Clinical trial results:
Optimising effectiveness and minimising toxicity of intravenous salbutamol in children with acute asthma

Summary

EudraCT number	2014-002996-27
Trial protocol	GB
Global end of trial date	30 June 2017

Results information

Result version number	v1 (current)
This version publication date	13 October 2018
First version publication date	13 October 2018
Summary attachment (see zip file)	13CC34 Final Study Report and Results (Clinical Study Report_v1.5 - 13CC34 (Salbutamol PKPD).pdf)

Trial information

Trial identification

Sponsor protocol code	13CC34

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Great Ormond Street Hospital for Children NHS Foundation Trust
Sponsor organisation address	30 Guilford Street , London, United Kingdom, WC1N 1EH
Public contact	Avani Shukla, Great Ormond Street Hospital and Great Ormond Institute of Child Health R&D Office, +44 (0) 2079052863, avani.shukla@gosh.nhs.uk
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective was to determine the best way to use a crucial drug called salbutamol in children with life-threatening asthma. We wish to analyse how the dose of salbutamol relates to its blood concentration level; and how the blood concentration level relates to effectiveness and toxicity. This study will allow us develop a population pharmacokinetic-pharmacodynamics (PKPD) model of salbutamol in children. This will enable to determine the optimal dose of salbutamol; to maximise its effectiveness but minimise harmful side effects.

Protection of trial subjects:

The study was conducted under appropriate UK ethics and regulatory approvals. The study was sponsored and monitored by Great Ormond Street Hospital.Annual progress report and Development Safety Update Reports were submitted to ethics committee and MHRA each year during the whole study enrolment duration. The study involved no active interventions except of taking blood samples for pharmacokinetic analysis. All patients were treated according to local policy for the management of acute severe asthma. All treatments were recorded but no modifications were made for the purposes of the study. To alleviate burden on participants the blood patients with an indwelling catheter had bloods taken at specific time points, as this does not require venesection. The blood sample was limited to 1ml/kg/day according to Medicines for Children Research Network (MCRN) guidelines.

since Intravenous Salbutamol (IVS) was considered an urgent treatment that could not be delayed while obtaining written informed consent from parents/guardians, written consent was usually obtained 24-48 hours after recruitment to the study by site research nurses for continuation in the study and for ongoing data collection This process was approved by ethics committee. Age-specific patient information leaflets were provided to each participant.

The patient details were processed according to data protection act confidentially during the course of the trial and all patients were assigned a unique trial number. Only the patient direct care team and those approved on consent (i.e. monitors and regulators) had access to data when required. The study data will be stored and archived according to GOSH local practice, data protection act 1998 and applicable research regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	17
Children (2-11 years)	29
Adolescents (12-17 years)	8
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between September 2014 and May 2017, 576 patients were screened. Of the 91 eligible patients, 8 refused or were unable to consent, one was previously recruited and 19 were missed.
Of the 63 patients subsequently recruited, 4 were withdrawn due to insufficient samples, 3 patients IVS was not started and 2 were withdrawn as found to be underage.

Pre-assignment

Screening details:

Participants were identified by the treating clinical teams, and recruited by site research nurses or the clinical teams. Patients were eligible for inclusion if they were aged 1-15 years (inclusive); admitted to hospital for acute severe asthma, as defined by the British Thoracic So. guidelines; and about to receive or receiving IV Salbutamol.

Period 1

Period 1 title	Baseline & Recruitment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	NO ARM - PKPD Study

Arm description:

The study is a PKPD model and does not have any interventional arms

Arm type	No Arms
Investigational medicinal product name	Ventolin Injection
Investigational medicinal product code	
Other name	Salbutamol
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Dosage schedule is as per local policy, expected to be in keeping with the BTS guidelines of acute severe asthma, incorporated into the BNF for children.

Number of subjects in period 1	NO ARM - PKPD Study
Started	54
Completed	54

Baseline characteristics

Reporting groups	
Reporting group title	Baseline & Recruitment

Reporting group description: -

Reporting group values	Baseline & Recruitment	Total	
Number of subjects	54	54	
Age categorical			
Patients aged 1-15 years were included			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	17	17	
Children (2-11 years)	29	29	
Adolescents (12-17 years)	8	8	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	21	21	
Male	33	33	

End points

End points reporting groups

Reporting group title	NO ARM - PKPD Study

Reporting group description:

The study is a PKPD model and does not have any interventional arms

Primary: Effectiveness measure

End point title	Effectiveness measure[1]

End point description:

Population PD modelling was also successfully performed. 111 effectiveness measurements were obtained within the ED cohort, and an Emax concentration-efficacy relationship gave the best model fit. The EC50 values for PASS and the individual variables were estimated to be between 0.2 ng/mL and 0.5 ng/mL, with Emax from 6.67 to 7.77. No covariants were found to be statistically significant, although a 5.3-fold difference between patients with heterozygous and with homozygous rs1042713 in β-2 adrenoceptor is demonstrated. Examining the baseline salbutamol concentration levels, we can see that many patients are saturated from an effectiveness perspective early in the course of their IVS treatment using current dosage regimens.

End point type	Primary

End point timeframe:

Between September 2014 and May 2017

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Sequential population pharmacokinetic/pharmacodynamic (PKPD) modelling was performed with NONMEM® (version 7.3) where a PK model was firstly developed and individual PK parameters were combined with a PD model to describe the time course of PD observations.
PASS scores were treated as categorical data and modelled with ordered logistic regression where the bronchodilation effect was linked with the probability of achieving PASS scores. A chart is attached to this endpoint.

End point values	NO ARM - PKPD Study			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Emax and EC50				
number (not applicable)				
PASS Emax	7.77			
PASS EC50 (ng/mL)	0.5			

Attachments (see zip file)	CSR Effectiveness Measures/CSR Effectiveness Measures.pdf

Statistical analyses

No statistical analyses for this end point

Primary: Toxicity Variable

End point title	Toxicity Variable[2]

End point description:

Toxic effects increased immediately with the increase of plasma concentrations, the opposite for pH and base excess measures; these findings were consistent with physiological observations. Parameter values for each toxicity measurement are outlined in Table 5 in the attached report. Heart rate and base excess were found to be the most sensitive to a change in IVS, with EC50 values of 6.23 ng/mL and 27.9ng/mL respectively.

End point type	Primary

End point timeframe:

Between September 2014 to March 2017

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The following continuous markers of toxicity were modelled: lactate, pH, base excess, blood glucose, heart rate, systolic and diastolic blood pressure. Toxicity effects were driven from an effect compartment with first-order equilibration with the plasma compartment, in order to examine whether delayed onset occurred for each toxicity measure after IVS. A sigmoidal Emax model was used to link effect compartment concentration with toxicity effects. A chart is attached to this endpoint.

End point values	NO ARM - PKPD Study			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: mean				
number (not applicable)				
lactate (mmol/L) Mean [Range 0.3-8.4]	1.6			
pH Mean [Range 6.9-7.5]	7.3			
base excess (mmol/L) Mean [Range -14.9-15.4]	-3.4			
respiratory exchange ratio Mean [Range 0.1-1.5]	0.6			
blood glucose (mmol/L) Mean [Range 4.0-19.6]	9.1			
heart rate Mean [Range 100-214]	157			
systolic blood pressure Mean [Range 64-162]	104			
diastolic blood pressure Mean[Range 16-109]	55.5			

Attachments (see zip file)	CSR Toxicity Variables/CSR Toxicity Variables.pdf

Statistical analyses

No statistical analyses for this end point

Primary: Salbutamol concentration levels

End point title	Salbutamol concentration levels[3]

End point description:

As anticipated from the current dosage schedule, salbutamol infusion doses ranged from 0-2 µg/kg/min in the ED cohort, and 0-4 µg/kg/min in the CATS cohort. Median duration of IVS treatment was 5 hours in the ED cohort (range 0.5 – 19.1), and 3.5 hours (range 0.2-196.2) in the CATS cohort. More information can be found in attached table.

End point type	Primary

End point timeframe:

Between September 2014 to March 2017

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: One- and two-compartment PK models were tested to describe the time course of salbutamol plasma concentration for individual patients, with baseline plasma concentration estimated due to uncertain and lengthy dosing history of nebulised salbutamol prior to enrolment. Allometric size scaling with body weight on clearance and volume of distribution was added a priori, and a sigmoidal maturation function describing the change of clearance over age was tested.

End point values	NO ARM - PKPD Study			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: median				
number (not applicable)				
Baseline concentration CATS (ng/mL) [1.8-163]	74.5			
Baseline concentration ED (ng/mL) [2.5-105]	12.3			

Attachments (see zip file)	CSR Salbutamol Concentrations/CSR Salbutamol

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

The time frame for reporting adverse events was from consent till patient discharge.

Adverse event reporting additional description:

As the safety profile of Salbutamol is very well known and documented in the Salbutamol (Ventolin) Summary of product characteristics, we did not record all non-serious adverse events outside of those recorded as signs of toxicity as per study protocol.

Assessment type	Systematic

Dictionary used

Dictionary name	Not applicable
Dictionary version	0

Reporting groups

Reporting group title	NO ARM - PKPD Study

Reporting group description:

The study is a PKPD model and does not have any interventional arms

Serious adverse events	NO ARM - PKPD Study		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	NO ARM - PKPD Study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: As the safety profile of salbutamol is very well known and documented in the Salbutamol (Ventolin) SmPC, we did not record all non-serious AEs outside of those recorded as signs of toxicity as per study protocol.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2016	1. To allow minimum of 2 salbutamol levels, 2 toxicity measures +/- 3 efficacy measures 2. Patients with only 2 salbutamol levels will require five effectiveness scores (PASS) to be included in the study. 3. Inclusion of Royal London Hospital PICU department (Please note Royal London is already an approved site) to maximise recruitment and allow modelling within the full clinical spectrum of acute severe asthma treatment. 4. To remove chronic asthma score from secondary objective as there is no sufficient evidence for the use of Chronic Asthma Score in these patients. 5. Administrative changes: Change of Sponsor Representative Contact on CTA application form
10 February 2017	Amendment for change in the chief investigator of the trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Recruitment numbers were less than anticipated from our audit data. We decided to end the study early however effectiveness measurements were only available in the self-ventilating ED cohort.

Notes: