Clinical trial results:
Chlorhexidine Versus Povidone-Iodine For Skin Anitsepsis Prior To Central Venous Catheter Insertion In Preterm Infants: Protocol For A Randomised Trial (The SKA Trial)

Summary

EudraCT number	2011-002962-19
Trial protocol	IE
Global end of trial date	19 December 2014

Results information

Result version number	v1 (current)
This version publication date	22 February 2019
First version publication date	22 February 2019
Summary attachment (see zip file)	2% chlorhexidine-70% isopropyl alcohol versus 10% povidone-iodine for insertion site cleaning before central line insertion in preterm infants: a randomised trial (Kieran et al - 2016 - 2% chlorhexidine–70% isopropyl alcohol versus 10% povidone–iodine for insertion site cleaning before central line insertion in preterm infants a randomised trial.pdf)

Trial information

Trial identification

Sponsor protocol code	SKA 001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University College Dublin
Sponsor organisation address	Belfield, Dublin, Ireland,
Public contact	UCD Clinical Research Centre, UCD Clinical Research Centre, 00353 017164597, peter.doran@ucd.ie
Scientific contact	UCD Clinical Research Centre, UCD Clinical Research Centre, 00353 017164597, peter.doran@ucd.ie

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 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2014
Global end of trial reached?	Yes
Global end of trial date	19 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether the use of 2% chlorhexidine in 70% isopropyl alcohol compared to 10% povidone-iodine for skin antisepsis prior to central venous catheter insertion results in fewer catheter related blood stream infections in infants<31 weeks gestation

Protection of trial subjects:

The decision to insert a central venous cathether and the type of central venous cathether to be inserted were made by the attending clinicians.
Central venous cathether were inserted under maximum sterile barrier precautions (sterile gown, sterile gloves, hat and mask and using
full-body drape) following local clinical guidelines that were common to both neonatal intensive care units.
Central venous catheters s could remain in place when sepsis was suspected. However, if a blood culture was positive, the central venous catheter was removed, the tip (5 cm length, cut using sterile blade) was sent for culture and a further blood culture was taken from a different peripheral site.
Infants at both centres suspected of having late onset sepsis were empirically treated with flucloxacillin and gentamicin as a first line. Vancomycin could subsequently be used if catheter-related bloodstream infection was confirmed, and treatment was considered appropriate. Antibiotics for catheter-related bloodstream infection were not given through a central venous catheter that was suspected to be infected.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 310
Worldwide total number of subjects	310
EEA total number of subjects	310

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	310
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from two stand-alone university maternity hospital: the National Maternaty Hospital, Holles Street, Dublin and the Coombe Women and Infants University Hospital, Dublin.

Pre-assignment

Screening details:

Infants born at less than 31 weeks of gestational age were eligible for enrolment if they were undergoing CVC insertion for the first time in the neonatal ICU. Infants with congenital anomalies and infants who had previously undergone CVC insertion before the agent used to clean the insertion site could be randomly assigned were excluded.

Pre-assignment period milestones

Number of subjects started	434[1]
Number of subjects completed	304

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 32
Reason: Number of subjects	Outborn central venous catheter in situ: 30
Reason: Number of subjects	Inborn umbilical venous catheter in delivery room: 2
Reason: Number of subjects	No-one to consent: 9
Reason: Number of subjects	Physician decision: 2
Reason: Number of subjects	not approached: 40
Reason: Number of subjects	Gestational age was 31 weeks: 1
Reason: Number of subjects	Adverse event, non-fatal: 14

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 6 subjects excluded after baseline due to meeting exclusion criteria. These were not included in baseline results.

Period 1

Period 1 title	Baseline Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	POV IOD

Arm description:

Subjects in the PI arm were randomised to be treated with povidone–iodine.

Arm type	Experimental
Investigational medicinal product name	10% w/w povidone–iodine
Investigational medicinal product code	
Other name	Videne 10% w/w antiseptic Solution
Pharmaceutical forms	Cutaneous liquid
Routes of administration	Cutaneous use, Local use

Dosage and administration details:

Approximately 3 ml of brown 10% w/w povidone–iodine was poured directly into a sterile dish, and a

sterile cotton swab was dipped into it for 1–2 seconds. The swab was squeezed to remove excess solution and used to clean the site for 30 seconds. The area was allowed to dry naturally before CVC insertion.

Arm title	CHX-IA

Arm description:

Subjects in the CHX–IA arm were randomised to be treated with chlorhexidine gluconate/isopropyl alcohol/water solution.

Arm type	Experimental
Investigational medicinal product name	2% w/v chlorhexidine in 70% v/v isopropyl alcohol
Investigational medicinal product code	
Other name	ChoraPrep 2% chlorhexidine w/v/isopropyl alcohol 70% v/v
Pharmaceutical forms	Cutaneous solution
Routes of administration	Cutaneous use, Local use

Dosage and administration details:

The CVC insertion site was cleaned with 1 0.67 ml ampoule of 2% w/v chlorhexidine in 70% v/v isopropyl alcohol using a single applicator for 30 seconds and then allowed to dry naturally before CVC insertion. If a second ampoule was used, the reason for use was documented on the CVC checklist.

Number of subjects in period 1[2]	POV IOD	CHX-IA
Started	156	148
Completed	156	148

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 6 subjects excluded after baseline due to meeting exclusion criteria. These were not included in baseline results.

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	CHX-IA

Arm description:

Infants randomised to CHX–IA group had the CVC insertion site cleaned with chlorhexidine gluconate/isopropyl alcohol/water solution.

Arm type	Experimental
Investigational medicinal product name	2% w/v chlorhexidine in 70% v/v isopropyl alcohol
Investigational medicinal product code	
Other name	ChoraPrep 2% chlorhexidine w/v/isopropyl alcohol 70% v/v
Pharmaceutical forms	Cutaneous solution
Routes of administration	Cutaneous use, Local use

Dosage and administration details:

The CVC insertion site was cleaned with 1 0.67 ml ampoule of 2% w/v chlorhexidine in 70% v/v isopropyl alcohol using a single applicator for 30 seconds and then allowed to dry naturally before CVC insertion. If a second ampoule was used, the reason for use was documented on the CVC checklist.

Arm title	POV IOD

Arm description:

Subjects in the PI arm were treated with povidone–iodine.

Arm type	Experimental
Investigational medicinal product name	10% w/w povidone–iodine
Investigational medicinal product code	
Other name	Videne 10% w/w antiseptic Solution
Pharmaceutical forms	Cutaneous liquid
Routes of administration	Cutaneous use, Local use

Dosage and administration details:

Approximately 3 ml of brown 10% w/w povidone–iodine was poured directly into a sterile dish, and a sterile cotton swab was dipped into it for 1–2 seconds. The swab was squeezed to remove excess solution and used to clean the site for 30 seconds. The area was allowed to dry naturally before CVC insertion.

Number of subjects in period 2	CHX-IA	POV IOD
Started	148	156
Completed	148	156

Baseline characteristics

Reporting groups	
Reporting group title	POV IOD
Reporting group description:	
Subjects in the PI arm were randomised to be treated with povidone–iodine.	
Reporting group title	CHX-IA
Reporting group description:	
Subjects in the CHX–IA arm were randomised to be treated with chlorhexidine gluconate/isopropyl alcohol/water solution.	

Reporting group values	POV IOD	CHX-IA	Total
Number of subjects	156	148	304
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Gestational age			
Units: weeks			
arithmetic mean	27	27	
standard deviation	± 2	± 2	-
Gender categorical			
Units: Subjects			
Female	87	67	154
Male	69	81	150
Antenatal steroid exposure			
Subjects treated with antanatal steroids			
Units: Subjects			
Exposed	155	144	299
Not exposed	1	4	5
Caesarean section			
Subjects born by caesarean section			
Units: Subjects			
Born by caesarean section	100	91	191
Not born by caesarean section	56	57	113
Clinical chorioamnionitis			
Subjects with clinical chorioamnionitis			
Units: Subjects			
Clinical chorioamnionitis	24	14	38
No clinical chorioamnionitis	132	134	266

Multiple birth			
Subjects who were part of a multiple birth			
Units: Subjects			
Multiple birth	54	62	116
No multiple birth	102	86	188
Ventilation prerandomisation			
Subjects who were ventilated before randomisation			
Units: Subjects			
Ventilated before randomisation	78	64	142
Not ventilated before randomisation	78	84	162
CPAP prerandomisation			
Subjects who were administered continuous positive airway pressure before randomisation.			
Units: Subjects			
CPAP before randomisation	100	102	202
No CPAP before randomisation	56	46	102
UVC as first CVC			
Subjects who received an umbilical venous catheter or a peripherally inserted central catheter as there first CVC.			
Units: Subjects			
UVC	104	96	200
PICC	52	52	104
Birth weight			
Units: gram(s)			
arithmetic mean	1014	1017	
standard deviation	± 326	± 289	-
Apgar score at 1 min			
The Apgar score at 1 minute post-delivery			
Units: arbitrary			
arithmetic mean	6	6	
standard deviation	± 2	± 2	-
Apgar score at 5 min			
The Apgar score at 1 minute post-delivery			
Units: arbritary			
arithmetic mean	8	8	
standard deviation	± 2	± 2	-
Day of life randomised			
Day of life on which subjects were randomised.			
Units: day			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 0	0 to 1	-
Number of CVCs per patient			
Number of central venous catheters per subject.			
Units: CVCs			
arithmetic mean	3	3	
standard deviation	± 1	± 1	-
Duration CVC in situ per patient			
Duration of central venous catheter left in situ per subject.			
Units: days			
median	9	9	
inter-quartile range (Q1-Q3)	6 to 13	6 to 12	-

End points

End points reporting groups	
Reporting group title	POV IOD
Reporting group description:	
Subjects in the PI arm were randomised to be treated with povidone–iodine.	
Reporting group title	CHX-IA
Reporting group description:	
Subjects in the CHX–IA arm were randomised to be treated with chlorhexidine gluconate/isopropyl alcohol/water solution.	
Reporting group title	CHX-IA
Reporting group description:	
Infants randomised to CHX–IA group had the CVC insertion site cleaned with chlorhexidine gluconate/isopropyl alcohol/water solution.	
Reporting group title	POV IOD
Reporting group description:	
Subjects in the PI arm were treated with povidone–iodine.	

Primary: Incidence of catheter-related bloodstream infection per infant	
End point title	Incidence of catheter-related bloodstream infection per infant
End point description:	
The primary outcome for our study was the number of infants with a CR-BSI. Infants were diagnosed with a CR-BSI if they were >72 hours of age and had a CVC in situ or removed within the previous 48 hours and met at least one of the following three criteria: a recognised pathogen (eg, Staphylococcus aureus and Candida species) in one peripheral blood culture (ie, not taken through CVC) that was not related to an infection at another site (eg, meningitis or skin abscess), a common skin commensal (eg, coagulase-negative Staphylococcus (CONS)) cultured from two or more peripheral blood cultures drawn on separate occasions, a common skin commensal (eg, CONS) isolated from one peripheral blood culture with a CVC tip culture growing >15 colony-forming units of a pure growth of the same organism.	
End point type	Primary
End point timeframe:	
>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.	

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: catheter-related bloodstream infections	10	8		

Statistical analyses

Statistical analysis title	Difference in proportion between arms
Comparison groups	CHX-IA v POV IOD

Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.631
Method	Fisher exact

Primary: Incidence of catheter-related bloodstream infection per catheter

End point title	Incidence of catheter-related bloodstream infection per catheter

End point description:

The primary outcome for our study was the number of infants with a CR-BSI. Infants were diagnosed with a CR-BSI if they were >72 hours of age and had a CVC in situ or removed within the previous 48 hours and met at least one of the following three criteria:
a recognised pathogen (eg, Staphylococcus aureus and Candida species) in one peripheral blood culture (ie, not taken through CVC) that was not related to an infection at another site (eg, meningitis or skin abscess),
a common skin commensal (eg, coagulase-negative Staphylococcus (CONS)) cultured from two or more peripheral blood cultures drawn on separate occasions,
a common skin commensal (eg, CONS) isolated from one peripheral blood culture with a CVC tip culture growing >15 colony-forming units of a pure growth of the same organism.

End point type	Primary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: catheter-related bloodstream infections	10	10		

Statistical analyses

Statistical analysis title	Difference in proportion between arms
Comparison groups	CHX-IA v POV IOD
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.824
Method	Fisher exact

Primary: Catheter-related bloodstream infection per 1000 catheter days

End point title	Catheter-related bloodstream infection per 1000 catheter

End point description:

The primary outcome for our study was the number of infants with a CR-BSI. Infants were diagnosed with a CR-BSI if they were >72 hours of age and had a CVC in situ or removed within the previous 48 hours and met at least one of the following three criteria:
a recognised pathogen (eg, Staphylococcus aureus and Candida species) in one peripheral blood culture (ie, not taken through CVC) that was not related to an infection at another site (eg, meningitis or skin abscess),
a common skin commensal (eg, coagulase-negative Staphylococcus (CONS)) cultured from two or more peripheral blood cultures drawn on separate occasions,
a common skin commensal (eg, CONS) isolated from one peripheral blood culture with a CVC tip culture growing >15 colony-forming units of a pure growth of the same organism.

End point type	Primary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

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: Statistical analysis used is unknown

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: CR-BSI/1000 catheter days				
number (not applicable)	6.8	6.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with skin damage from IMP

End point title	Number of subjects with skin damage from IMP

End point description:

Any area of skin irritation, erythema, excoriation or breakdown that was in the distribution of contact with the investigational medicinal product, and brought to the attention of the research team, was reported as an adverse skin reaction caused by a study solution.

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: subjects	3	2		

Statistical analyses

Statistical analysis title	Difference in proportion between arms
Comparison groups	CHX-IA v POV IOD
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.677
Method	Fisher exact

Secondary: Incidence of raised thyroid-stimulating hormone on screening

End point title	Incidence of raised thyroid-stimulating hormone on screening

End point description:

Thyroid-stimulating hormone (TSH) values from 8 to 15 mU/L trigger a request for a repeat sample, and if persistently >15 mU/L prompt a
request for formal serum thyroid function tests. Any abnormal TSH levels on newborn screening card or subsequent serum sample were recorded.

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: incidence of raised TSH	0	12		

Statistical analyses

Statistical analysis title	Difference in proportion between arms
Comparison groups	CHX-IA v POV IOD
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Secondary: Incidence of raised thyroid-stimulating hormone

End point title	Incidence of raised thyroid-stimulating hormone

End point description:

Thyroid-stimulating hormone (TSH) values from 8 to 15 mU/L trigger a request for a repeat sample, and if persistently >15 mU/L prompt a
request for formal serum thyroid function tests. Any abnormal TSH levels on newborn screening card or subsequent serum sample were recorded.

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: incidence of raised TSH	0	10		

Statistical analyses

Statistical analysis title	Difference in proportion between arms
Comparison groups	CHX-IA v POV IOD
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Fisher exact

Secondary: Number of subjects requiring thyroxine replacement therapy

End point title	Number of subjects requiring thyroxine replacement therapy

End point description:

Number of subjects treated with thyroxine replacement therapy on the advice of paediatric endocrinologists.

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: subjects	0	8		

Statistical analyses

Statistical analysis title	Difference number of subjects requiring thyroxine
Comparison groups	CHX-IA v POV IOD

Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Fisher exact

Secondary: Number of subjects with confirmed LOS (non-CR-BSI)

End point title	Number of subjects with confirmed LOS (non-CR-BSI)

End point description:

Number of subjects with confirmed late-onset sepsis (non-CR-BSI). Defined as laboratory confirmed sepsis (positive blood or cerebral spinal fluid culture for a recognised pathogen) after 72 hours of age and not related to a CVC.

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: subjects				
Confirmed LOS	17	26		
No confirmed LOS	131	130		

Statistical analyses

Statistical analysis title	Differen in incidence of confirmed LOS
Comparison groups	POV IOD v CHX-IA
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.249
Method	Fisher exact

Secondary: Number of subjects with suspected sepsis

End point title	Number of subjects with suspected sepsis

End point description:

Defined as clinical signs of sepsis, for example, increased frequency of apnoea, tachycardia or temperature instability, with negative blood culture, and treated with ≥5 days antibiotics.

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or

discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: subjects				
Suspected sepsis	13	12		
No suspected sepsis	135	144		

Statistical analyses

Statistical analysis title	Difference in subjects with susupected sepsis
Comparison groups	CHX-IA v POV IOD
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.835
Method	Fisher exact

Secondary: Courses of antibiotics per subject

End point title	Courses of antibiotics per subject

End point description:

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: Courses of antibiotics per subject				
median (inter-quartile range (Q1-Q3))	2 (2 to 4)	3 (2 to 4)		

Statistical analyses

Statistical analysis title	Difference in mean courses of antibiotic/patient
Comparison groups	CHX-IA v POV IOD

Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.588
Method	t-test, 2-sided

Secondary: Total days of antibiotics per subject

End point title	Total days of antibiotics per subject

End point description:

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: days				
median (inter-quartile range (Q1-Q3))	5 (2 to 12)	5 (2 to 12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of blood cultures performed per subject

End point title	Number of blood cultures performed per subject

End point description:

Number of blood cultures performed per subject. Decisions to remove CVCs and to perform blood cultures were at the discretion of treating clinicians to determine the presence of sepsis. If the blood culture was positive a further blood culture was taken from a different peripheral site. A second blood culture was not taken if the first was negative.

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: blood cultures				
arithmetic mean (inter-quartile range (Q1-Q3))	3 (2 to 5)	3 (2 to 5)		

Statistical analyses

Statistical analysis title	Difference in blood cultures/subject
Comparison groups	POV IOD v CHX-IA
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.319
Method	t-test, 2-sided

Secondary: Number of subjects with any respiratory support on day 28

End point title	Number of subjects with any respiratory support on day 28

End point description:

The number of subjects who were receiving any respiratory support on day 28

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: subjects				
Respiratory support on day 28	77	89		
No respiratory support on day 28	71	67		

Statistical analyses

Statistical analysis title	Difference subjects on respiratory support day 28
Comparison groups	CHX-IA v POV IOD

Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42
Method	Fisher exact

Secondary: Number of subjects with oxygen at 36 weeks CGA

End point title	Number of subjects with oxygen at 36 weeks CGA

End point description:

The number of subjects who were being treated with supplemental oxygen at a corrected gestational age of 36 weeks

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: subjects				
Oxygen at 36 weeks CGA	27	47		
No oxygen at 36 weeks CGA	141	109		

Statistical analyses

Statistical analysis title	Difference in subjects with oxygen at 36 weeks CGA
Comparison groups	CHX-IA v POV IOD
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	Fisher exact

Secondary: Number of subjects with NEC ≥ Bell stage 2

End point title	Number of subjects with NEC ≥ Bell stage 2

End point description:

The number of subjects with necrotising enterocolitis ≥ Bell stage 2.

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: subjects				
NEC ≥ Bell stage 2	14	15		
No NEC ≥ Bell stage 2	134	141		

Statistical analyses

Statistical analysis title	Difference in subjects with NEC≥Bell stage 2
Comparison groups	CHX-IA v POV IOD
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Number of subjects with any ROP

End point title	Number of subjects with any ROP

End point description:

The number of sujects with any retinopathy of prematurity.

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: subjects				
ROP	31	15		
No ROP	117	141		

Statistical analyses

Statistical analysis title	Difference in subjects with any ROP
Comparison groups	CHX-IA v POV IOD

Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.845
Method	Fisher exact

Secondary: Number of subjects with CRUSS IVH III/IV or PVL

End point title	Number of subjects with CRUSS IVH III/IV or PVL

End point description:

The number of subjects with intraventricular haemorrhage grade III/IV or periventricular leukomalacia as determined by cranial ultrasound scan.

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: subjects				
CRUSS IVH III/IV or PVL	16	22		
No CRUSS IVH III/IV or PVL	132	134		

Statistical analyses

Statistical analysis title	Difference subjects with CRUSS IVH III/IV or PVL
Comparison groups	CHX-IA v POV IOD
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.488
Method	Fisher exact

Secondary: Number of deaths prior to hospital discharge

End point title	Number of deaths prior to hospital discharge

End point description:

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: deaths				
Dead	15	18		
Alive	133	138		

Statistical analyses

Statistical analysis title	Difference in deaths
Comparison groups	CHX-IA v POV IOD
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.716
Method	Fisher exact

Secondary: Duration of hospital stay

End point title	Duration of hospital stay

End point description:

End point type	Secondary

End point timeframe:

>72 hours after birth and had a CVC in situ or removed within the previous 48 hours until death or discharge of subject.

End point values	CHX-IA	POV IOD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	156		
Units: days				
median (inter-quartile range (Q1-Q3))	59 (49 to 85)	67 (46 to 90)		

Statistical analyses

Statistical analysis title	Difference in duration of hospital stay
Comparison groups	CHX-IA v POV IOD

Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.199
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were recorded over 39 months with non-serious adverse events reported every 3 months and serious adverse events reported within 24 hours.	
Assessment type	Systematic

Dictionary used	
Dictionary name	NA
Dictionary version	NA

Reporting groups	
Reporting group title	POV IOD
Reporting group description:	
Subjects in the PI arm were randomised to be treated with povidone–iodine.	
Reporting group title	CHX-IA
Reporting group description:	
Subjects in the CHX–IA arm were randomised to be treated with chlorhexidine gluconate/isopropyl alcohol/water solution.	

Serious adverse events	POV IOD	CHX-IA	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 156 (11.54%)	15 / 148 (10.14%)	
number of deaths (all causes)	18	15	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Death before hospital discharge			
subjects affected / exposed	18 / 156 (11.54%)	15 / 148 (10.14%)	
occurrences causally related to treatment / all	0 / 18	0 / 15	
deaths causally related to treatment / all	0 / 18	0 / 15	

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

Non-serious adverse events	POV IOD	CHX-IA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 156 (1.28%)	3 / 148 (2.03%)	
Skin and subcutaneous tissue disorders			
Skin reaction			
subjects affected / exposed	2 / 156 (1.28%)	3 / 148 (2.03%)	
occurrences (all)	2	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29074717