

BMJ Open 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

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ABSTRACT

Introduction Community-acquired pneumonia (CAP) causes around 10 hospitalisations per 1000 child-years, each associated with an average 13 non-routine days experienced and more than 4 parent workdays lost. In adults, steroid treatment shortens time to clinical stabilisation without an increase in complications in patients with CAP. However, despite promising data from observational studies, there is a lack of high-quality evidence for the use of steroids.

Methods and analysis The KIDS-STEP trial is a multicentre, randomised, double-blind, placebo-controlled superiority trial of betamethasone treatment on outcome of hospitalised children with CAP. Children are enrolled in paediatric emergency departments of hospitals across Switzerland and randomised to adjunct oral betamethasone for 2 days or matching placebo in addition to standard of care treatment. The co-primary outcomes are the proportion of children clinically stable 48 hours after randomisation and the proportion of children with CAP-related readmission within 28 days after randomisation. Secondary outcomes include length of hospital stay, time away from routine childcare and healthcare utilisation and total antibiotic prescriptions within 28 days from randomisation.

Each of the co-primary outcomes will be analysed separately. We will test clinical stability rates using a proportion test; to test non-inferiority in readmission rates, we will construct $1-\alpha$ % CI of the estimated difference and test if it contains the pre-defined margin of 7%. Success is conditional on both tests. A simulation-based sample size estimation determined that recruiting 700 patients will ensure a power of 80% for the study.

Ethics and dissemination The trial protocol and materials were approved by ethics committees in Switzerland (lead: Ethikkommission Nordwest und Zentralschweiz) and the regulatory authority Swissmedic. Participants and caregivers provide informed consent prior to study procedures commencing. The trial results will

Strengths and limitations of this study

- This well-powered multi-centre trial will provide high-quality evidence on efficacy of adjunct steroid treatment for uncomplicated community-acquired pneumonia (CAP) in children.
- Because clinically defined CAP contains mixed severities and aetiologies, overall results may miss divergent effects in specific subpopulations.
- Despite exclusion of children with alternative diagnoses, a clinical diagnosis may have limited specificity for CAP.
- The pragmatic approach to eligibility employed by the KIDS-STEP trial is aligned with clinical practice and so will facilitate rapid knowledge translation.
- The generalisability of the KIDS-STEP trial findings will be maximised by the wide age range and the diverse aetiology of CAP in the enrolled population.

be published in peer-reviewed journals and at national and international conferences. Key messages will also be disseminated via press and social media where appropriate.

Trial registration number NCT03474991 and SNCTP000002864.

INTRODUCTION

The incidence of community-acquired pneumonia (CAP) in young children remains high (30–40/1000 child-years) even in high-income settings with routine pneumococcal vaccination, and is associated with a high rate of hospitalisation (around 10/1000 child-years).¹ In low-income and middle-income settings, pneumonia is the leading infectious cause of death in children less than 5 years of



age.² In high-income settings, working mothers of children hospitalised with CAP have been reported to lose on average 4.2 workdays compared with 1.7 workdays for children with CAP managed in primary care.³ In addition to this economic burden, there is a substantial impact on quality of life for the affected child and the family.³ Children who are admitted with CAP experience on average 13 non-routine days as judged by their parents or caregivers when assessed with a standardised quality of life questionnaire. Periods of decreased appetite (8.5 days), disordered sleep (4.5 days) and the absence from routine out-of-home childcare (7.5 days) were slightly shorter.³ Any intervention that ensures rapid clinical stabilisation allowing for early hospital discharge without negative impacts on the overall recovery in children hospitalised with CAP would, therefore, carry substantial socioeconomic benefits.

Adjunct systemic corticosteroids shorten the time until clinical stability is reached in adult patients.⁴ Comparable data for paediatric patients applicable to an unselected group of children with moderate–severe CAP are not available. The most recent Cochrane meta-analysis found evidence for a benefit from steroid treatment, but for children this was based on a small number of very heterogeneous and mostly unblinded trials aiming to investigate the efficacy of steroids in pneumonia with detection of specific pathogens, for example, *Mycoplasma pneumoniae* or respiratory syncytial virus (RSV).⁵

Infection-related unwanted effects of adjunct steroids are potentially relevant in the context of childhood CAP. A higher proportion of children hospitalised with CAP reaching early clinical stability would only be desirable if this would not to be offset by a higher rate of clinically relevant CAP recurrence. A rebound phenomenon after corticosteroid discontinuation has been postulated to explain a higher rate of infection recurrence (19% compared with 9% in placebo group) among adults.⁶ Data from a recent individual patient's data meta-analysis, however, indicate that an increased risk of CAP recurrence may be observed,⁷ potentially associated with a longer duration of adjunct steroids in adults with CAP. To the best of our knowledge, the question about the effect of adjunct steroid treatment in childhood CAP in relation to a postulated rebound phenomenon measured clinically as CAP recurrence has not been formally addressed in a trial. CAP-specific readmission rates for children are low at around 5%.^{8,9} In bronchiolitis, another acute lower respiratory tract infection for which oral corticosteroid treatment has been investigated, an increased risk of hospital revisits associated with steroid treatment could not be identified in a Cochrane meta-analysis.¹⁰

WHO has identified studies on the effect of steroids in the novel COVID-19 as a priority during the current pandemic.¹¹ While there is no evidence suggesting a harmful effect of steroids on paediatric patients, studies in adults have identified a longer duration of viral shedding after steroid treatment as a potential adverse effect in other coronaviruses.¹²

The **primary objective** of the trial is to concurrently evaluate:

- ▶ Whether treatment of children hospitalised for CAP with oral betamethasone is superior to placebo in terms of the proportion of children reaching clinical stability (defined as ready for discharge or with normal vital signs) at 48 hours after hospitalisation.
 - ▶ Whether inpatient treatment of childhood CAP with oral betamethasone is non-inferior to placebo in terms of the proportion of children with CAP-related readmission to hospital up to 28 days after randomisation.
- Secondary objectives** include the evaluation of effects of oral betamethasone treatment (vs placebo) in children hospitalised for CAP on:
- ▶ Duration of primary hospital stay.
 - ▶ Severity and duration of CAP symptoms.
 - ▶ Parental absence from work and/or child absence from routine out-of-home care or school.
 - ▶ Overall duration of antibiotic exposure and inpatient days during the follow-up period.
 - ▶ Intensive care unit admissions.
 - ▶ Mortality.
 - ▶ Rate and severity of solicited clinical adverse events.

METHODS AND ANALYSIS

KIDS-STEP is a phase III strategic investigator-initiated, randomised, placebo-controlled, fully blinded, multi-centre superiority trial with two parallel groups. Eligible children aged 6 months to less than 14 years and hospitalised with CAP at participating sites are randomised 1:1 to receive either adjunct oral betamethasone 0.1–0.2 mg/kg per day for 2 days (Celestamine, a liquid formulation; 0.5 mg/mL betamethasone) or to receive oral placebo (matched in aspect, taste and dose) for 2 days in addition to regular standard of care. Dosing is done by 5 kg weight bands (table 1). Randomisation is stratified by site. Data on on-going symptoms and healthcare services utilisation are collected daily until discharge from hospital and during three telephonic follow-up visits up to and including at 4 weeks. While in hospital, vital signs and

Table 1 Dosing table for dose selection of betamethasone and placebo solutions

Weight band	Weight range (kg)	Milligrammes per dose	Millilitres per dose
0	≥5–<7	1.0	2
1	≥7–<10	1.5	3
2	≥10–<15	2.0	4
3	≥15–<20	2.5	5
4	≥20–<25	3.0	6
5	≥25–<30	3.5	7
6	≥30–<35	4.0	8
7	≥35–<40	4.5	9
8	≥40–<45	5.0	10

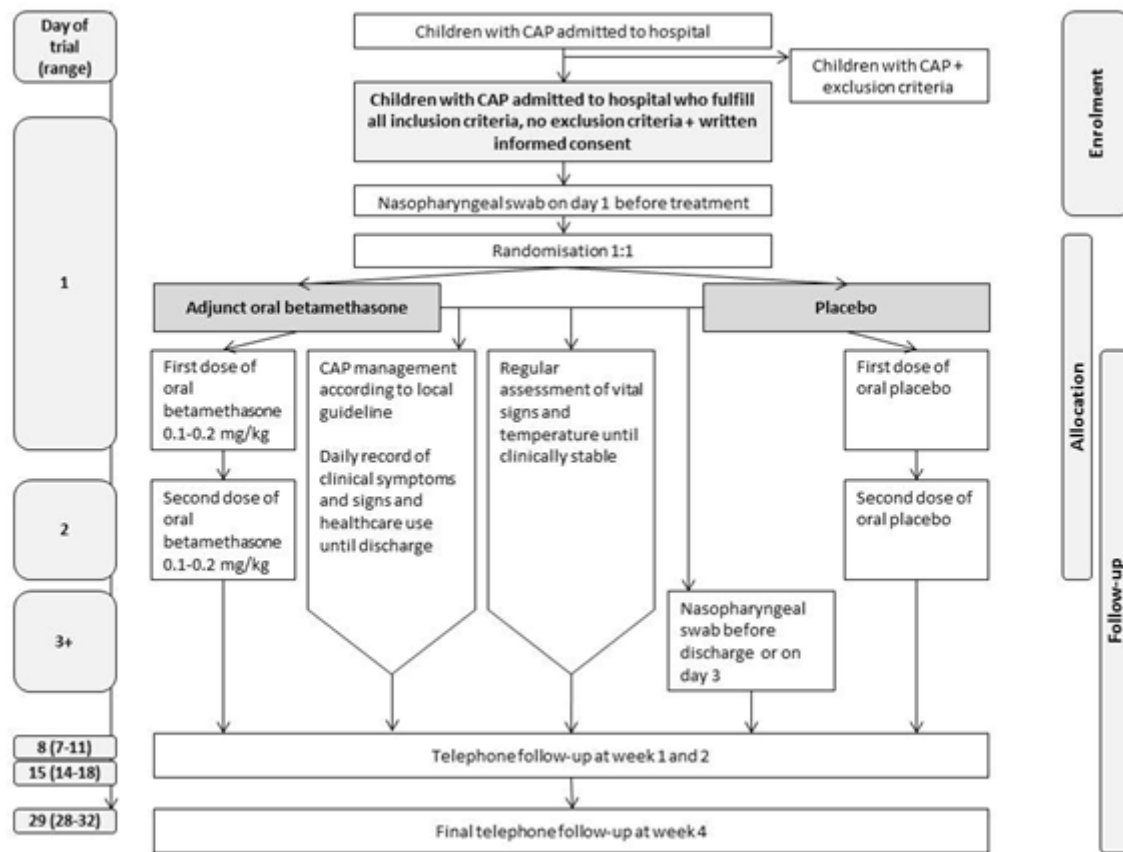


Figure 1 Trial flowchart. CAP, community-acquired pneumonia.

temperature are assessed at least every 8 hours. A trial flow chart is presented in [figure 1](#).

Trial setting

KIDS-STEP recruits participants in paediatric emergency departments of secondary and tertiary hospitals across Switzerland where potentially eligible patients present and can be admitted for inpatient care. Participants are recruited throughout the year.

Trial population

Children from age 6 months weighing at least 5 kg and up to a body weight of 45 kg admitted to one of the participating sites with signs and symptoms of CAP are considered potentially eligible for participation. Eligibility criteria are listed in [table 2](#).

Screening, recruitment and consent

Information material for KIDS-STEP for participating sites includes posters placed in the waiting areas of the emergency department and a short informational film. A KIDS-STEP website will further be created with public and member-only areas. Any information material reviewed and endorsed by the relevant ethics committee will be deposited in the publicly accessible area of the KIDS-STEP website.

Eligible children are identified in the emergency department when the decision to admit for CAP has been made by the treating physician. A screening log is kept at each site to document all children admitted for CAP. All children are assessed against the inclusion and exclusion criteria as listed above, and are considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria. There are no exceptions to eligibility requirements at the time of randomisation. Eligibility is reviewed and documented by an appropriately qualified member of the investigator's study team (a clinician or nurse who has been trained in study procedures and has been delegated the responsibility by the site principal investigator) at each participating site before children are randomised into the study.

Written informed consent for the child to enter into the trial and be randomised must be obtained from the parent or guardian and where appropriate the participant after explanation of the aims, methods, benefits and potential hazards of the trial and before any trial-specific procedures are performed. Consent may only be obtained once eligibility has been confirmed. The English-language version of the participant information and informed consent form is available as an online supplement to this article. A trial register is kept at each

Table 2 Eligibility criteria**Inclusion criteria (all must be fulfilled)**

At least 6 months of age and less than 14 years of age	A. Temperature $\geq 38^{\circ}\text{C}$ measured by any method or history of fever in last 48 hours reported by parents and
Body weight between 5 kg and 45 kg	B. at least two of the following signs and/or symptoms:
Admission to hospital (ie, assignment of an inpatient case number or receipt of in-hospital treatment in a designated short stay unit)	▶ The presence of cough (observed or reported in last 72–96 hours)
Clinical diagnosis of CAP (A. and B., right column)	▶ Increased age-specific respiratory rate as defined by American Heart Association's accredited Pediatric Advance Life Support guidelines during assessment in the paediatric emergency department (first or second triage or clinical examination)
Parent and/or child (as age appropriate) willing to accept all possible randomised allocations and to be contacted for three telephonic follow-up visits up to and including at 4 weeks after randomisation	▶ Hypoxaemia ($<92\%$ arterial oxygen saturation) in room air as measured by pulse oximetry (SpO_2) ^{36 37}
Informed consent form for trial participation signed by participants and/or caregivers	▶ Signs of laboured/difficult breathing, including nasal flaring, chest retractions, grunting, abdominal breathing and shortness of breath
	▶ Clinical signs of lobar pneumonia, including focal dullness to percussion, focal reduced breath sounds and crackles with asymmetry

Exclusion criteria (excluded if any of the following are present)

- ▶ The presence of local complications (empyema or pleural effusion with clinically identified need for drainage, pneumothorax and pulmonary abscess)
- ▶ Chronic underlying disease associated with an increased risk of very severe CAP or CAP of unusual aetiology, such as sickle cell disease, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis
- ▶ Bilateral wheezing without focal chest signs and clinical indication for primary administration of steroids (most likely to represent respiratory tract infection affecting the medium airways, ie, not pneumonia)
- ▶ Admission to hospital with a primary clinical diagnosis of bronchiolitis
- ▶ Inability to tolerate oral medication
- ▶ Documented allergy or any other known contraindication to any trial medication
- ▶ Subacute or chronic conditions requiring higher betamethasone equivalent or known primary or secondary adrenal insufficiency
- ▶ Known diabetes mellitus (type 1)
- ▶ Hospitalisation within the last 2 weeks preceding current admission with the possibility that pneumonia could be hospital-acquired or healthcare-associated
- ▶ Completion of a course of systemic corticosteroids within 2 weeks from enrolment for courses of >5 days
- ▶ Transfer for any reason to a non-participating hospital directly from the paediatric emergency department
- ▶ Parents are unlikely to be able to reliably participate in telephone follow-up because of significant language barriers
- ▶ Participation in another study with an investigational drug within the 30 days preceding and during the present study
- ▶ Previous enrolment into the current study
- ▶ Enrolment of the investigator, his/her family members and other dependent persons

CAP, community-acquired pneumonia.

site listing the trial ID numbers to be used. The date of randomisation is added to the register.

Randomisation and blinding

Treatment assignment is sequential, through the dispensation of trial medication. Centre-specific randomisation lists were prepared in advance following a big stick design with a maximum tolerated imbalance of three patients.¹³ Randomisation lists were constructed by an independent statistician at the Clinical Trial Unit of the University Hospital Basel and conveyed to the Pharmaceutical Unit at the University Hospital Basel, which prepared the trial medication. Randomisation lists are kept concealed at the trial pharmacy. Each bottle has a unique code and this is entered into the trial database under the participant's trial ID.

Blinding is ensured through the use of placebo, which is indistinguishable from the active treatment in any way but the active ingredient. All caregivers (including nurses and treating physicians), the patients and their parents, the investigators, the outcome assessors and the data analysts are blinded to the allocated treatment.

We envisage optimal blinding because the active drug is a product not widely used in Switzerland with very little advance knowledge of the aspect, taste and texture of the product and individual patients are receiving either active treatment or placebo with no cross-over.

Outcome measures and assessments

The co-primary outcomes are:

- ▶ The proportion of children clinically stable at 48 hours after randomisation in the active treated group

Box 1 Secondary outcomes

- ▶ Time to hospital discharge after index hospitalisation in days.
- ▶ Time away from routine childcare and/or pre-school/school (for participating children) and away from work (for parents) in days up to 28 days after randomisation.
- ▶ Total antibiotic exposure in days up to 28 days after randomisation.
- ▶ Total duration of hospitalisation in days up to 28 days after randomisation.
- ▶ Proportion of children (re)treated with antibiotics after discharge for any reason at 28 days after randomisation.
- ▶ Proportion of children admitted to intensive care during the initial hospitalisation and up to 28 days after randomisation.
- ▶ Proportion of children experiencing solicited side effects of the trial treatment and/or serious adverse events.
- ▶ Duration of individual moderate–severe CAP symptoms in days assessed by a telephone questionnaire at week 1, 2 and 4 after randomisation.
- ▶ Mortality up to 28 days after randomisation.

(oral betamethasone for 2 days) as compared with the control group (placebo) (efficacy).

- ▶ The proportion of children with CAP-related readmission within 28 days after randomisation comparing oral betamethasone and placebo (safety).

Clinical stability is defined as the clinician assessing the child as being ready for hospital discharge and/or recorded normal respiratory rate, heart rate and oxygen saturation. Children discharged before 48 hours after randomisation are assumed to be clinically stable at 48 hours as per last clinician assessment. For respiratory rate and heart rate, at least two consecutive age-related normal values as specified in the American Heart Association's accredited Pediatric Advance Life Support documentation is taken to indicate stability. Arterial oxygen saturation in room air of 92% or above measured by pulse oximetry is considered normal.

CAP-related readmissions are recorded by active surveillance at participating centres and in addition identified through parental reporting.

Additional outcomes (box 1) are captured to further evaluate the efficacy and safety of adjunct oral steroids in the management of childhood CAP.

Trial visit and contact schedules are prepared for each child at randomisation and children are followed on that same schedule until the final follow-up visit regardless of adherence to trial medication. The schedule defines visit times (with windows) necessary for data collection. An overview of trial contacts is given in figure 2.

Sample size and power

A simulation approach was used to estimate the sample size required. Each sample size $n_{i=1, \dots, 43} = 580, \dots, 748$ was evaluated by simulating 9999 times n_i individual patients. Events were simulated once for the proportion of 48 hours clinically stable patients and once for the rate of CAP-related readmission, from binomial distributions assuming the two event types are correlated with a

correlation coefficient ρ . For each simulation run, each co-primary objective was tested with a two-sided type-I error level of $\alpha=0.05$. Since the trial's success is defined as showing a successful result in both co-primary endpoints, no correction for multiplicity is required.

To test the superiority of the active treatment arm over the placebo arm with regards to the proportion of patients achieving clinical stability within 48 hours, Pearson's χ^2 test with Yates continuity correction was applied in each simulation run. To examine the influence of the actual difference in rates on sample size, simulations were performed with effect sizes (absolute difference $\varpi_{\text{stability-A}} - \varpi_{\text{stability-P}}$) ranging from 5% to 15%.

To test the non-inferiority of the active versus the placebo with regards to hospital readmission rates, we constructed in each simulation run the $1-\alpha$ % CIs for the difference in rates, using a continuity-corrected modification of Wilson score method.¹⁴ Non-inferiority was determined if the upper bound of the CI lay below the specified non-inferiority margin $\delta=7\%$. The chosen non-inferiority margin was based on clinical relevance and decided by the investigators.

Assuming an absolute difference of 10% between study arms in terms of the first co-primary endpoint, it was assumed that 80% and 70% of children will achieve clinical stability within 48 hours in the active and placebo arms, respectively. In addition, it was assumed that CAP-related rehospitalisation within 28 days is 5% for both study arms. Finally, it was assumed that the correlation between both endpoints is 0.8, which simulations showed to be the most conservative assessment, leading to the highest sample size (figure 3).

Under these assumptions, 700 patients need to be recruited to the study—for both arms combined—to ensure 664 patients for the non-inferiority test, while allowing 5% of drop-out.

The incidence rates of the co-primary endpoints are difficult to estimate in advance. A substantial deviation from the assumed rates may lead to an inappropriate sample size due to the critical dependency of the sample size estimation on the assumed rates. To counter this problem, a sample size re-estimation¹⁵ will be performed in a blinded manner once a substantial proportion of the patients have been recruited and information on both co-primary endpoints has been collected. The blinded sample size re-estimation (often referred to as an internal pilot design) allows adjusting the sample size in case the actual rate of events differs substantially from the assumptions taken.

For the sample size re-estimation, the overall (ie, not treatment arm specific) rates of achieving clinical stability and of readmission will be estimated in a treatment-blind fashion. The sample size estimation procedure, as described above, will be repeated with the updated assumptions. If, based on the newly collected data, a larger sample size is required for the study, the overall sample size will be increased to the new number, preserving

ASSESSMENTS Face to face Telephone Face to face or Telephone Days in trial	DAYS IN TRIAL (telephone follow-up visits -1 to +3 days)								
	Enrol- ment	Rando- misation	Postallocation					Close- out	Unscheduled or End-of-Study visit
			1	2	3	4+	8		
Trial participation									
Eligibility screen	X								
Parent/Guardian/Child information sheet	X								
Informed consent	X								
Drug supply dispensing		X							
Administration of first dose of trial medication		X							
Administration of second dose of trial medication			X						
Clinical assessment									
Medical history		X							
Physical examination		X							X°
Vital signs and temperature		X	X	X	X*				X°
Symptoms and clinical signs record		X	X	X	X*	X	X	X	X
Concomitant care/healthcare utilisation record		X	X	X	X*	X	X	X	X
Laboratory assessment									
Nasopharyngeal specimen		X			X§				(X°)
Haematology	(X)	(X)							(X)
Biochemistry	(X)	(X)							(X)
Virology	(X)	(X)							(X)
Radiological assessment									
Chest X-ray	(X)	(X)							(X)
Sub-studies									
Diagnostics: Expired air sample			X	X					
Diagnostics: Antibody- secreting cell (ASC) response to infection		X		X				X	
COVID-19: Duration of virus shedding						X	X		

Figure 2 Trial schedule: X* indicates to be collected, if child is still in hospital and until discharge home. X§ indicates to be collected before discharge home. (X) indicates tests that may be done if the child's condition requires it or allows it but are not mandatory. X° indicates tests to be done if visit is face to face.

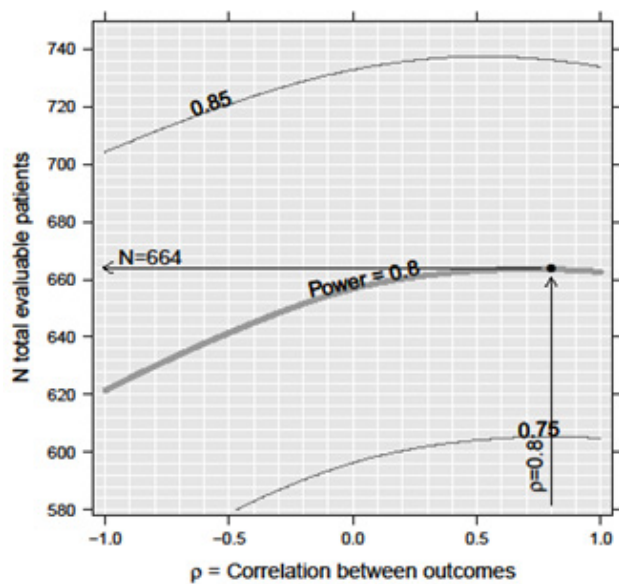


Figure 3 Required sample size simulations for different strengths of correlation between the primary endpoints.

the study's power. If the newly calculated sample size is smaller or equal to the originally calculated sample size, no changes will be made in the study's sample size.

The sample size re-estimation will be performed after 80% of the patients have been recruited and data on both co-primary endpoints collected, or after a seasonality peak in recruitment is finished (ie, spring) and at least 65% of patients have been recruited. Recruitment may be extended if the sample size re-estimation suggests that an increased sample is necessary.

Analysis plan

The analysis will be performed by the trial statistician using the R language and environment for statistical computing (V.3.6 or higher). Reporting will follow the Consolidated Standards of Reporting Trials guidelines.

The All Randomised Set (ARS) will consist of all patients randomised to the study; protocol violations will be disregarded in this data set.

The complete follow-up (CFUP) set will consist of all patients randomised to the study who were not lost to follow-up after 28 days; patients with major protocol violations will be excluded from this set.

The study has two co-primary endpoints, each analysed separately:

Stability rate: the proportion of children achieving clinical stability within 48 hours post randomisation.

Readmission rate: the proportion of children readmitted to hospital within 28 days post randomisation.

The treatment is declared successful on showing success for both endpoints together. Each endpoint will be analysed and tested separately using a type-I error rate level of $\alpha=0.05$.

Rates of achieving clinical stability will be calculated for each study arm, and the risk difference between them reported with 95% CI. A logistic regression model will be fit with study arm as fixed predictor to compare the odds of achieving clinical stability between the study arms. An OR, risk differences and respective 95% CIs will be presented. The superiority analysis will be performed on the ARS and based on the intention to treat principle.

To test the non-inferiority of the active treatment compared with placebo treatment with regards to readmission rates, the 95% CI of the difference between the two rates ($p_{\text{readmission-A}} - p_{\text{readmission-P}}$) will be calculated and compared with the predefined non-inferiority margin ($\delta=7\%$). Non-inferiority of the treatment will be declared if the upper bound of the 95% CI is smaller than the non-inferiority margin. The non-inferiority analysis will be performed on the CFUP set based on the principle that this is the more conservative approach in a non-inferiority analysis.

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

Careful trial planning and conduct minimise the occurrence of missing data as far as possible.

For the ARS, missing values will be replaced by multiple imputation using chained equations based on predefined baseline characteristics.

The analyses described above of ARS data will be performed on each imputed data set, and results combined using Rubin's rule for multiple imputation.

As a sensitivity analysis, the primary analysis will be repeated for each of the co-primary endpoints using the alternative analysis set: for superiority using the CFUP set and for non-inferiority using the ARS.

A detailed analysis plan for all secondary objectives will be finalised before the trial's database closure and will be under version control at the Clinical Trial Unit, University of Basel.

Ancillary and substudies

Substudies will have their own analysis plans, which will be finalised before the respective databases are locked.

Ancillary study: impact on nasopharyngeal microbiology:

Given the expected immunomodulatory effects of adjunct corticosteroids, different patterns of change in viruses and bacteria in the airways may be observed in children exposed to betamethasone and placebo. This ancillary study will, therefore, evaluate changes in the presence and load of viruses and bacteria in the nasopharynx during adjunct corticosteroid treatment, comparing baseline and pre-discharge nasopharyngeal samples.

Substudy 1: exhaled air pneumonia diagnostics:

Definitive identification of a causative agent in childhood CAP is hindered by the fact that significant samples cannot generally be obtained from the lower airways and the relevance of pathogens detected in upper airways secretions is not always clear. This substudy will, therefore, evaluate a novel non-invasive diagnostic method (mass spectrometry of exhaled air) to determine the relationship between pathogen identification in nasopharyngeal samples by PCR and mass spectrometry of exhaled air.

Substudy 2: antibody-secreting cell (ASC) response to infection:

Determining the causative pathogen of childhood CAP is complicated by the low yield of blood cultures and difficulty obtaining specimens from the lower respiratory tract of children.¹⁶ Therefore, clinicians attempt to detect potential pathogens in upper respiratory tract (URT) specimens. However, PCR of URT samples and immunoglobulin M (IgM) serology are unreliable in differentiating infected patients and carriers suffering from CAP caused by several pathogens.^{16 17} We recently demonstrated that the detection of pathogen-specific IgM ASCs using the enzyme-linked immunospot assay differentiated between *M. pneumoniae* infection and carriage.¹⁸ *M. pneumoniae*-specific IgM ASCs were detected only for a few days or weeks after symptom onset, while *M. pneumoniae*'s DNA in the URT and/or specific IgM in serum persisted for months.¹⁹ Therefore, pathogen-specific ASCs may be an optimal target for determining disease aetiology in childhood CAP. The objective of this substudy is to evaluate the presence and kinetics of pathogen-specific ASCs against several CAP pathogens in patients of the KIDS-STEP study, and to compare ASCs to DNA/RNA load in URT and serum antibody levels.

Substudy 3: duration of viral shedding in children tested positive for SARS-CoV-2

Evidence from observational studies in adults showed a longer duration of virus shedding in lower airways after prolonged treatment with steroids during infections with related SARS-CoV-1 or MiddleEast respiratory syndrome-related coronavirus.^{20 21} Lower airway shedding has low impact on transmission but extended upper airway shedding would be an important finding for infection control strategies. In children tested positive for SARS-CoV-2 in the URT at admission or during the initial hospitalisation, the proportion of children with persistent detection of SARS-CoV-2 at 1 week and 2 weeks after randomisation will be assessed.

Substudy 4: acceptability of and information recall after video-supported informed consent

Audiovisual aids for informing patients, parents and the general public are increasingly used in clinical research.^{22 23} Although they are widely accepted to be beneficial, little evidence exists on their effectiveness

and the way they work. The substudy aims at comparing parental information recall on the key study aspects and assessing the acceptability of the informational video. A standardised questionnaire with six knowledge and three perception items is added to the telephone follow-up at 1 week for all parents.

Monitoring

Representatives of the trial management team and a designated external study monitor from the Clinical Trial Unit, University of Basel, conducted a site initiation visit at each study site to inspect the site facilities, verify qualifications of the local investigators and inform the local teams of responsibilities and the procedures for ensuring adequate and correct documentation and use of the electronic data capture system as well as providing training on implementing all trial activities.

In addition, the study monitor will conduct three routine monitoring visits per site, the first after inclusion of 5–10 participants, the second after inclusion of 40–50 participants and the third after inclusion of the last participant, as well as a site closure visit together with representatives of the trial management team at the end of the study to resolve any remaining queries.

The local investigators ensure that source data and documents are made accessible to the study monitor and answer questions posed by the study monitor.

An independent data monitoring committee (IDMC) composed of external experts monitors the accrued data for arising evidence for treatment harm. Additional roles for the IDMC include consideration of implications of arising external evidence for safety and trial continuation, as well as advising on protocol modifications proposed by the investigators.

In accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines,²⁴ audits may be performed by the ethics committee and competent authority during the course of the study.

ETHICS AND DISSEMINATION

Ethical and regulatory compliance

Prior to study conduct, protocol, proposed patient information, consent form and other study-specific documents were approved by the local ethics committee of the trial centre (Ethikkommission Nordwest und Zentralschweiz, study no. 2018–00563), other local ethics committees in Switzerland for participating sites and Swissmedic (2018 DR 3070).

The study category under Swiss law is class C, that is, the drug under investigation is not licensed in Switzerland. However, celestamine is licensed for medical use in Germany, including recommendations for use in children.

This study is registered on <https://clinicaltrials.gov> (NCT03474991) and on the Swiss National Clinical Trials Portal (SNCTP000002864).

The study is carried out according to the protocol and with principles enunciated in the current version of the Declaration of Helsinki,²⁵ the guidelines of GCP issued by ICH,²⁴ the European Directive on medical devices 93/42/EEC and the ISO Norm 14155,²⁶ and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements. The lead ethics committee and regulatory authorities receive annual safety and interim reports and will be informed about study stop/end in agreement with local requirements.

Patient and public involvement

This protocol was written without patient involvement. Patients or guardians were not invited to comment on the study design or to contribute to the writing or editing of this document for readability or accuracy.

Dissemination of results

The data from all centres will be analysed together and published as soon as possible in peer-reviewed journals, as well as being presented at national and international conferences.

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 in Europe. The work will be presented at key medical conferences. To maximise the impact of the trial across Europe, its findings will be disseminated more widely through abstracts for oral and poster presentations submitted to some of the main relevant national and international conferences.

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 organisations 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 European media, to encourage press coverage. This will enable a wider audience to be reached.

TRIAL STATUS AND DISCUSSION

The first participant was enrolled in October 2018. Currently, 141 children have been enrolled in the trial. Follow-up has been completed for 138, with the remaining 3 still being within the 4-week follow-up interval. Recruitment accrual is at 36% of target, mainly due to (1) late/stepwise opening of several study sites, (2) slow performance in the first winter season and (3) complete absence of recruitment during the COVID-19 lockdown in Switzerland (March–April 2020). Between December 2019 and March 2020, actual recruitment has exceeded pre-trial projections. Recruitment is projected to be complete in late 2021. There has not been any loss to follow-up. Until publication, no emergency unblinding of any participants occurred.

Only few small trials have addressed the potential impact of oral steroid treatment in CAP during childhood.⁵ Nagy *et al* reported a significant reduction in fever duration (2 days vs 4 days) and length of stay (11 days vs 16.5 days) in children with severe CAP receiving methylprednisolone for 5 days compared with children receiving placebo in a randomised trial with 59 participants.²⁷ A randomised trial comparing adjunct dexamethasone or methylprednisolone against standard of care (no placebo) planning to enrol 40 participants was being set up but has been withdrawn prior to recruitment.²⁸ A placebo-controlled randomised trial of adjunct corticosteroids in CAP complicated by pleural effusion and/or empyema with 56 participants has been completed,²⁸ but has not yet reported on its findings. An observational analysis using propensity scores found that adjunct corticosteroids were associated with a shorter hospital stay only in children also receiving beta-agonist therapy, concluding that any benefit might only be seen in children with acute wheezing.²⁹ At the same time, children without beta-agonist therapy experienced longer hospital stays and increased rates of readmission when treated with steroids in this study. However, one-third of children with steroid treatment received long-term medication for asthma, and both intensive care unit admission and invasive ventilation were significantly more frequent in the steroid group. The stratified analysis comparing steroid effects between beta-agonist co-treatment positive and negative children was unadjusted for these factors, leading to the conclusion that the steroid group may have consisted of subgroups of (a) asthmatic children, that would respond well to steroids, and (b) non-asthmatic children that were more severely ill than children not treated with steroids and that would be less likely to be co-treated with beta-agonists. Thus, the different effect of steroids in children with or without treatment with beta-agonists may simply reflect very different patient groups with different decision criteria for steroid treatment. A subgroup analysis in another retrospective study with 2000 children with CAP found that the risk for treatment failure, defined as switch to another antibiotic therapy regimen than initially prescribed, was higher in non-asthmatic children with CAP when treated with adjunct steroids.³⁰ However, in this subgroup, only 5% of children received steroids and again residual confounding is likely to limit the conclusions that can be drawn. All in all, there is a lack of randomised controlled trials with sufficient power and high external validity to provide a definitive answer to the question of the effect of adjunct steroids in children hospitalised with CAP. Betamethasone was selected as the investigational drug because it is the steroid most widely used in respiratory conditions in the trial setting. A 2016 Cochrane review on steroids in asthma identified only one comparative trial on the use of different steroids in children.³¹ There was no difference in effect of relative strength adjusted doses of dexamethasone and prednisolone. Betamethasone and dexamethasone have comparably high glucocorticoid activity. We, therefore, expect the findings to be transferable to the use of lower potency steroids.



In contrast to previous trials, we chose clinical stability at 48 hours as the endpoint for superiority. Clinical stability is relevant to patients and their families as a prerequisite for hospital discharge and can have considerable socio-economic impacts on the child and parents by allowing a return to normal activity for the whole family. A rapid recovery with no respiratory problems and no need for supplemental oxygen represents directly patient-relevant components of this outcome.

The average length of stay of hospitalised children with CAP is 2 days and by 3–4 days more than 75% of children with this diagnosis have been discharged home.^{32 33} This reflects the relatively rapid recovery of children with CAP compared with adults. An early assessment of clinical stability at 48 hours has, therefore, been selected to be of main interest.

Following WHO's recommendation to not routinely administer steroids in patients with suspected or confirmed COVID-19, we were initially facing concerns on whether to keep the trial open during the pandemic. Russell *et al* reviewed the evidence on use of steroids in relation to COVID-19 and concluded that the evidence at the beginning of the pandemic did not support steroid administration.¹² The only paediatric evidence included in this review was a study on RSV and corticosteroids and it showed neither a beneficial nor a detrimental effect.³⁴

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial provided evidence for a benefit of steroids in hospitalised COVID-19 patients.³⁵ Although this trial did not exclude children, the average age of participants was around 65 years and only few paediatric patients were included. While this evidence is not yet sufficiently conclusive to support routine administration of corticosteroids to paediatric COVID-19 patients, it is clear that their use may be an important adjunct therapy for the disease.

Paediatric CAP is a common condition with diverse aetiology. Although lethality in high-resource settings is low, an adjunct therapy reducing length of hospital stay and shortening the duration of symptoms has a high potential to reduce strain on healthcare resources and improve children's and parents' well-being. The KIDS-STEP trial will provide conclusive evidence on the effectiveness and safety of steroids for this purpose.

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