trial use only”, study name, name of sponsor, medication ID, expiry date, storage conditions, “shake well before use”, and empty fields to write the patient ID, the date of reconstitution, and the dose on the label. IMP supply, accountability, and destruction at the local centers will be documented in the drug accountability log. Subsequent orders can be placed with the ZüriPharm AG through completion of a shipment request form. The trigger level for orders will be dependent on predicted recruitment rate and may vary from site to site. The planned trigger level will be defined at the time of opening of the site.

8.1.4 Storage conditions

Azithromycin Pfizer® must be stored in a dry place at room temperature (temperature monitoring required). Sites are responsible for the safe and proper storage of IMP, which must be kept separately from routine clinical drug supplies in a secured area with limited access.

8.2 Administration of experimental and control interventions

8.2.1 Experimental intervention

Study medication will be administered orally once a day on 5 consecutive days (section 3.4). A dose of 10mg/kg/day on day 1 and 5mg/kg/day on days 2-5 will be used. Dosing will be by weight band (Table 7).

The 1st dose of IMP will be administered immediately after randomization at the ED by study nurse or care-givers (including nurses and treating physicians). Administration of the 2nd to 5th dose of IMP during hospitalization will be done by the care-givers. The parent (and patient) will receive detailed instructions for the administration of the consecutive doses either at home, at the ED (for ambulatory patients), or at the ward. The dose and time point of administration is shown in the patient self-documentation with secuTrial® or study diary.

Table 7. Dosing table for dose selection of azithromycin and placebo oral suspension.

Weight band	Weight range	Day 1		Days 2-5		Total per treatment course	
	kg	mg/dose	**mL/dose**	mg/dose	**mL/dose**	mg	**mL**
0	≥10 - <15*	100	**2.50**	50	**1.25**	300	**7.50**
1	≥15 - <20	150	**3.75**	80	**2.00**	470	**11.75**
2	≥20 - ≤25	200	**5.00**	100	**2.50**	600	**15.00**
3	>25 - ≤35	300	**7.50**	150	**3.75**	900	**22.50**
4	>35 - ≤45	400	**10.00**	200	**5.00**	1200	**30.00**
5	>45	500	**12.50**	250	**6.25**	1500	**37.50**

Doses will be rounded to 0.25mL according to the oral syringe supplied with the IMP.
* Inclusion from 3 years of age.

8.2.2 Control intervention

Dosing (in milliliters) and administration of placebo will be the same as for patients in the active comparator arm using the weight-banded dose selection table shown in Table 7.

8.3 Dose modifications

AE caused by drug toxicity and demanding discontinuation of the drug are expected to be extremely rare when azithromycin is used for 5 days. Discontinuation of IMP may occur in the situations listed in section 6.3 (Table 6) and section 7.4. Dose modifications will not be allowed.

8.4 Compliance with study intervention

A MYTHIC Pharmacy Manual of Operations will be made available with detailed instructions for staff administering IMP on how study medication should be dispensed, prepared, and administered to patients, including what to do in case of the patient spitting medication or vomiting. The parent (and patient) will receive instructions for the correct storage and administration of IMP either at the ED (for ambulatory patients) or at the ward (for hospitalized patients if discharge occurs before completion of the 5-day treatment). Adherence will be recorded in the eCRF via patient self-documentation with secuTrial® or study diary. The parent (and patient) will be instructed to return the IMP bottles at the close-out visit on day 28 in the hospital to measure and record the remnant of suspension in bottles.

8.5 Data collection and follow-up for withdrawn participants

In case of a parent (and patient) choosing to discontinue the trial treatment but willing to attend the follow-up visits the patient will be followed up as scheduled. If a patient is withdrawn from the trial, the medical data collected until that timepoint will be kept and used in analysis. After analysis, data of withdrawn participants will be anonymized to avoid traceability. Samples obtained for the study from withdrawn patients will be processed according to the protocol. Consent for future use of stored samples already collected can be refused when leaving the trial early. Samples of patients who have refused future use will be destroyed after analysis or after 10 years of study closure. Prior to transferring to routine FUP, the participant will be asked to have assessments performed as appropriate for the close-out visit. In addition, permission will be requested to contact primary care providers and to collect data from any hospital visits or admissions registered at the recruiting center during the 28-day FUP period. Parent (and patient) will be at liberty to refuse any or all individual components of the assessment and data collection.

8.6 Trial-specific preventive measures

In situations with a clinical indication for treatment modification as defined in section 6.3 (Table 6, **"Modification criteria"**), the IMP may be modified with another antibiotic against atypical pathogens, such as clarithromycin (as another potent macrolide) or doxycycline in children ≥8 years of age (also as treatment option for infections with MRMP) [9]. This situation is expected to be rare and is unlikely to impact the trial results. Decision-making by the local investigators and the TMT will be possible and safe in such situation without the need to unblind the treatment allocation. However, the use of treatment modification will be recorded in secuTrial®. Patients should remain in the study for FUP and should continue to follow the assessment schedule.

8.7 Concomitant interventions (treatments)

The diagnosis of CAP will be based on clinical criteria (section 7.1). Decisions about hospital admission or ICU transfer (during hospitalization) will be made by the local clinical team and will not be influenced by the study. All participating patients will receive standard of care supportive treatment for CAP according to international guidelines and local recommendations, including supplemental oxygen, intravenous treatment/fluids and/or nasogastric feeds/fluids, as clinically indicated.

Antibiotic treatment decisions will be made according to local, national, and international guidelines and based on the clinical assessment of the patient by the treating physicians. Current international guidelines recommend empirical amoxicillin treatment as first choice for antibiotic therapy in children with CAP [8, 9]. Decision about additional treatment with beta-lactams (such as amoxicillin) to avoid potential non-treatment of co-infecting bacterial pathogens (e.g., *Streptococcus pneumoniae*) in study patients will be made by the treating physician (section 6.3). Importantly, the lack of a bacterial cell wall makes *Mp* resistant to beta-lactams and those antibiotics do not exhibit anti-inflammatory effects.

All necessary concomitant medications are allowed and must be recorded. If a medication with a known major drug interaction with azithromycin is essential for a child's management and cannot be replaced by a drug that does not have an interaction with azithromycin, then the IMP should be stopped and the concomitant medication used (section 6.3, Table 6, **"Discontinuation criteria"**).

8.8 Study drug accountability

Drug accountability will be regularly monitored using a drug accountability log and the remaining stocks checked against the amounts dispensed by the ZüriPharm AG. The ZüriPharm AG will monitor drug accountability centrally including IMP receipt from Pfizer, storage, and shipping to local sites, and the local sites will monitor drug accountability locally (including IMP receipt from the ZüriPharm AG, storage, dispensation to patients, and local disposal of expired IMP), which will be monitored during site visits by the sponsor and the monitor.

8.9 Return or destruction of study drug

Used IMP will be disposed of in accordance with local practice following reconciliation and the completion of the relevant log (section 8.8). At the end of the study, all remaining IMPs will be destroyed at the local sites. Expired IMP and any unused IMP at the end of MYTHIC will be quarantined and reported to the sponsor to authorize local disposal after monitoring during the close-out visit by the monitor. The disposal of all expired and unused IMP should be documented by completing the relevant drug accountability log. If there is a drug recall, the ZüriPharm AG will contact all affected sites with the appropriate instructions.

9. STUDY ASSESSMENTS

9.1 Study flow and assessments

The frequency of assessments and FUP visits are detailed in the Study schedule section with a patient timeline on page 27 and Study flow on page 29.

Before discharge, the parent (and patient) will be thoroughly instructed by the local investigators about the further study schedule. If applicable, the information will contain details about the correct storage and administration of the IMP, the precise measurement of VS and its documentation in secuTrial® or study diary, as well as the procedure in case of progression and/or deterioration of disease.

9.2 Assessments of outcomes

9.2.1 Assessment of co-primary outcomes

1.1: **Time to normalization of all VS (efficacy)**

The index time point for the assessment will be defined as the last VS measurement in the ED prior to IMP administration (or prior to the administration of antipyretic medication at the ED). VS will be measured after having the patient relax (without running, crying, etc. for at least 5min). Measurements will be taken until VS (T, RR, HR, and SpO_2) are normalized in 3 consecutive measurements within 24 hours (section 5.1).

The VS measurement method will depend on the patient care status:

Hospitalized patients:

VS will be measured by routine clinical monitoring every 8h after the index time point using locally available equipment and procedures: T by ear thermometer; HR and SpO_2 by pulse oximeter on room air; RR by clinical assessment. VS will be documented in the clinical information system and in secuTrial®.

Ambulatory patients:

VS will be measured 3x/24h (the first time within 8h after the index time point) until 3 consecutive normal measurements of all VS within 24h are documented. The parent will receive a trial box including the following items:

- IMP (labelled)
- Ear thermometer
- Masimo SafetyNet™ Radius PPG™
- Study diary and instructions for the use of the patient self-documentation with secuTrial®
- Instruction sheet (incl. QR code to the MYTHIC website)

The ear thermometer for temperature measurement will be standardized and is a validated medical device with memory function to verify the data entry in the patient self-documentation with secuTrial®.

The Masimo SafetyNet™ Radius PPG™ will be used to measure SpO_2, respiratory rate, and heart rate. Masimo SafetyNet™ is a commercial available CE mark sensor that can be connected to a secure, cloud-based patient management platform allowing for spot-checking and continuous measurements. Patients will receive a multi-day supply of disposable Radius PPG™ sensors, along with access to the Masimo SafetyNet™ mobile application (Masimo SafetyNet™ App).

Patients will have access to their personal data and health information on their mobile device through the Masimo SafetyNet™ App. When the patient uninstalls the Masimo SafetyNet™ App or “deletes” his or her account, all personal data held by Masimo or stored on the Masimo SafetyNet™ App is permanently deleted. All personal data is encrypted at rest and in transit across public networks. Masimo is HDS:2018 certified. Masimo operates an Information Security Management System for Health Information Hosting Provision that complies to the requirements of HDS Certification Standard – Requirements and Controls – rev. 1.1 of June 2018. Masimo SafetyNet™’s data is processed and stored on a private “cloud” server provided by Amazon Web Services (AWS). The server resides in Germany with a backup server in Ireland. AWS’ cloud services are certified for compliance with multiple widely

recognized and accepted data security standards. Only authorized registered staff of the TMT has access to Masimo SafetyNet™ Clinician Portal with individual authentication. Masimo and AWS have taken comprehensive steps to comply with the EU General Data Protection Regulation ("GDPR"). In case that participants do not have a personal device where the Masimo SafetyNet™ App can be installed study-specific mobile devices will be handed out in exchange of a deposit.

Each Patient will register to the Masimo SafetyNet™ App with a personal and de-identified email address, which will be specifically generated for the MYTHIC study. No identifying information will be entered into the Masimo SafetyNet™ App. Patients will be asked to perform spot-checks and to transfer displayed parameters on their mobile device into their study diary or directly into the patient self-documentation with secuTrial®.

Measurements will be documented via patient self-documentation with secuTrial® or study diary. The patients will be able to choose between these two self-documentation methods. If parents choose to use the patient self-documentation with secuTrial®, the study team will generate a user profile for the patient within secuTrial®. Next, the person holding the user profile will receive two different emails: the first email contains the User-ID and the link to the data capture site for data entry on mobile devices. The second email contains a link for the user to set a password. After the user defines a personal password, the data capture site can be reached. The user will only have access to their own data and eCRFs, which have been previously assigned to the patient. One prerequisite for the use of the patient self-documentation with secuTrial® is access to the internet, as data capture cannot be inserted offline. If parents choose to use the study diary, they will be provided with a paper-based and pre-printed study diary for data capture. This data will then be entered manually by the study team into the secuTrial® system. The patient self-documentation with secuTrial® or study diary will inform the parent about age-specific normal ranges of VS. The trial box will be returned at the close-out visit including the IMP bottles to measure the remnant of suspension in bottles. Upon return at the local study center, trial boxes will be cleaned, devices connected (for data export), controlled, recharged, and thoroughly disinfected at the local study site. Return status of trial boxes and data on paper included in the study diary will be recorded in the eCRF. Trial boxes will be distributed to each participating center so that at least 5(-10) trial boxes are in stock on site at any given time.

1.2: **CAP-related change in patient care status (safety)**

Any change in patient care status from ambulatory to hospitalized (admission or re-admission) or from hospitalized on general ward to ICU (transfer) within 28 days after randomization will be documented by local investigators during each FUP visit (section 5.1). (Re-)Admission will be assumed to be CAP-related if the same constellation of clinical signs as outlined in the inclusion criteria ("Clinical diagnosis of CAP") is present (section 7.1). At each FUP visit, the parent (and patient) will be asked to report (re-)admissions and whether these were due to on-going or relapsing signs and symptoms of CAP, because of another infection, or for another reason. In case of (re-)admission at nonparticipating centers, the parent (and child) will be asked for permission to request medical reports.

9.2.2 Assessment of secondary outcomes

2.1: **Overall clinical outcome based on benefits and harms (DOOR)**

"Adequate clinical response" (section 5.2, Table 3) and "solicited AEs" (section 5.2, Table 3) will be documented and ranked according to DOOR (section 5.2) [65] on day 3 (in-hospital visit), day 5 (end of treatment), day 7, 14, 21 (phone calls), and day 28 (close-out visit) by local investigators or delegated staff. Ambulatory patients will be asked to enter the day-5 assessment in the patient self-documentation with secuTrial® or study diary.

2.2: **Time (days) to normalization of CAP-related symptoms**

CAP-related symptoms according to a validated measure for childhood respiratory infections [68, 69] (i.e., cough, shortness of breath, wheeze, chest pain, congestion and/or rhinorrhea, sore throat, ear pain, pallor, headache, muscle aches or muscle pains, reduced food or fluid intake, not sleeping well, interference with normal activity) will be documented 1x/24h until normalization depending on the patient care status either in the clinic information system or in the patient self-documentation with secuTrial® or study diary by the parent (and patient).

2.3: **QoL assessment of patients and their families**

A standardized and validated QoL questionnaire (Appendices, section 17.4) [70] will be answered by the parent (and patient) in the patient self-documentation with secuTrial® or study diary on day 3 (in-hospital visit) and day 28 (close-out visit). At the FUP visits on days 7, 14, and 21, the questionnaire will be answered during the phone calls.

2.4: **Time (days) to return to daily routine, defined as return to childcare/school/work of patients and their families**

Exact dates of return to childcare or school (patient) and return to work (parent) will be documented in the patient self-documentation with secuTrial® or study diary and reported by parent at the FUP visits until day 28 after randomization.

2.5: **Development of *Mp*-associated extrapulmonary manifestations**

The following signs/symptoms/syndromes suggestive of *Mp*-associated extrapulmonary manifestations as described in [71] will be assessed by evaluation of the patient during hospitalization or in-hospital visits (day 3 and 28):

- Dermatological (e.g., maculopapular skin eruptions, mucositis, urticaria, erythema multiforme, Stevens-Johnson syndrome)
- Eye involvement (e.g., conjunctivitis, uveitis)
- Neurological (e.g., aseptic meningitis, encephalitis, myelitis, Guillain-Barré syndrome)
- Hematological (e.g., hemolytic anemia)
- Cardiovascular (e.g., pericarditis, Kawasaki-like disease)
- Digestive organ involvement (e.g., hepatitis, pancreatitis)
- Musculoskeletal (e.g., arthritis, rhabdomyolysis)
- Urogenital (e.g., glomerulonephritis)

9.2.3 Assessment of additional outcomes

Other outcomes of interest (section 5.3) will be assessed by direct observation and evaluation of the patient, collection of data from routine electronic healthcare records at participating centers, and parental reports during in-hospital visits or FUP phone calls.

Other additional outcomes independent of study intervention:

- Participants and their parents will be asked about their perception of the study film with different questions on a 5-point Likert scale at the close-out visit on day 28.

9.2.4 Assessment of safety outcomes

The assessment of safety outcomes is described in section 5.4. Safety outcomes will also be assessed by direct observation and evaluation of the patient, collection of data from routine electronic healthcare records at participating centers, and parental reports during in-hospital visits or FUP phone calls.

Safety outcomes include the following outcomes (the numbering for the objectives/outcomes is the same in each chapter and throughout the whole document, section 5.4):

Co-primary outcome:

1.2: Proportion of children with CAP-related change in patient care status

Secondary outcomes:

2.1: Overall clinical outcome based on benefits and harms (DOOR)

2.5: Development of Mp-associated extrapulmonary manifestations

Additional outcomes:

- Unscheduled medical visits
- (Re-)treatment with antibiotics
- Side effects/AEs/SAEs of IMP

9.2.4.1 Adverse events (AEs)

Solicited AEs will be asked from parental report and/or will be identified in routine electronic healthcare records at participating centers. Solicited AEs are summarized in section 5.2, Table 2. These solicited AEs will be used to determine **DOOR** (section 5.2).

9.2.4.2 Laboratory parameters

No clinical safety laboratory studies will be performed as part of this protocol.

Routine clinical care will provide the following laboratory parameters:

- Hematology assessment: hemoglobin (g/L), leukocytes (G/L), neutrophils (G/L), and erythrocyte sedimentation rate (mm/h).
- Biochemistry assessment: CRP (mg/L), PCT (ng/mL), sodium (mmol/L), and potassium (mmol/l).
- Microbiological investigations: respiratory sample (location [nasopharyngeal, oropharyngeal, other], type [swab, aspirate, other], method [multiplex-PCR, PCR, culture, antigen test, other], pathogen[s] detected, detection of antimicrobial resistances), and blood cultures (pathogen[s] detected, detection of antimicrobial resistances).

The following laboratory parameters will be assessed as part of the study (Study schedule, page 27):

- NPS for pathogen detection by multiplex PCR (Biofire® Filmarray® Respiratory 2.1 plus panel [Waites, 2017]), *Mp* genotyping and antimicrobial resistance determination [80] on days 1, 3, and 28. If a NPS is performed for clinical reasons, remaining sample will be stored locally (and transferred later in batches to the MYTHIC Biobank at University Children's Hospital Zurich) so that no more than one swab will be performed on patients on day 1. The study results will not be available before the close-out visit.
- Capillary blood on day 1 for *Mp* IgM LFA (as screening) and biomarkers, as well as on day 3 and 28 for biomarkers. The *Mp* IgM LFA results will be available within 10min and will be communicated to the treating physician as part of the inclusion criteria for the intervention phase. All other results will not be available before the close-out visit.
- If venous blood is available on day 1, *Mp* IgM LFA and biomarkers will be directly assessed from venous blood instead of capillary blood together with *Mp* IgM ASC ELISpot assay [22] and *Mp* IgM ELISA (Serion® ELISA classic Mycoplasma pneumoniae IgM/IgG/IgA [81]).

9.2.4.3 Vital signs

Vital signs will be recorded for the assessment of the co-primary objectives as described in section 9.2.1.

9.2.5 Assessments in participants who prematurely stop the study

As described in section 8.5, if consent is provided for contacting primary care providers and/or reviewing the routine electronic healthcare records at the recruiting center, the data of interest will primarily be focused on the co-primary outcomes.

9.3 Procedures at each visit

Study visits and contact schedules will be prepared for each patient at randomization, and patients will be followed on that schedule until the close-out visit even if IMP is discontinued prematurely. The target dates for study visits and contacts are determined by the calendar date of randomization and are not affected by subsequent events. The schedule defines study visit times (with windows) necessary for data collection (Study schedule, page 27). Study visits/contacts are scheduled as follows and will include the following procedures:

9.3.1 Pre-screening (day 1)

- Eligibility check (CAP clinically diagnosed and age of 3-17 years).
- Information on and obtaining of the **written screening consent**.

Each study site will determine the most efficient procedures to identify potentially eligible patients.

9.3.2 Screening (day 1)

Participation in screening phase:

- Capillary blood for *Mp* IgM LFA (or directly venous blood if IV line or venous blood sample required for clinical reasons).
- NPS for *Mp* PCR (if a NPS is performed for clinical reasons, remaining sample will be stored locally, and transferred later in batches to the MYTHIC Biobank at University Children's Hospital Zurich, so that no more than one swab will be performed on patients on day 1).

9.3.3 Enrollment (day 1)

The *Mp* IgM LFA result will be available within 10min, and in case of a positive result, the following procedures will be performed:

Participation in intervention phase:

- Careful check for inclusion and exclusion criteria.
- Information on and obtaining of the **written informed consent**.
- Venous blood sampling for *Mp* IgM ASC ELISpot assay. Venous blood sampling is often routinely available because an IV line and/or venous blood sampling is performed for clinical reasons in many CAP patients presenting to the hospital. However, the venous blood sample is not required for study inclusion (to avoid exclusion because of refusal to draw blood for the study).

Clinical assessment:

- Medical history (e.g., duration of cough and/or fever before presentation to the ED).

Laboratory and radiological assessment:

- Capillary blood for biomarkers (could be taken together with the blood sample for the *Mp* IgM LFA).
- Venous blood sampling for *Mp* ELISA (if venous blood is available for the *Mp* IgM ASC ELISpot assay).
- CXR (no inclusion criteria but desirable to confirm the clinical diagnosis and often routinely performed in cases with CAP presenting to the hospital).

9.3.4 Randomization (day 1)

- IMP dispensing.

Clinical assessment:

- Physical examination.
- VS (T, RR, HR, SpO_2) just prior to and/or the last time before randomization (or prior to the administration of antipyretic medication at the ED).
- Symptom review incl. AEs.
- Concomitant care review.

9.3.5 Treatment phase (day 1-5)

- IMP administration.

Clinical assessment:

Every day until 3 consecutive normal measurements of all VS within 24h are documented (or at least until discharge) the following procedures will be performed:

- VS (T, RR, HR, SpO_2) measured every 8h for hospitalized patients or 3x/24h for ambulatory patients, *for co-primary outcome 1.1* (section 5.1).
- Symptom review, including AE's,
  for secondary outcomes 2.1, 2.2, and 2.5 (section 5.2).

- Concomitant care review,
  for co-primary outcome 1.2 (section 5.1) *and secondary outcome 2.1* (section 5.2).

9.3.5.1 In-hospital study visit day 3 (time window day 3-5)

The following will be performed at the day 3 in-hospital study visit (day 3-5 in trial):

Clinical assessment:

- Physical examination.
- VS (T, RR, HR, SpO_2).
- Symptom review incl. AEs.
- Concomitant care review.
- QoL assessment,
  for secondary outcomes 2.3 and 2.4 (section 5.2).

Laboratory and radiological assessment:

- Capillary blood for biomarkers.
- NPS for *Mp* PCR.

9.3.6 FUP (day 6-28)

9.3.6.1 Daily clinical assessment until normalization of VS

Every day until 3 consecutive normal measurements of all VS within 24h are documented (or at least until discharge) the following procedures will be performed:

- VS (T, RR, HR, SpO_2) measured every 8h for hospitalized patients or 3x/24h for ambulatory patients,
  for co-primary outcome 1.1 (section 5.1).
- Symptom review, including AE's,
  for secondary outcomes 2.1, 2.2, and 2.5 (section 5.2).
- Concomitant care review,
  for co-primary outcome 1.2 (section 5.1) *and secondary outcome 2.1* (section 5.2).

9.3.6.2 Phone call study visits

The following will be recorded on day 7 (time window ±1day, day 6-8), day 14 (time window ±2day, day 12-16), and day 21 (time window ±3day, day 18-24):

Clinical assessment:

- VS (T, RR, HR, SpO_2), if not yet 3 consecutive normal measurements of all VS within 24h are documented.
- Symptom review incl. AEs.
- Concomitant care review.
- QoL assessment.

9.3.7 Close-out visit (day 28)

The following will be performed in the hospital at the close-out visit on day 28 (time window ±4day, day 24-32):

Trial participation:

- IMP bottle return (to measure the final height of bottle-content).
- Study diary/worksheet return (if not documented via patient self-documentation with secuTrial®).
- Return of trial box return with ear thermometer and mobile pulse oximeter.

Clinical assessment:

- Physical examination.
- VS (T, RR, HR, SpO_2).
- Symptom review incl. AEs.
- Concomitant care review.
- QoL assessment.

Laboratory and radiological assessment:

- Capillary blood for biomarkers.
- NPS for *Mp* PCR.

10. SAFETY

The principles of GCP require that both investigator and sponsor follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol.

10.1 Drug studies

During the entire duration of the study, all AEs (section 5.2, Table 2, and section 9.2.4) and all serious adverse events (SAEs) are collected and documented in the secuTrial®. Study duration encompasses the time from when written informed consent is obtained until the last protocol-specific procedure has been completed.

10.1.1 Definition and assessment of (serious) adverse events and other safety related events

The definitions of ICH E6 [2] based on the principles of GCP apply to this trial protocol (Table 8).

Table 8. Definitions for safety reporting in this study based on ICE E6 definitions [2].

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences which do not necessarily have a causal relationship with the study procedure. An 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.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An "unexpected" adverse drug reaction is an AR, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for drugs that are not yet approved and Product Information for approved drugs, respectively).
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Respectively any AE or AR that: • **Results in death** • **Is life-threatening*** • **Requires hospitalization or prolongation of existing hospitalization**** • **Results in persistent or significant disability or incapacity** • **Is another important medical condition***** In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. Medical judgement should be exercised in deciding whether an AE or AR is serious.
Suspected Unexpected SAR (SUSARs)	The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality, and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

* The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it would be more severe, for example, a silent myocardial infarction.

** Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. SAE exemptions are hospitalizations for a pre-existing condition that has not worsened or for an elective procedure. These do not constitute an SAE.

*** An example of such an event potentially encountered in MYTHIC is transfer from general ward to ICU.

In MYTHIC, solicited AEs (section 5.2) must be assessed, and if positive, graded at each study visit according to Table 2 (section 5.2) and documented in secuTrial®. SAEs should be followed until resolution or stabilization. Participants with ongoing SAEs at study termination will be further followed up until recovery or until stabilization of the disease after 30 days of termination.

Assessment of causality:

Both investigator and sponsor make a causality assessment of the event to the study drug, based on the criteria listed in Table 9 and in accordance with ICH E2A guidelines [82].

Assessment of severity:

The severity of all symptoms and signs observed during SAEs in MYTHIC should be graded using the solicited AEs grading (section 5.2, Table 2).

Table 9. Criteria for causality assessment of the SAE in accordance with ICE E2A guidelines [82].

Relationship	Description	SAE type
Unrelated	There is no evidence of any causal relationship.	Unrelated SAE
Unlikely	There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (for example, the patient's clinical condition, other concomitant treatment).	Unrelated SAE
Possible	There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (for example, the patient's clinical condition, other concomitant treatments).	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

10.1.2 Reporting of serious adverse events (SAE) and other safety related events

Local investigator responsibilities:

All AESIs should be recorded in the electronic healthcare records and reported in the appropriate eCRF. AEs leading to cessation of trial treatment should be recorded in the relevant section of the eCRF.

SAEs and SARs occurring from the time of randomization until the last FUP visit at day 28 should be reported to the sponsor within 24 hours of the local investigator becoming aware of the event, and assessed by the local investigator as follows:

- **Seriousness:**

  When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 8. If the event is serious, then the sponsor must be notified within 24 hours.

- **Severity:**

  The severity of all reportable events in MYTHIC should be graded as detailed in Table 2 (section 5.2).

- **Causality:**

  The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 9.

- **Expectedness:**

  If there is at least a possible involvement of the trial treatment (or comparator), the investigator should make an initial assessment of the expectedness of the event, however the sponsor has the final responsibility for determination of expectedness. The definition of an UAR is given in Table 8.

The completed SAE form in the eCRF must be signed by the local investigator (or if absent, by a member of the site trial team) and sent within 24 hours of the investigator becoming aware of the event by email to the study center:

mythic-study@kispi.uzh.ch

The minimum criteria required for reporting an SAE are the patient ID, name of local investigator reporting, the event, and why it is considered serious. This initial report must be followed by the completed and signed SAE form in the eCRF within 7 days.

Sponsor responsibilities:

- **SAEs:** All SAEs must be reported immediately and within a maximum of 24 hours to the sponsor of the study. The sponsor will re-evaluate the SAE and return the form to the site. In the case of disagreement with regards to the causality assessment, both opinions will be provided in any subsequent reports. The sponsor is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (Swissmedic) and the CECs, as appropriate.

- **SAEs resulting in death:** All SAEs resulting in death must be reported to the lead CEC via sponsor within 7 days. The other in the trial involved CECs receive SAEs resulting in death in Switzerland via sponsor within 7 days.
- **SUSARs:** A SUSAR needs to be reported to the lead CEC and to Swissmedic via sponsor within 7 days, if the event is fatal, or within 15 days (all other events). The sponsor must inform all investigators participating in the trial of the occurrence of a SUSAR. All in the trial involved CECs will be informed about SUSARs in Switzerland via sponsor according to the same timelines.
- **Safety Signals:** All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures, i.e., so called safety signals, must be reported to the sponsor within 24 hours. The sponsor must report the safety signals within 7 days to the local CEC and to Swissmedic via sponsor. The sponsor must immediately inform all participating investigators about all safety signals. The other in the trial involved CECs will be informed about safety signals in Switzerland via the sponsor.

Periodic reporting of safety:

An annual safety report is submitted once a year to the local CEC and to Swissmedic via the sponsor.

10.1.3 Follow-up of (serious) adverse events

SAEs should be followed until resolution or stabilization. Participants with ongoing SAEs at study termination will be further followed up until recovery or until 30 days after stabilization of the disease termination. FUP should continue after completion of protocol treatment if necessary. A further SAE form, indicated as 'Follow-up' should be completed in the eCRF and sent to the sponsor as information becomes available. The patient must be identified by patient ID only. The patient's name and date of birth should not be used on any correspondence and should be deleted from any test results.

10.2 Assessment, notification and reporting on the use of radiation sources

Not applicable.

11. STATISTICAL METHODS

It should be noted that in this section, the abbreviation HR will be used for hazard ratio and not heart rate.

11.1 Hypothesis

Both co-primary endpoints are compared to show the non-inferiority of placebo to azithromycin, both with a specific non-inferiority margin δ. For the co-primary endpoint **time to normalization of all VS** (time-to-event), for which we will calculate the hazard ratio (HR, as $HR=hazard_{placebo}/hazard_{azithromycin}$), the null hypothesis ($H_0$) and the alternative hypothesis (H_1) are as follows:

$$H_0: HR \leq \delta_{HR} \; vs. \; H_1: HR > \delta_{HR}$$

For the co-primary endpoint **CAP-related change in patient care status** (binary), for which we will calculate the absolute risk difference (ARD, as $ARD=risk_{azithromycin}-risk_{placebo}$) the null hypothesis ($H_0$) and the alternative hypothesis (H_1) are as follows:

$$H_0: ARD \leq \delta_{ARD} \; vs. \; H_1: ARD > \delta_{ARD}$$

The justification of these margins is detailed below (section 11.2).

11.2 Determination of sample size

Sample size calculations were done with regard to the per protocol set (PPS), which includes patients who are positive for *Mp* by PCR (section 6.1, Table 5). To handle multiplicity with two co-primary endpoints, we apply the "at least one" success criterion [83]: We estimated the sample size for both co-primary endpoints at a one-sided significance level (α) of 1.25% (which corresponds to two-sided 97.5% confidence intervals [CI]) and a power of 80% (β=20%), and use the larger of the two sample sizes for the trial. This assures a minimum power of 80% to reject at least one null hypothesis.

The primary endpoint **time to normalization of all VS** is considered as a time-to-event endpoint, i.e., the number of days until normalization. Although we expect all patients to normalize VS during the 28-day FUP period, we used an overall event rate of 99% for the sample size calculation, in order to allow censoring. This endpoint will be compared between trial arms by a Cox proportional hazards model to estimate a hazard ratio for placebo vs. azithromycin (a hazard ratio <1 would indicate longer duration to normalization with placebo than with azithromycin). We expect no difference between treatments and thus a hazard ratio of 1. The sample size was estimated to show the non-inferiority of placebo vs. azithromycin treatment in *Mp* PCR-positive patients using the method given in Chow et al. [84] (page 177), with a non-inferiority margin (δ_{HR}) of 0.7 for the HR. Assuming exponential survival times (with an overall event rate of 99% within 28 days), this non-inferiority margin of 0.7 would be equivalent to the inverse ratio of median survival times, which would be 4.8 days for placebo and 3.3 days for azithromycin (with a HR of 1 the median survival time would be 4.2 days). The maximum prolongation of the duration to VS normalization by 1.5 days may be acceptable from a clinical perspective, especially when weighed against side effects, effect of antibiotics on microbiome, increased antibiotic resistance, and costs. These aspects are also discussed for patients with group A β-hemolytic streptococcal pharyngitis, in which modest effects of antibiotics have been observed (symptomatic improvement by only 1-2 days) [85]. Under the assumptions stated above, 302 *Mp* PCR-positive patients are needed for this study (Figure 2). Considering a drop-out rate of 14.5%, 354 patients should be enrolled. This drop-out rate is calculated from an expected drop-out of 10% due to negative *Mp* PCR (false-positive screening by *Mp* IgM LFA, section 6.1, Table 5) and an additional overall drop-out rate of 5% (due to loss to FUP or insufficient compliance), i.e., 0.1+0.05*(1-0.1)=0.145 (14.5%).

The co-primary endpoint **CAP-related change in patient care status** (binary) will be compared in terms of the absolute risk difference (ARD) between the two arms ($ARD=risk_{azithromycin}-risk_{placebo}$, ARD <0 would indicate a lower risk with macrolide than placebo). We expect an absolute risk for this unfavorable event of 5% in both trial arms and thus an ARD of 0. The sample size was estimated to show the non-inferiority of placebo vs. macrolide treatment in *Mp* PCR-positive patients, using the method given in Chow et al. [84] (page 90), with a non-inferiority margin (δ_{ARD}) of -7.5% for the ARD (Figure 3). This non-inferiority

would allow a maximum event rate of 12.5% in the placebo arm, which is less than 13.5%, the median acceptable failure rate in treatment of CAP identified in a survey of infectious disease physicians [86, 87]. Under the assumptions stated above, 322 *Mp* PCR-positive patients are needed for this study. Considering a drop-out rate of 14.5% (as above), 376 patients should be enrolled.

As we consider the larger of these two sample sizes (above), 376 patients should be recruited for the trial. We assume that 66.7% of patients agree to screening and study participation (according to [22] and unpublished observations in KIDS-STEP [75] at participating center Zurich) and that 15% of screened patients are *Mp*-positive (section 3.1), which results in 10% of screened patients available for recruiting (0.67×0.15=0.10).

Thus, we expect that the number of patients to screen is 3,760.

Figure 2. Sensitivity of the sample size for the co-primary endpoint duration to normalization of VS with regard to the non-inferiority margin, δ_{HR}, expecting no difference between treatments (HR=1).

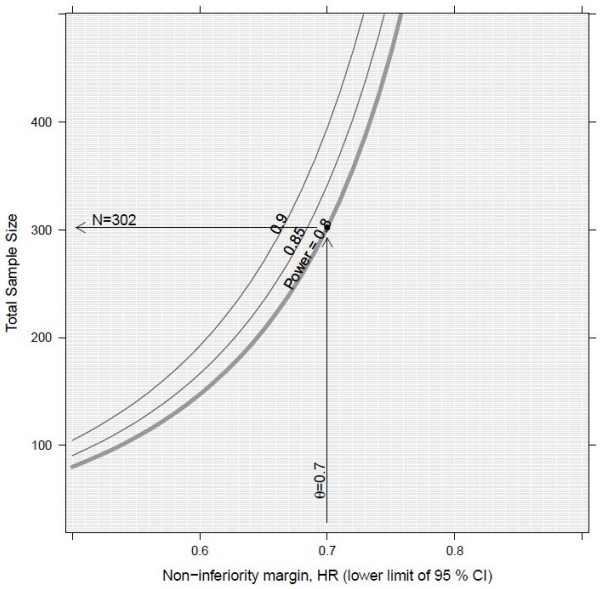
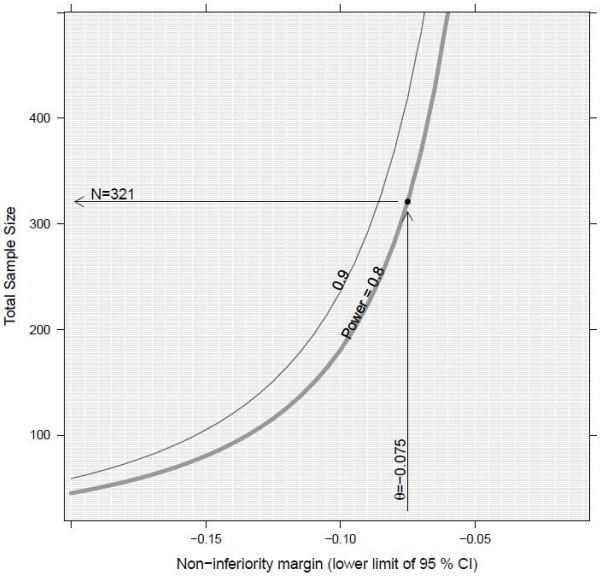


Figure 3. Sensitivity of the sample size for the co-primary endpoint CAP-related change in patient care status with regard to the non-inferiority margin, δ_{ARD}, expecting no difference between placebo and azithromycin (ARD=0), assuming a probability for a change in patient care status of 0.05.



Based on these considerations, the numbers of enrolled subjects predicted for each trial site is shown in Table 10:

Table 10. The MYTHIC Study timeline with predicted patient enrollment per trial site:

Years	1		2		3		4		5		**Total**
Months	1-6	7-12	13-18	19-24	25-30	31-36	37-42	43-48	49-54	55-60	
Study phases:											
Preparatory phase	X										
Recruitment		X	X	X	X	X	X	X	X		
Interim analysis					X		X				
Sample size review							X				
Analysis									(X)	X	
Patient recruitment per center:											
Zurich	0	0	8	8	8	9	9	9	9	0	60
Triemli*	0	2**	3	3	3	3	3	3	3	0	23
Winterthur*	0	2**	3	3	3	3	3	3	3	0	23
Basel	0	0	6	6	6	6	6	6	6	0	42
St. Gallen	0	0	3	3	3	3	3	3	3	0	21
Chur*	0	2**	3	3	3	3	3	3	3	0	23
Lucerne	0	0	4	4	4	4	4	4	4	0	28
Aarau	0	0	4	4	4	4	4	4	4	0	28
Bern	0	0	6	6	6	6	6	6	6	0	42
Geneva	0	0	3	3	3	3	3	3	3	0	21
Lausanne	0	0	3	3	3	3	3	3	3	0	21
Fribourg	0	0	3	3	3	3	3	3	3	0	21
Bellinzona*	0	2**	3	3	3	3	3	3	3	0	23
Total	**0**	**8**	**52**	**52**	**52**	**53**	**53**	**53**	**53**	**0**	**376**

* 4 centers which are not included in KIDS-STEP [75].
** 6-month set-up phase at the 4 centers not included in KIDS-STEP.

11.3 Statistical criteria of termination of trial

Formal statistical stopping rules will not be used in MYTHIC although the IDMC charter will specify guidelines for when the IDMC will alert the coordinating principal investigator or TMT to the need to discontinue the trial. These guidelines will be conservative to guard against premature discontinuation of the trial from early inspection of the data.

11.4 Planned analyses

Detailed methodology for summaries and statistical analyses of the data collected in MYTHIC will be documented in a separate statistical analysis plan. The statistical analysis plan will be finalized before database closure and will be under version control at the Department of Biostatistics, University of Zurich.

Analyses of sex differences are also planned.

11.4.1 Datasets to be analyzed, analysis populations

The full analysis set (FAS) will include **all patients who gave written informed consent and were enrolled**. Patients in the FAS will be analyzed according to the randomly assigned treatment, adhering to the intention-to-treat principle.

The per protocol set (PPS) will include all patients from the FAS who are ***Mp* PCR-positive** (section 6.1, Table 5) and who are sufficiently compliant to treatment (≥80% of the medication used).

The strict per protocol set (strict PPS) will include all patients from the PPS who additionally have **confirmed *Mp* infection by IgM ASC ELISpot assay** (section 6.1, Table 5).

Patients in the PPS and strict PPS will be analyzed according to the received treatment (in case there are any deviations from the randomized treatment).

11.4.2 Primary analysis

To assess the non-inferiority of placebo vs. azithromycin regarding the co-primary endpoint **time to**

normalization of VS, we will estimate the hazard ratio of placebo vs. azithromycin with a two-sided 97.5% CI using a Cox proportional hazards model on the PPS (defined in section 11.4.1). Non-inferiority of placebo will be declared if the lower limit of the CI will be larger than the non-inferiority margin (i.e., the whole CI lies entirely above the margin).

To assess the non-inferiority of placebo vs. macrolide regarding the co-primary endpoint **CAP-related change in patient care status**, we will estimate the absolute risk difference ($ARD=risk_{azithromycin}-risk_{placebo}$) with a two-sided 97.5% CI on the PPS. Non-inferiority of placebo will be declared if the lower limit of the CI will be larger than the non-inferiority margin (i.e., the whole CI lies entirely above the margin).

The two non-inferiority tests will be performed and interpreted independently (of each other) and the trial considered successful if non-inferiority can be shown for at least one of the primary outcomes. Should the resulting CIs exclude the reference value for no difference (1 for hazard ratio, 0 for ARD), the result can be interpreted as superiority of either treatment [88].

To complement the main analyses above, the following sensitivity and additional analyses are planned:

- We consider the **PPS as the main set for showing non-inferiority** (section 6.1, Table 5), and the sample size calculation was also done with regard to the PPS (section 11.2). In addition, we will also test non-inferiority in the strict PPS and the FAS. Since the three analysis sets (FAS, PPS, and strict PPS) differ considerably in size and composition (section 6.1, Table 5), we will consider the PPS as the relevant set for concluding non-inferiority, but we will discuss differences in the conclusions based on the different sets. For a robust interpretation of the non-inferiority test these analyses should lead to similar conclusions as the main analysis [87].
- For CAP-related change in patient care status, we will present the 2×2 table of events per treatment arm and an unadjusted odds ratio (OR) estimate for all three analysis sets.
- For time to VS normalization, we will plot Kaplan-Meier curves and estimate median time-to-event by trial arm.
- Covariate-adjusted analyses will be performed for both endpoints and all analysis sets, considering all variables used in the minimization for treatment allocation (section 6.2.1). For time to VS normalization, a mixed-effects Cox proportional hazards model with a random intercept per center will be used [88]. For change in patient care status, a generalized linear mixed-effects model will be used. Explanatory variables in both models are treatment (placebo vs. azithromycin), age (continuous), patient care status (ambulatory vs. hospitalized), and prodromal symptom duration (continuous).

11.4.3 Secondary Analyses

The secondary outcome “overall clinical outcome based on benefits and harms” will be compared between treatment groups in terms of the probability of having a more desirable outcome with placebo than with azithromycin (Wilcoxon-Mann-Whitney statistic) as a summary contrast measure, as usual with the DOOR/RADAR approach [65]. DOOR is constructed using the (1) categorization of all patients into the overall clinical outcome, and (2) ranking patients in the trial according to two rules: (2a) when ranking the outcomes of two patients with different overall clinical outcomes, the patient with a better overall clinical outcome receives a higher rank; and (2b) when ranking the outcomes of two patients with the same overall clinical outcome, the patient treated with placebo receives a higher rank. This DOOR outcome is then compared with a Wilcoxon-Mann-Whitney test with a confidence interval on the Wilcoxon-Mann-Whitney statistic that is compatible with the test. In addition, we will estimate the probability of a more desirable outcome without adjusting for antibiotic use, i.e., just comparing the overall clinical outcome between treatment groups, otherwise using the same method.

Other secondary outcomes which measure a duration will be analyzed by mixed-effects Cox proportional hazards models (with a random intercept per center) to estimate a hazard ratio. Binary secondary outcomes within 28 days will be analyzed by binary generalized linear mixed-effects models (with logit-link) to estimate OR. Repeated measurements of the secondary outcome QoL will be analyzed by a linear mixed-effects model with random intercepts for center and subject (nested within center). The serial autocorrelation of residuals within subjects will be modeled using a first order autoregressive correlation structure. Treatment, visit, and the interaction between treatment and visit will be used as explanatory terms. All effect size estimates for secondary outcomes will be reported with

a 95% CI. We will perform unadjusted analyses, with treatment as the only explanatory variable. Adjusted analyses like those specified for the co-primary outcomes may be performed in addition. Analyses of secondary outcomes will be applied primarily to the FAS. Additional analyses using the PPS or the strict PPS may be performed. In addition, all outcomes (primary, secondary, and other outcomes) as well as patient baseline characteristics will be descriptively analyzed by trial arm. We will tabulate mean and standard deviation for continuous variables with approximately normal distribution, median and interquartile range for ordinal or continuous variables with skewed distribution, and frequency and percentage for categorical variables. In addition, all side effects of trial treatment and/or serious adverse events will be listed by trial arm.

Exploratory subgroup analyses are planned for the following baseline characteristics regarding the two co-primary outcomes: (1) Age (3-9 vs. 10-17 years and continuous in years); (2) Patient care status (ambulatory vs. hospitalized); (3) Prodromal symptom duration (≤6 days vs. >6 days and continuous in days); (4) Confirmation of *Mp* infection by both PCR and IgM ASC ELISpot assay (binary yes vs. no); (5) CXR-confirmed CAP (binary yes vs. no); and (6) sex (binary male vs. female). For each subgroup variable, a mixed-effects Cox proportional hazards model will be fitted to the time to normalization and a generalized linear mixed-effects model to the CAP-related change in patient care status. Treatment, the subgroup variable, and the interaction between the subgroup variable and treatment will be included as explanatory variables. A statistically significant interaction between one of the subgroup variables and treatment would indicate a different treatment effect in the corresponding subgroups (or along age gradient). We will also compute group-specific treatment effects (with 95% CI), fitting a separate model for the corresponding subgroups, which will be reported together with the interaction *p*-value.

We will compare the LFA test results with PCR as gold standard (available for all screened patients) and calculate diagnostic measures. In addition, we will compare positive LFA test results with the ELISpot test results (only available for patients with positive LFA test who were enrolled). Test results of the current gold standard PCR (available for all enrolled patients) will be compared with the ELISpot test results.

We will further descriptively analyze the degree of usefulness of the informational video about the study for the parents and participants by trial arm.

11.4.4 Interim analyses

An interim analysis for safety will be conducted after 1/3 and 2/3 of the patients have completed the 28-day FUP (Table 10). The IDMC (section 1.6) will oversee and discuss the results. Access to interim data and interim analysis results will be limited to the IDMC and the statistician. We will do a blinded sample size review, using an internal pilot study design. The sample size review will be done for the binary co-primary endpoint, since the sample size estimation for this endpoint depends on the overall risk of a change in patient care status as a nuisance parameter [89]. The overall event rate for the time-to-event co-primary endpoint (proportion of patients with VS normalization within 28 days) is less uncertain and larger (less important nuisance parameter). We will estimate the overall risk of a change in patient care status ad interim, after 250 patients have the primary outcome measurement (2/3 of the planned sample size, $\hat{N}_{init}$), as the proportion of patients who had the event, ignoring treatment groups. This estimate of the overall risk will then be used to recalculate the sample size, $\hat{N}_{recalc}$, as described above in section 11.2. The final sample size will be the larger of the original sample size and the recalculated sample size, $\hat{N}$=max($\hat{N}_{init}$; $\hat{N}_{recalc}$).

11.4.5 Safety analysis

Safety will be assessed via:

- Analysis of the safety outcomes as detailed in section 5.4: proportion of children with CAP-related change in patient care status (1.2), overall clinical outcome based on benefits and harms (DOOR/RADAR approach, 2.1), development of *Mp*-associated extrapulmonary manifestations (2.4), unscheduled medical visits, (re-)treatment with antibiotics, and side effects/AEs/SAEs of IMP.
- Rigorous and detailed examination of side effects/AEs/SAEs of IMP. Frequencies and types of AEs will be reported per study arm, together with the proportion of patients experiencing AEs.
- Interim analysis for safety after 1/3 and 2/3 of the patients have completed the 28-day FUP (section 11.4.4).

11.4.6 Deviation(s) from the original statistical plan

If substantial deviations of the analyses as outlined in these sections are needed for whatever reason, the protocol will be amended. All deviations of the analyses from the protocol or from the detailed statistical analysis plan will be listed and justified in a separate section of the final statistical report.

11.5 Handling of missing data and drop-outs

In order to analyze all patients in the FAS (and the other sets), missing outcome and important covariate data will be multiply imputed using chained equations, as implemented in the R package mice [90], using m=100 imputations per missing value.

12. QUALITY ASSURANCE AND CONTROL

The CTC Zurich will implement a quality control system on behalf of the sponsor and coordinating PI to ensure adherence to study procedures at all study sites and monitor the conduct of the study. Written standard operating procedures (SOPs) and manuals of operation will be issued to all sites and adherence to guidance monitored during site visits. The SOPs for monitoring of study sites will be reviewed by the sponsor and coordinating PI.

12.1 Data handling and record keeping / archiving

All data collected for central analysis in the study, whether clinical data recorded in the electronic data capture (EDC) system or other data, will be coded by a unique randomly generated patient ID.

12.1.1 Electronic case report forms (eCRFs)

Relevant clinical study data for each enrolled study participant, i.e., observations, tests and assessments specified in the protocol, are recorded in eCRFs via the web-based EDC system implemented in secuTrial® at the study centers. Personal data will include, month and year of birth, and sex. The patient's name and address will not be recorded. The EDC system includes guidance for study sites on how to perform data entry and will also be used for query handling.

Local investigators and site trial members will be authorized for the eCRF entries of study participants enrolled at the site. Investigators will be trained to use the EDC system during the site initiation visit. The investigators ensure the accuracy, completeness, and timeliness of the data recorded and provide answers to data queries, as specified in the study protocol and in accordance with additional instructions. The identity of the local investigator entering data and date and time of data entry will be recorded as meta-data in the study database.

12.1.2 Specification of source documents

The local investigator is required to maintain an accurate medical record of all original documents and data relevant to the study as source documentation. The patient ID will be noted in the screening log (backup for secuTrial®) and a copy of the signed informed consent form will be filed in the medical record to identify study participants locally at the study site.

Clinical source data will be kept at the study sites in the patients' medical records and include demographic and clinical data, medical history, current medication at the time of and during admission, all clinical examinations and all laboratory and radiological evaluations undertaken as part of routine clinical care. Furthermore, the assigned trial medication ID will also be entered in the patients' medical record. Data which are directly recorded in the eCRF will also be considered as source documents and include detailed documentation of all study eligibility criteria as well as a confirmation that the participant has signed the informed consent form.

In case an AE or SAE leads to treatment or hospitalization, any record thereof will also be considered as source documentation. All information recorded on the eCRF must be consistent with the study participants' source documentation.

As soon as the study database has been locked at the end of the study, a copy of the investigator documentation and patient self-documentation with secuTrial® output will be archived at the study sites for each participant.

12.1.3 Record keeping / archiving

All study data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial. Study-relevant source data and documents will be archived at study sites for a minimum of 10 years.

The clinical trial data will be collected, processed and managed in the EDC system secuTrial® (interActive systems; iAs, Berlin). secuTrial® is a professional, entirely browser-based GCP-compliant EDC system for collecting patient data in clinical studies. secuTrial® meets the Swiss regulatory requirements regarding the collection of patient data in clinical or non-interventional studies and patient registries.

Data collection occurs via eCRFs, which are generated by the CTC Zurich in close collaboration with the TMT and undergo a thorough data validation process.

eCRFs consists of:

- Forms and data entry fields to enter data (parameters as defined in the study protocol);
- Visits, that specify the events for which data collection is scheduled.

Ongoing maintenance and use of this software is managed by agreement between the study sponsor and the CTC Zurich. Each study site will be responsible for data entry into the EDC system.

12.2 Data management

12.2.1 Data management system

The clinical trial data will be collected in the EDC system secuTrial®. secuTrial® is a professional, entirely browser-based GCP-compliant EDC system for collecting patient data in clinical studies. The EDC system runs on a server maintained by the IT-department of the University Hospital Zurich. The eCRF will be implemented (set-up and adjusted) by the data management group at the CTC Zurich. Each study site will be responsible for data entry into the EDC system.

12.2.2 Data security, access and back-up

The EDC system is accessible via a standard browser on a WWW-connected device. Password protection ensures that only authorized persons can enter the system to view, add or edit data according to their permissions. User administration and user training is performed by the CTC Zurich according to predefined processes. Regular back-up of secuTrial® study data is performed according to the processes of the IT-department of the University Hospital Zurich.

The EDC system is accessible via a standard browser on a WWW-connected device. Appropriate coded identification (e.g., pseudonymisation) is used in order to enter subject data into the database. A role-based user concept with personal login and passwords (e.g., for site investigator, statistician, monitor, administrator etc.) regulates permission for each user to access the system and database when required. The role- and user-based settings control access to various functionality and modules, such as being able to enter data, export reports, and view the logging records. In multi-centric studies the data entered by one institution are not accessible or viewable by other participating centers. User administration and user training is performed by the CTC Zurich according to predefined processes.

A current list with signatures and names of all authorized study personnel with access to the study records will be filed in the study site file and the trial master file, respectively. A built-in data logging tool (audit trail) ensures that any changes to the project or user activity (date and time stamp and user log), including contextual information (e.g., the project record being accessed), are continuously tracked in real-time and accessible online or via downloadable audit table.

The server hosting the EDC system and the database is kept in an off-site locked server-room. Only system administrators have direct access to the server and back-up tapes. Regular back-up of secuTrial® study data is performed according to the processes of the IT-department of the University Hospital Zurich.

An audit trail system maintains a record of initial entries and changes (including timed and dated reasons for these and user identification). At all times the investigator has final responsibility for the accuracy and authenticity of all clinical data.

12.2.3 Analysis and archiving

The EDC will be locked after all data was monitored, cleaned, and all raised queries have been resolved. Data will be archived by the investigator for a minimum of 10 years.

12.2.4 Electronic and central data validation

The EDC system supports data checks for completeness and plausibility. Furthermore, selected data points are cross-checked for plausibility with previously entered data for that participant. Additional

central data validity checks against pre-determined parameters are run either automatically or *ad hoc*, to detect inconsistencies and identify missing data for source data verification. Data will be reviewed for inconsistent impossible or missing data by an independent monitor from CTC Zurich and, if necessary, data queries raised using the EDC system. The local investigators will be asked to respond to the query and confirm or correct the corresponding data.

Clinical study data will be source-data-verified, where relevant, during monitoring visits. After completion of all data queries the eCRF is signed electronically by the coordinating principal investigator. When all data have been coded, validated, signed and locked the study database will be frozen and then locked to prevent further editing.

12.3 Monitoring

The monitoring activities will be conducted by the Clinical Trials Center (CTC) of the University Hospital Zurich. Extent and nature of monitoring activities will be defined and described in a study specific Monitoring Plan.

The purpose of the monitoring visits is to confirm the following:

- The study is being conducted according to the protocol and within the specified time frame.
- The data are being collected accurately and completely on the eCRF and any source documents.
- The study medication is being correctly prepared, dispensed and accounted for.
- Adverse events are being correctly reported.
- The facilities and staff remain adequate.

The coordinating principle investigator and sponsor need to ensure that source data and documents are accessible to the study monitor(s) and will answer questions posed by the study monitor(s).

12.4 Audits and Inspections

In accordance with ICH GCP guidelines [2], audits may be performed by the CEC and CA during the course of the study. The audits will include control of adherence to the protocol, standard operating procedures, ICU GSP guidelines and national legislation. Source data verification and checking of the data entered in the eCRF will be used for assessment of complete and reliable documentation. The local investigators ensure that source data and documents are made accessible to auditors and inspectors, and answer their questions. All involved parties must keep the participant data strictly confidential.

12.5 Confidentiality, data protection

Clinical data collected as part of this study are coded by the patient ID. No personal data are stored apart from initials, age, and sex. For the purposes of site monitoring (section 12.3), and audits and inspections (section 12.4), study monitors or designated staff of the CEC or CA will be granted access to source documents. However, all involved parties will keep personal data of participants strictly confidential.

The coordinating principal investigator, sponsor, and authorized staff at CTC Zurich will have access to the coded clinical data of study participants in the EDC system database during and after the study.

Study results disseminated at conferences or published in medical journals will include summary data of study participants. Under no circumstances will the identity of study participants be revealed.

12.6 Storage of biological material and related health data

All unused samples (blood, NPS) will be stored in the MYTHIC Biobank under guidance of the Children's Research Center at University Children's Hospital Zurich. Biobank storage will only be done with written confirmation of the participant informed consent independent from the MYTHIC Study.

13. PUBLICATION AND DISSEMINATION POLICY

The data from all centers will be analyzed together and published as soon as possible in peer-reviewed journals, as well as being presented at national and/or international conferences. Individual groups and clinicians must not publish data concerning their participants that are directly relevant to questions posed by the study until the TMT has published its report. The TMT will form the basis of the writing committee and will advise on the nature of all publications.

The results of this trial will be submitted for Open Access publication in high impact peer-review journals likely to be read by health professionals in the management of CAP in children around the globe. The work will be presented at key medical conferences. To maximize the impact of the trial its findings will be disseminated more widely through abstracts for oral and poster presentations submitted to the main relevant national and international conferences.

Once the trial has been published, all families who participated will be notified of the results by post or email. A study website will be developed providing information for collaborators, participants, and the public, with the results of the trial eventually posted here. The social media presence of the organizations involved will also be used to highlight news about the trial.

For the main results of the trial a press release will be produced, in collaboration with the press office of the journal publishing the results, which will be distributed to Swiss and global media, to encourage press coverage. This will enable a wider audience to be reached.

Data will not normally be released externally prior to the publication of the trial's main outcome measures.

All external data release must be approved by the TMT.

There are expected to be a number of resulting publications and the authorship will vary for each. Individual authors are likely to include relevant members of the TMT and collaborators, as well as high-recruiting investigators. All participating centers and corresponding PIs will be acknowledged in all relevant publications by name and all relevant expert advisors and members of the TMT and IDMC will be listed. All families who participated in the trial will be thanked as a group (not by name).

14. FUNDING AND SUPPORT

14.1 Funding

The MYTHIC Study is funded by the Swiss National Science Foundation (SNSF) under the IICT call. Project title: A randomized controlled non-inferiority trial of placebo versus macrolide antibiotics for Mycoplasma pneumoniae infection in children with community-acquired pneumonia: the MYTHIC Study (SNSF ID: 207286).

15. INSURANCE

Insurance will be provided by the sponsor through AXA, General-Guisan-Strasse 40, 8400 Winterthur. A copy of the certificate is filed in each investigator site file and the trial master file.

16. REFERENCES

1. World Medical Association (WMA) Declaration of Helsinki. 2013. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (accessed March 31, 2023).
2. International Conference on Harmonization. E6 Guideline for Good Clinical Practice 1996. 2016. Available from: https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline (accessed March 31, 2023).
3. Pfizer Laboratories Div Pfizer Inc. Zithromax prescribing information. 2021. Available from: https://labeling.pfizer.com/showlabeling.aspx?id=511 (accessed January 17, 2024).
4. World Health Organisation. Global action plan on antimicrobial resistance. January 1, 2016. Available from: https://www.who.int/publications/i/item/9789241509763 (accessed January 17, 2024).
5. Walker CLF, et al. Global burden of childhood pneumonia and diarrhoea. Lancet 2013;381:1405-16.
6. PERCH study group. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. Lancet 2019;394:757-79.
7. Jain S, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med 2015;372:835-45.
8. Harris M, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. Thorax 2011;66 Suppl 2:ii1-23.
9. Bradley JS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis 2011;53:e25-76.
10. McCaig LF, et al. Trends in antimicrobial prescribing rates for children and adolescents. JAMA 2002;287:3096-102.
11. Gerber JS, et al. Identifying targets for antimicrobial stewardship in children's hospitals. Infect Control Hosp Epidemiol 2013;34:1252-8.
12. Nyquist AC, et al. Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis. JAMA 1998;279:875-7.
13. Williams DJ, et al. Effectiveness of beta-lactam monotherapy vs macrolide combination therapy for children hospitalized with pneumonia. JAMA Pediatr 2017;171:1184-91.
14. Michelow IC, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics 2004;113:701-7.
15. Versporten A, et al. The Worldwide Antibiotic Resistance and Prescribing in European Children (ARPEC) point prevalence survey: developing hospital-quality indicators of antibiotic prescribing for children. J Antimicrob Chemother 2016;71:1106-17.
16. Wallihan RG, et al. Molecular distance to health transcriptional score and disease severity in children hospitalized with community-acquired pneumonia. Front Cell Infect Microbiol 2018;8:382.
17. Foy HM, et al. Long-term epidemiology of infections with *Mycoplasma pneumoniae*. J Infect Dis 1979;139:681-7.
18. Waites KB, et al. *Mycoplasma pneumoniae* and its role as a human pathogen. Clin Microbiol Rev 2004;17:697-728.
19. Waites KB, et al. *Mycoplasma pneumoniae* from the respiratory tract and beyond. Clin Microbiol Rev 2017;30:747-809.
20. Denny FW, et al. *Mycoplasma pneumoniae* disease: clinical spectrum, pathophysiology, epidemiology, and control. J Infect Dis 1971;123:74-92.
21. Gadsby NJ, et al. Increased reports of *Mycoplasma pneumoniae* from laboratories in Scotland in 2010 and 2011 - impact of the epidemic in infants. Euro Surveill 2012;17:pii: 20110.
22. Meyer Sauteur PM, et al. Circulating antibody-secreting cell response during *Mycoplasma pneumoniae* childhood pneumonia. J Infect Dis 2020;222:136-47.
23. Fleming-Dutra KE, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010-2011. JAMA 2016;315:1864-73.

24. Fleming-Dutra KE, et al. Variations in antibiotic and azithromycin prescribing for children by geography and specialty-United States, 2013. Pediatr Infect Dis J 2018;37:52-58.
25. Schroeder MR, et al. Macrolide resistance in *Streptococcus pneumoniae*. Front Cell Infect Microbiol 2016;6:98.
26. Bebear C, et al. *Mycoplasma pneumoniae*: susceptibility and resistance to antibiotics. Future Microbiol 2011;6:423-31.
27. Meyer Sauteur PM, et al. Infection with and carriage of *Mycoplasma pneumoniae* in children. Front Microbiol 2016;7:329.
28. Meyer Sauteur PM, et al. Survey of macrolide-resistant *Mycoplasma pneumoniae* in children with community-acquired pneumonia in Switzerland. Swiss Med Wkly 2014;144:w14041.
29. Wagner K, et al. Evaluation of Lightmix *Mycoplasma* macrolide assay for detection of macrolide-resistant *Mycoplasma pneumoniae* in pneumonia patients. Clin Microbiol Infect 2019;25:383.e5-e7.
30. Zimmermann P, et al. The immunomodulatory effects of macrolides-A systematic review of the underlying mechanisms. Front Immunol 2018;9:302.
31. Gardiner SJ, et al. Antibiotics for community-acquired lower respiratory tract infections secondary to *Mycoplasma pneumoniae* in children. Cochrane Database Syst Rev 2015;1:CD004875.
32. Biondi E, et al. Treatment of mycoplasma pneumonia: a systematic review. Pediatrics 2014;133:1081-90.
33. Spuesens EB, et al. Carriage of *Mycoplasma pneumoniae* in the upper respiratory tract of symptomatic and asymptomatic children: an observational study. PLoS Med 2013;10:e1001444.
34. Meyer Sauteur PM, et al. Diagnosis of *Mycoplasma pneumoniae* pneumonia with measurement of specific antibody-secreting cells. Am J Respir Crit Care Med 2019;200:1066-69.
35. Meyer Sauteur PM, et al. The art and science of diagnosing *Mycoplasma pneumoniae* infection. Pediatr Infect Dis J 2018;37:1192-95.
36. Lai WC, et al. A potent antibody-secreting B cell response to *Mycoplasma pneumoniae* in children with pneumonia. J Microbiol Immunol Infect 2022;55:413-20.
37. Tanigake A, et al. The bitterness intensity of clarithromycin evaluated by a taste sensor. Chem Pharm Bull (Tokyo) 2003;51:1241-5.
38. Dinos GP. The macrolide antibiotic renaissance. Br J Pharmacol 2017;174:2967-83.
39. World Health Organisation. Guideline on mass drug administration of azithromycin to children under five years of age to promote child survival. 2020. Available from: https://apps.who.int/iris/handle/10665/333942 (accessed January 17, 2024).
40. Ray WA, et al. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012;366:1881-90.
41. Mosholder AD, et al. Cardiovascular risks with azithromycin and other antibacterial drugs. N Engl J Med 2013;368:1665-8.
42. Gould IM. BTS guidelines on CAP. Community acquired pneumonia. Thorax 2002;57:657.
43. Meyer Sauteur PM, et al. Improved diagnostics help to identify clinical features and biomarkers that predict *Mycoplasma pneumoniae* community-acquired pneumonia in children. Clin Infect Dis 2020;71:1645-54.
44. Reimann HA. An acute infection of the respiratory tract with atypical pneumonia: A disease entity probably caused by a filtrable virus. JAMA 1938;111:2377-84.
45. Finland M, et al. Virus pneumonia II, primary atypical pneumonia of unknown etiology. N Engl J Med 1942;227:342-50.
46. Smith CB, et al. *Mycoplasma pneumoniae* infections in volunteers. Ann N Y Acad Sci 1967;143:471-83.
47. Smith CB, et al. Inactivated *Mycoplasma pneumoniae* vaccine. Evaluation in volunteers. JAMA 1967;199:353-8.
48. Fonseca-Aten M, et al. *Mycoplasma pneumoniae* induces host-dependent pulmonary inflammation and airway obstruction in mice. Am J Respir Cell Mol Biol 2005;32:201-10.
49. Jones HP, et al. Depletion of CD8+ T cells exacerbates CD4+ Th cell-associated inflammatory lesions during murine mycoplasma respiratory disease. J Immunol 2002;168:3493-501.

50. Tanaka H, et al. Relationships between radiological pattern and cell-mediated immune response in *Mycoplasma pneumoniae* pneumonia. Eur Respir J 1996;9:669-72.
51. Tanaka H, et al. Role of interleukin-18 and T-helper type 1 cytokines in the development of *Mycoplasma pneumoniae* pneumonia in adults. Chest 2002;121:1493-7.
52. Yang M, et al. Cytokine signatures associate with disease severity in children with *Mycoplasma pneumoniae* pneumonia. Sci Rep 2019;9:17853.
53. Panisova E, et al. *Mycoplasma pneumoniae*-specific IFN-gamma-producing CD4(+) effector-memory T cells correlate with pulmonary disease. Am J Respir Cell Mol Biol 2021;64:143-46.
54. Bacharier LB, et al. Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial. JAMA 2015;314:2034-44.
55. Magaret AS, et al. Long-term azithromycin use is not associated with QT prolongation in children with cystic fibrosis. J Cyst Fibros 2021;20:e16-e18.
56. Meyer Sauteur PM. Challenges and progress toward determining pneumonia etiology. Clin Infect Dis 2020;71:514-16.
57. Jain S, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med 2015;373:415-27.
58. Bergman M, et al. Macrolide and azithromycin use are linked to increased macrolide resistance in *Streptococcus pneumoniae*. Antimicrob Agents Chemother 2006;50:3646-50.
59. Neuman MI, et al. Emergency department management of childhood pneumonia in the United States prior to publication of national guidelines. Acad Emerg Med 2013;20:240-6.
60. Hauser C, et al. Serotype/serogroup-specific antibiotic non-susceptibility of invasive and non-invasive *Streptococcus pneumoniae*, Switzerland, 2004 to 2014. Euro Surveill 2016;21:21.
61. Fleming S, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011;377:1011-8.
62. Bradley JS, et al. Unique considerations in the evaluation of antibacterials in clinical trials for pediatric community-acquired pneumonia. Clin Infect Dis 2008;47 Suppl 3:S241-8.
63. Lu YJ, et al. Macrolide use shortens fever duration in *Mycoplasma pneumoniae* infection in children: a 2-year experience. J Microbiol Immunol Infect 2008;41:307-10.
64. Ambroggio L, et al. Comparative effectiveness of empiric beta-lactam monotherapy and beta-lactam-macrolide combination therapy in children hospitalized with community-acquired pneumonia. J Pediatr 2012;161:1097-103.
65. Evans SR, et al. Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR). Clin Infect Dis 2015;61:800-6.
66. Tsalik EL, et al. Efficacy and safety of azithromycin versus placebo to treat lower respiratory tract infections associated with low procalcitonin: a randomised, placebo-controlled, double-blind, non-inferiority trial. Lancet Infect Dis 2023;23:484-95.
67. Williams DJ, et al. Short- vs Standard-Course Outpatient Antibiotic Therapy for Community-Acquired Pneumonia in Children: The SCOUT-CAP Randomized Clinical Trial. JAMA Pediatr 2022;176:253-61.
68. Jacobs B, et al. Canadian Acute Respiratory Illness and Flu Scale (CARIFS): development of a valid measure for childhood respiratory infections. J Clin Epidemiol 2000;53:793-9.
69. Butler CC, et al. Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial. Lancet 2020;395:42-52.
70. Shoham Y, et al. Community-acquired pneumonia in children: quantifying the burden on patients and their families including decrease in quality of life. Pediatrics 2005;115:1213-9.
71. Narita M. Classification of extrapulmonary manifestations due to *Mycoplasma pneumoniae* infection on the basis of possible pathogenesis. Front Microbiol 2016;7:23.
72. Meyer Sauteur PM, et al. Frequency and clinical presentation of mucocutaneous disease due to *Mycoplasma pneumoniae* infection in children with community-acquired pneumonia. JAMA Dermatol 2020;156:144-50.
73. Liu TY, et al. Role of Biocard *Mycoplasma* immunoglobulin M rapid test in the diagnosis of *Mycoplasma pneumoniae* infection. Pediatr Respirol Crit Care Med 2018;2:7-10.

74. Meyer Sauteur PM, et al. Evaluation of IgM lateral flow assay as screening tool for *Mycoplasma pneumoniae* infection in childhood pneumonia. J Clin Microbiol 2020;58:e01498-20.
75. Kohns Vasconcelos M, et al. Randomised placebo-controlled multicentre effectiveness trial of adjunct betamethasone therapy in hospitalised children with community-acquired pneumonia: a trial protocol for the KIDS-STEP trial. BMJ Open 2020;10:e041937.
76. Grimes DA, et al. Refining clinical diagnosis with likelihood ratios. Lancet 2005;365:1500-5.
77. Fierz W, et al. Likelihood ratio approach and clinical interpretation of laboratory tests. Front Immunol 2021;12:655262.
78. SPIRIT group. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158:200-7.
79. Kutty PK, et al. *Mycoplasma pneumoniae* among children hospitalized with community-acquired pneumonia. Clin Infect Dis 2019;68:5-12.
80. Meyer Sauteur PM, et al. *Mycoplasma pneumoniae* genotypes and clinical outcome in children. J Clin Microbiol 2021;59:e0074821.
81. Beersma MF, et al. Evaluation of 12 commercial tests and the complement fixation test for *Mycoplasma pneumoniae*-specific immunoglobulin G (IgG) and IgM antibodies, with PCR used as the "gold standard". J Clin Microbiol 2005;43:2277-85.
82. International Conference on Harmonization. E2A Guideline for Clinical Safety Data Management. 1995. Available from: https://www.ema.europa.eu/en/ich-e2a-clinical-safety-data-management-definitions-standards-expedited-reporting-scientific (accessed March 31, 2023).
83. Kieser M. Multiple comparisons. Methods and Applications of Sample Size Calculation and Recalculation in Clinical Trials. Springer 2020;Multiple comparisons. 2020.133-56.
84. Chow S-C, et al. Sample size calculations in clinical research. 2nd ed. Biostatistics Series, Chapman & Hall/CRC 2008;Sample size calculations in clinical research. 2008.
85. ESCMID. Guideline for the management of acute sore throat. Clin Microbiol Infect 2012;18 Suppl 1:1-28.
86. Kaye KS, et al. Measuring acceptable treatment failure rates for community-acquired pneumonia: potential for reducing duration of treatment and antimicrobial resistance. Infect Control Hosp Epidemiol 2008;29:137-42.
87. Pernica JM, et al. Short-course antimicrobial therapy for pediatric community-acquired pneumonia: the SAFER randomized clinical trial. JAMA Pediatr 2021;175:475-82.
88. CPMP. Points to consider on switching between superiority and non-inferiority. Br J Clin Pharmacol 2001;52:223-28.
89. Friede T, et al. Blinded sample size reestimation in non-inferiority trials with binary endpoints. Biom J 2007;49:903-16.
90. van Buuren S, et al. mice: Multivariate imputation by chained equations in R. J Stat Softw 2011;45:1-67.

17. APPENDICES

Documents that do frequently change during the course of the study, will be mentioned as “documents provided separately” and listed here:

17.1 IMP: Summary of product characteristics (SPC)

Appendix 1.1: Azithromycin Pfizer®, Pfizer SPC, Swissmedic (accessed July 6, 2023).

Appendix 1.2: Zithromax®, Pifzer SPC, FDA (accessed July 6, 2023).

17.2 Parameter list for electronic case report form (eCRF)

Appendix 2: Parameter list, Version 1.2, January 17, 2024.

17.3 Patient information and informed consent forms

Patient information and informed consent forms for children (11-13 years), adolescents (14-17 years), and parents separately for each participating site in the corresponding language.

17.4 QoL questionnaire

Appendix 4.1: PedsQL™ Pediatric Quality of Life Inventory, Version 4.0, Parent report for children (ages 8–12).

Appendix 4.2: PedsQL™ Family Impact Module, Version 2.0, Parent report.