



Clinical trial results:

Exploratory Propofol Dose Finding Study In Neonates receiving a single intravenous propofol bolus for endotracheal intubation during (semi-) elective INSURE (intubation-surfactant-extubation) procedure (preterm neonates) and (semi-)elective non-INSURE procedures (term-preterm neonates). NEOPROP.

Summary

EudraCT number	2012-002648-26
Trial protocol	BE
Global end of trial date	17 July 2014

Results information

Result version number	v1 (current)
This version publication date	19 December 2024
First version publication date	19 December 2024

Trial information

Trial identification

Sponsor protocol code	S54472
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01621373
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospitals Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Liesbeth Thewissen, University Hospitals Leuven, +32 16343211, Liesbeth.thewissen@uzleuven.be
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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	01 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 July 2014
Global end of trial reached?	Yes
Global end of trial date	17 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

-What is the most effective intravenously (iv) administered single propofol dose for successful INSURE procedure in neonates? INSURE-procedure is defined as (semi-)elective intubation, intratracheal administration of surfactant and extubation within 60 minutes after propofol administration.
-What is the most effective intravenously (iv) administered single propofol dose for successful (semi-)elective intubation of neonates during non-INSURE conditions (e.g. surgery)?

Protection of trial subjects:

Neonates of the University Hospitals Leuven needing preintubation sedation were included after consent from their parents was obtained. Patients had to be hemodynamically stable and not receiving sedatives or analgesics (except acetaminophen) in the previous 24 hours.

Background therapy:

It is standard of care to give premedication before (semi-)elective intubation in neonates. Drug selection and dosing for this procedure is highly variable and not yet evidence-based. One of the compounds used is propofol, a short-acting anesthetic. Postmenstrual age (PMA) and postnatal age (PNA) have been shown to affect propofol clearance,⁴ but pharmacodynamic (PD) data in neonates are limited. Because optimal propofol dosing and its PD effects in newborns are lacking, we combined a prospective dose-finding approach with PD assessment in neonates receiving propofol as intravenous bolus for preintubation sedation (The Exploratory Propofol Dose-Finding Study In Neonates [NEOPROP] study). The primary objective was to define the ED₅₀ (ie, effective dose for 50% of patients) for successful intubation and to determine the rate of successful extubation in those patients with planned intubation, surfactant administration, and immediate extubation^{12,13} (INSURE procedure).

Evidence for comparator: -

Actual start date of recruitment	01 July 2012
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	Belgium: 47
Worldwide total number of subjects	47
EEA total number of subjects	47

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	47
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:

Neonates of the University Hospitals Leuven needing preintubation sedation were included after consent from their parents was obtained.

Pre-assignment

Screening details:

Patients had to be hemodynamically stable and not receiving sedatives or analgesics (except acetaminophen) in the previous 24 hours.

Period 1

Period 1 title	ED 50 calculation propofol (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Stratum 1

Arm description:

Postmenstrual age < 28 w Postnatal age < 10 days

Arm type	Stratum 1
Investigational medicinal product name	Propofol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for emulsion for injection
Routes of administration	Intravenous use

Dosage and administration details:
up and down dose-response design

Arm title	Stratum 3
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Arm description:

Postmenstrual age 28 to <32 w Postnatal age < 10 days

Arm type	Stratum 3
Investigational medicinal product name	Propofol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:
Up-)and-down dose-response design

Arm title	Stratum 5
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Arm description:

Postmenstrual age 32 to <37 w Postnatal age < 10 days

Arm type	Stratum 5
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Investigational medicinal product name	Propofol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use
Dosage and administration details:	
Up-and-down dose-response design	

Number of subjects in period 1	Stratum 1	Stratum 3	Stratum 5
Started	12	23	12
Completed	12	23	12

Baseline characteristics

Reporting groups

Reporting group title	ED 50 calculation propofol
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Reporting group description: -

Reporting group values	ED 50 calculation propofol	Total	
Number of subjects	47	47	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	47	47	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	18	18	
Male	29	29	

End points

End points reporting groups

Reporting group title	Stratum 1
Reporting group description:	
Postmenstrual age < 28 w Postnatal age < 10 days	
Reporting group title	Stratum 3
Reporting group description:	
Postmenstrual age 28 to <32 w Postnatal age < 10 days	
Reporting group title	Stratum 5
Reporting group description:	
Postmenstrual age 32 to <37 w Postnatal age < 10 days	

Primary: Effective dose for 50% of patients for Successful intubation and subsequent extubation in case of planned extubation after INSURE procedure

End point title	Effective dose for 50% of patients for Successful intubation and subsequent extubation in case of planned extubation after INSURE procedure
End point description:	
An up-and-down dose-response design was used to calculate ED50 (mg/kg) in strata with effective sampling size of at least 6, by use of the Dixon-Massey method for small samples.	
End point type	Primary
End point timeframe:	
1 hour after propofol administration	

End point values	Stratum 1	Stratum 3	Stratum 5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	23	12	
Units: mg/kg				
arithmetic mean (confidence interval 95%)	0.792 (0.392 to 1.192)	0.713 (0.424 to 1.002)	1.350 (0.932 to 1.767)	

Statistical analyses

Statistical analysis title	Propofol ED50 Calculation
Statistical analysis description:	
An up-and-down dose-response design was used to calculate ED50 (mg/kg) in strata with an effective sampling size (N) of at least 6, by use of the Dixon-Massey method ¹⁴ for small samples. N is the number of trials reduced by 1 less than the number of similar responses at the beginning. $ED50 = \sum Xi / N + d(A + C)/N$, with Xi: initial dose, d: interval between dose levels (0.5 mg/kg) and A, C: tabulated values provided by Dixon. ¹⁴ SAS 9.2 for Windows (SAS Institute, Inc, Cary, North Carolina)	
Comparison groups	Stratum 1 v Stratum 3 v Stratum 5

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	< 0.05
Method	up-and-down dose response
Parameter estimate	ED50
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	4
Variability estimate	Standard deviation
Dispersion value	0.5

Notes:

[1] - An up-and-down dose-response design was used to calculate ED50 (mg/kg) in strata with an effective sampling size (N) of at least 6, by use of the Dixon-Massey method¹⁴ for small samples. N is the number of trials reduced by 1 less than the number of similar responses at the beginning. $ED50 = \sum X_i / N + d(A + C)/N$, with X_i : initial dose, d: interval between dose levels (0.5 mg/kg) and A, C: tabulated values provided by Dixon.¹⁴ SAS 9.2 for Windows (SAS Institute, Inc, Cary, North Carolina)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

not specified

Assessment type	Systematic
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Dictionary used

Dictionary name	neonatal
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Dictionary version	1
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Reporting groups

Reporting group title	ED50
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Reporting group description: -

Serious adverse events	ED50		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 47 (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	ED50		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 47 (40.43%)		
General disorders and administration site conditions			
permissive hypotension	Additional description: Permissive hypotension was noted with a duration of blood pressure decrease at least 120-200 minutes after propofol administration.		
subjects affected / exposed	19 / 47 (40.43%)		
occurrences (all)	19		

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/27597733>