Final study report

Study title:	Less-invasive Surfactant Application in the Treatment of Neonatal RDS in Routine Practice - a Registry Study
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Table of contents

General information about the study

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2. Study title

Less-invasive Surfactant Application in the Treatment of Neonatal RDS in Routine Practice -registry study

3. Study number / alias

CHI-CUR-PL-03 / START study

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6. Study dates

Ethics Committee approval: December 12, 2017

Start of enrollment (First Patient First Visit): January 17, 2018

End of enrollment (Last Patient First Visit): March 15, 2019

End of study (Last Patient Last Visit): June 26, 2019

7. Study centers

1. Polish Mother's Memorial Hospital Research Institute
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3. Independent Public Specialized Health Care Center "Zdroje"
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    ul. Reymonta 8, Opole
13. Masovian Bródno Hospital
    ul. Kondratowicza 8, Warszawa
14. Tomaszów Health Center
    ul. Jana Pawła 35, Tomaszów Mazowiecki
15. Jan Biziel University Hospital No. 2
    ul. Ujejskiego 75, Bydgoszcz
16. Provincial Integrated Hospital
    ul. Królewiecka 146, Elbląg
17. Provincial Integrated Hospital
    ul. Grunwaldzka 15, Kielce
18. Independent Public Clinical Hospital No. 2
    Al. Powstańców Wlkp. 72, Szczecin
19. St. Sophia's Specialist Hospital
    ul. Żelazna 90, Warszawa
20. K. Marcinkowski University Hospital
    ul. Zyty 26, Zielona Góra
21. Multispeciality Municipal Hospital
    ul. Szpitalna 19, Bydgoszcz
22. Ujastek Medical Center
    ul. Ujastek 3, Kraków
23. Independent Public Clinical Hospital No. 1
    ul. Staszica 16, Lublin
24. T. Chałubiński Hospital
    ul. Limanowskiego 20/22, Ostrów Wielkopolski
25. Mazovian Specialist Hospital
    ul. Aleksandrowicza 5, Radom

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    ul. Hubalczyków 1, Słupsk
27. Mother and Newborn Center
    ul. Prosta 30, Kielce
28. Independent Public Clinical Hospital No. 1
    ul. Siedlecka 2, Police
29. University Clinical Center
    ul. Kliniczna 1A, Gdańsk
30. L. Rydygier Provincial Hospital
    ul. św. Józefa 53-59, Toruń
31. A. Falkiewicz Specialist Hospital
    ul. Warszawska 2, Wrocław

List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
BiPAP	Biphasic Positive Airway Pressure
BPD	Bronchopulmonary dysplasia
CI	Confidence interval
FiO_2	Fraction of inspired oxygen
g	Gram
HFNC	High-flow Nasal Cannulas
HFOV	High Frequency Oscillatory Ventillation
INSURE	Intubation – Surfactant – Extubation
IQR	Interquartile range
IVH	Intraventricular hemorrhage
LISA	Less Invasive Surfactant Administration
min	Minutes
MV	Mechanical ventilation
nCPAP	Nasal Continuous Positive Airway Pressure
NICU	Neonatal Intensive Care Unit
NIPPV	Nasal Intermittent Positive Pressure Ventilation
OR	Odds ratio
PDA	Persistent ductus arteriosus
PVL	Periventricular leukomalacia
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of prematurity
SADR	Serious Adverse Drug Reaction
SD	Standard deviation
SF	Surfactant
SpO_2	Blood oxygen saturation

1. Introduction

The method of less-invasive surfactant administration (LISA / MIST) invented in early 90s [1] was initially used only in leading neonatal centers and under controlled clinical trials [2,3]. LISA / MIST became increasingly widespread and according to the European survey of 2017, was used by 52% of neonatologists [4].

In the 2016 update to the European Guidelines for the Management of Respiratory Distress Syndrome, LISA/MIST was included as an alternative to the already established INSURE (intubation-surfactant-extubation) technique [5].

Published meta-analyzes of randomized clinical trials indicate clinical benefits of LISA / MIST, including, but not limited to, lower risk of death or bronchopulmonary dysplasia, compared to conventional surfactant administration and compared to nasal CPAP alone [6]. Similarly, Rigo's meta-analysis from 2016 showed that LISA compared to INSURE reduced the risk of death or BPD and reduced the rate of early CPAP failure [7].

In Poland, LISA has not been widely used, and the reasons included lack of a dedicated catheter for the administration of surfactant, and - until recently - no information in surfactant labelling on the possibility of using such a method. The few Polish publications containing data on LISA indicated that it had about 4% share in the total number of surfactant therapies [8].

In April 2017, the SmPC of Curosurf® was extended with LISA / MIST mode of administration, and at the end of 2017 a dedicated surfactant catheter (LISAcath®) was introduced into the Polish market. All these factors were expected to significantly increase the popularity of LISA / MIST.

The countrywide registry of surfactant administrations with LISA / MIST technique, performed in non-interventional (observational) setting, was intended to allow the collection of systematized clinical data for evaluation of the process of LISA / MIST implementation in Poland.

2. Study design

START study was a prospective, multicenter, non-interventional cohort study of 500 premature infants with Respiratory Distress Syndrome (RDS), treated with Less-Invasive Surfactant Administration (LISA). The study was conducted in 31 Neonatal Intensive Care Units (NICUs), distributed evenly across Poland.

Technical details of the LISA procedure have been documented alongside treatment outcomes recorded at hospital discharge, or transfer to another hospital (if applicable), or death.

Baseline neonatal characteristics included date and time of birth, sex, use of antenatal steroids, gestational age, birth weight, Apgar score at 1 and 5 minutes, oxygen requirement at the Delivery Room.

Technicalities of LISA /MIST encompassed venue of the procedure (Delivery Room vs NICU), , type of endotracheal catheter, use of Magilla forceps, premedication, type of non-invasive

respiratory support during the procedure, number of attempts to insert a catheter into the trachea, speed (duration) of surfactant injection and qualification of the proceduralist (specialist in neonatology vs resident)

Data on surfactant included the name of the medicinal product, volume of the initial dose, time of initial dose (from birth), total number of doses and method of surfactant administration (if repeated doses required). Also, treatment with caffeine citrate was noted.

Each LISA performer reported his/her experience in endotracheal intubation on a 0 – 10 scale, where 0 = “no experience” and 10 = “expert level”.

Ease of performing LISA / MIST procedure was analyzed based on self-assessments by the performers. Each procedure was rated on a six-grade scale, encompassing the following categories: “very easy”, “easy”, “not too difficult”, “difficult”, “very difficult”, and “impossible to perform”.

LISA uptake was defined as the percentage share of LISA in all surfactant therapies in the study centers during the study period.

In-hospital mortality was recorded together with the following outcomes that were captured at hospital discharge: need for intubation and invasive ventilation (during hospital stay and within 72 hours of birth), total duration of invasive ventilation (if applicable), total duration of non-invasive respiratory support, complications of prematurity: bronchopulmonary dysplasia (BPD), intraventricular hemorrhage, persistent ductus arteriosus (PDA) requiring pharmacological or surgical treatment, periventricular leukomalacia (PVL), retinopathy of prematurity (ROP) requiring treatment.

Safety and tolerance of the LISA / MIST procedure were assessed with questions concerning the occurrence of adverse events of special interest which included: (1) surfactant reflux, (2) unilateral surfactant deposition, (4) clinically relevant bradycardia, (3) clinically relevant apnea, (5) clinically relevant desaturation, and (6) the need for rescue intubation due to clinical deterioration during LISA / MIST procedure (7) other, not listed above. In addition, data were collected on the lowest oxygen saturation (SpO_2) and the highest fraction of inspired oxygen (FiO_2) during the LISA / MIST procedure, as well as baseline values prior to the procedure.

The investigators were obliged to report all adverse events during the observation period.

All study data were captured using the electronic platform (electronic Case Report Form - eCRF), managed by an external company (CRO - Biostat Sp. z o.o., www.biostat.com.pl).

The structure of the eCRF reflected all information required by the study protocol.

3. Study objectives

Primary study objective was to describe how LISA procedure is carried out in everyday neonatal practice and to evaluate percentage share of LISA in all surfactant therapies in the study sites.

Secondary goals included assessment of safety and tolerability of LISA and evaluation of clinical outcomes in neonates treated with LISA.

Also, it was planned to compare neonatal outcomes between LISA (the START study cohort) an INSURE group, based on a historical cohort of infants from the previous neonatal study conducted in 2015.

4. Enrollment criteria

To be eligible for enrollment in this study the infant had to fulfill the following criteria:

Inclusion Criteria

1. Premature infant with known RDS or at risk of developing RDS
2. Presence of spontaneous breathing
3. Prior decision of the attending physician to administer surfactant with LISA

Exclusion Criteria

1. Newborn with clinically significant maxillo-facial, tracheal or known pulmonary malformations
2. The need for intubation and mechanical ventilation in the Delivery Room

5. Statistical methods

For each continuous variable descriptive statistics (i.e., mean, standard deviation, median, interquartile range, minimum and maximum) were presented. For categorical variables, counts and percentages were provided. The denominator for each percentage was the number of subjects in the study cohort, unless otherwise specified.

For percentage comparisons, the chi-square test or Fisher's exact test was used.

Oxygenation parameters before and during LISA were compared with Wilcoxon matched-pairs signed rank test.

All AEs, Adverse Drug Reactions (ADRs), Adverse of Special Interest (AESI) and Serious Adverse Events (SAEs) were summarized in terms of frequency of patients with at least one AE as well as the number of events. Summary is also presented by severity and seriousness.

Two-sided Student's t-test (in the case of normal distribution) or U-Mann-Whitney test (non-normal distribution) was used to compare baseline characteristics between the study cohort and the historical INSURE cohort. For subsequent comparison of neonatal outcomes propensity score matching (PSM) was employed to adjust for the impact of baseline characteristics differences. The two groups were balanced regarding gestational age, gender, antenatal steroids, birth weight, 5 min Apgar score and delivery method. PSM was performed employing the nearest neighbor without replacement method. To minimize the number of

poor matches, a caliper equal to 0.05 of the standard deviation of the propensity score was used.

All calculations have been performed in R statistical software version 3.5 (2019), Foundation for Statistical Computing, Vienna, Austria. P-values <0.05 were considered significant.

5.1. Sample size

Taking the objectives of the study and its explorative nature, the sample size was set arbitrarily at 200 patients by the Scientific Study Committee which included neonatology experts - members of the Executive Board of the Polish Neonatal Society. The recruitment goal was regarded achievable in the pre-planned 24-months of study period.

However, 200 infants were recruited within approximately 8 months and the Scientific Study Committee strongly advocated continuing the study for the originally planned period of time. Following re-assessment of the recruitment rate, a new target of 500 infants was set and deemed achievable. The study protocol was amended accordingly on 19.09.2018.

6. Demographic and baseline characteristics

Out of 503 screened newborns, three infants have not met enrollment criteria and 500 were eligible.

Distribution of site enrollment is presented in Table 1.

Table 1. Distribution of site enrollment

Study center	No. of patients
1. Polish Mother's Memorial Hospital Research Institute, Łódź	48
2. Municipal Hospital, Ruda Śląska	43
3. Independent Public Specialized Health Care Center "Zdroje", Szczecin	40
4. Department of Neonatology, University of Medical Sciences, Poznań	38
5. University Centre of Mother and Child's Health, Warszawa	35
6. M. Pirogow Provincial Specialist Hospital, Łódź	25
7. F. Chopin District Specialist Hospital, Rzeszów	24
8. University Clinical Hospital, Wrocław	24
9. Specialist Hospital No. 2, Bytom	22
10. Specialist Hospital Pro-Familia, Rzeszów	21
11. Princess Anna Mazowiecka Clinical Hospital, Warszawa	19
12. Center for Gynaecology, Obstetrics and Neonatology, Opole	17
13. Masovian Bródno Hospital, Warszawa	17
14. Tomaszów Health Center, Tomaszów Mazowiecki	14
15. Jan Biziel University Hospital No. 2, Bydgoszcz	12
16. Provincial Integrated Hospital, Elbląg	10
17. Provincial Integrated Hospital, Kielce	10

18. Independent Public Clinical Hospital No. 2, Szczecin	10
19. St. Sophia's Specialist Hospital, Warszawa	8
20. K. Marcinkowski University Hospital, Zielona Góra	8
21. Multispeciality Municipal Hospital, Bydgoszcz	6
22. Ujastek Medical Center, Kraków	6
23. Independent Public Clinical Hospital No. 1, Lublin	6
24. T. Chałubiński Hospital, Ostrów Wielkopolski	6
25. Mazovian Specialist Hospital, Radom	6
26. Provincial Specialist Hospital, Słupsk	6
27. Mother and Newborn Center, Kielce	5
28. Independent Public Clinical Hospital No. 1, Police	5
29. University Clinical Center, Gdańsk	3
30. L. Rydygier Provincial Hospital, Toruń	3
31. A. Falkiewicz Specialist Hospital, Wrocław	3
All	500

Male newborns were slightly predominant (54.8%) in the study cohort. Median gestational age was 30 weeks, with a range of 22.6 – 36.9 weeks. Most of the deliveries were via caesarean section (90.6%) and the rate of antenatal corticosteroids was 78.4%.

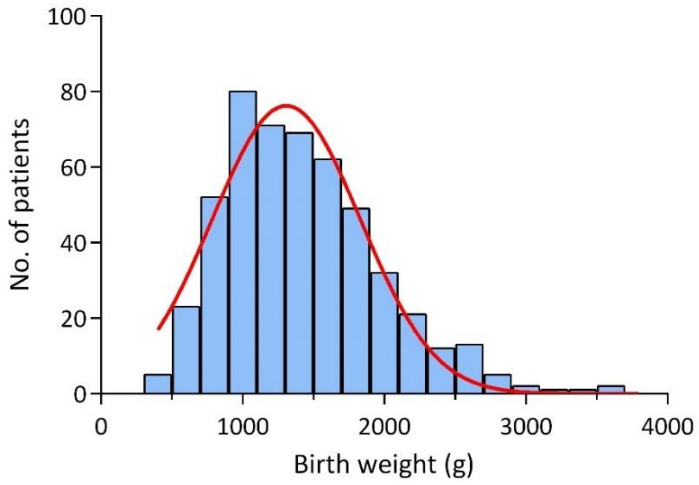
Median birth weight equaled 1,330 g and the median Apgar score at 5 minutes was 8 points.

Table 2. Baseline characteristics

Variable	Parameter	Total (N=500)
Sex	Female	226 (45.2%)
	Male	274 (54.8%)
Gestational age [weeks]	Number of observations	500
	Mean (SD)	30.09 (2.71)
	Median	30
	IQR	28 - 32
	Range	22.57 - 36.86
Antenatal corticosteroids	Yes	392 (78.4%)
	No	108 (21.6%)
Mode of delivery	Vaginal birth	47 (9.4%)
	Caesarean section	453 (90.6%)
Multiparity	Yes	153 (30.6%)
	No	347 (69.4%)
Birth weight [g]	Number of observations	500
	Mean (SD)	1412.85 (544.74)
	Median	1330
	IQR	990 - 1721.25
	Range	450 - 3630

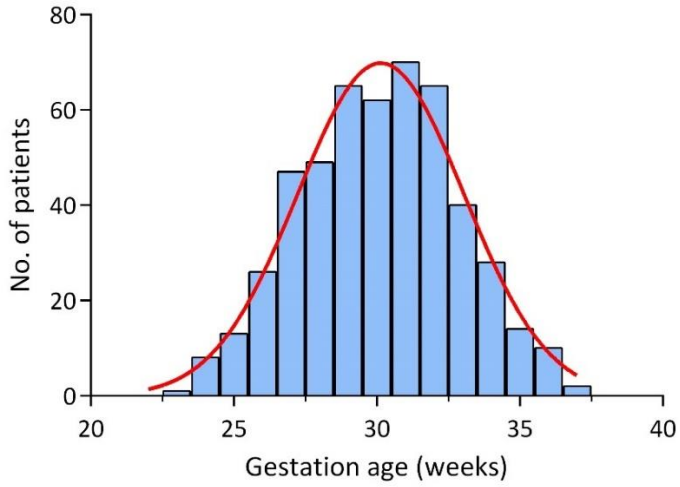
Variable	Parameter	Total (N=500)
Apgar 1 min	Number of observations	500
	Mean (SD)	6.5 (1.75)
	Median	7
	IQR	6 - 8
	Range	1 - 10
Apgar 5 min	Number of observations	500
	Mean (SD)	7.73 (1.18)
	Median	8
	IQR	7 - 8
	Range	2 - 10

Figure 1. Distribution of birth weight (g) in the study cohort



Bin Center (g)	# values
400	5
600	23
800	52
1000	80
1200	71
1400	69
1600	62
1800	49
2000	32
2200	21
2400	12
2600	13
2800	5
3000	2
3200	1
3400	1
3600	2
3800	0

Figure 2. Distribution of gestational age (weeks) in the study cohort



Bin Center (wks)	# values
22	0
23	1
24	8
25	13
26	26
27	47
28	49
29	65
30	62
31	70
32	65
33	40
34	28
35	14
36	10
37	2

7. Stabilization in the Delivery room

Upon delivery all newborns were placed under the radiant warmer and occlusive wrapping was used in 56% of infants. Positive pressure lung inflation was performed in 73.6% infants, almost exclusively (97%) with Neopuff™ Infant T-piece resuscitator, Fisher & Paykel, New Zealand. Oxygen supplementation was used in 84.0% of infants, with initial FiO_2 of 0.3 (median) and titrated to a maximum FiO_2 of 0.35 (median).

Table 3. Stabilization in the Delivery room

Variable	Parameter	Total
Thermal protection (polyethylene bag)	Yes	280 (56%)
	No	220 (44%)
Positive pressure lung inflation	Yes	368 (73.6%)
	No	132 (26.4%)
	Self-inflating bag	10 (2.7%)
	Neopuff™	357 (97%)
	Other	1 (0.3%)
Oxygen therapy in the Delivery Room	Yes	420 (84%)
	No	80 (16%)
Initial FiO_2	Number of observations	420
	Mean (SD)	0.29 (0.1)
	Median	0.3
	IQR	0.25 - 0.3
	Range	0.21 - 1
Maximum FiO_2	Number of observations	420
	Mean (SD)	0.42 (0.18)
	Median	0.35
	IQR	0.3 - 0.5
	Range	0.21 - 1

8. Premedication for LISA

About a fifth of infants (21.4%) were given premedication before LISA, mainly with ketamine (9% of all infants).

Details regarding the use of particular medicinal product is provided in the below table.

Table 4. Medication used for premedication for LISA

Premedication pattern	**N**	**% of all infants**
No premedication	393	78.6
With premedication	107	21.4
Monotherapy		
Ketamine	46	9.2
Midazolam	16	3.2
Glucose 30%	14	2.8
Propofol	8	1.6
Atropine	5	1.0
Phenobarbital	4	0.8
Morphine	3	0.6
Sufentanil	1	0.2
Thiopental	1	0.2
Polytherapy		
Ketamine + Atropine	5	1.0
Midazolam + Atropine	2	0.4
Fentanyl + Phenobarbital	1	0.2
Midazolam + Glucose 30%	1	0.2

9. Performance of LISA procedure

Only 2.2% LISA procedures were performed in the Delivery room. Mostly, the procedure was performed in the Neonatal Intensive Care Unit (NICU). The proceduralist was mainly neonatology consultant (74.6%), and 25% of proceduralists assessed their intubation experience at expert level.

Lisacath®, Chiesi Farmaceutici S.p.A. was the most commonly used catheter (86%). Alternative catheters included nasogastric tubes (7%), vascular catheters (2.4%) and others (3.4%). Magill forceps were used in only 2.4% of all cases.

The most common techniques of non-invasive respiratory support were nasal continuous positive airway pressure - nCPAP (40.2%) and biphasic positive airway pressure - BiPAP (38.4%). Double nasal cannula was the most often used interface (260 out of 500, 52.0%).

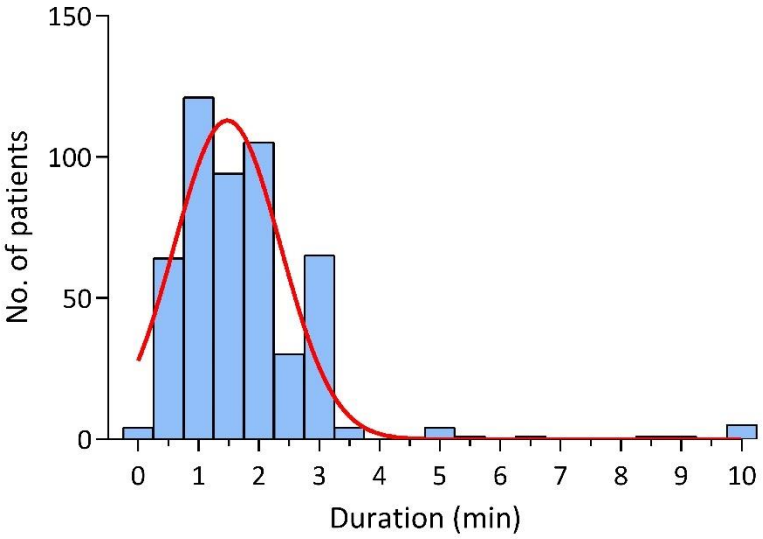
On average, the catheter was inserted into the trachea on the first attempt (87,4% of cases).

Table 5. LISA procedure performance

Variable	Parameter	Total
LISA procedure localization	Delivery room	11 (2.2%)
	NICU	489 (97.8%)
LISA proceduralist	Neonatology consultant	373 (74.6%)
	Neonatology resident	127 (25.4%)
Experience in intubation [0-10, where 0=none, 10=expert]	Number of observations	500
	Mean (SD)	8.04 (2.14)
	Median	9
	IQR	7 - 10
	Range	1 - 10
Type of catheter	Lisacath®	430 (86%)
	Nasogastric tube	35 (7%)
	Vascular catheter	12 (2.4%)
	Suction catheter	6 (1.2%)
	Other	17 (3.4%)
Use of Magill forceps	Yes	12 (2.4%)
	No	488 (97.6%)
Non-invasive respiratory support	nCPAP	201 (40.2%)
	BiPAP	193 (38.6%)
	NIPPV	119 (23.8%)
	HFNC	1 (0.2%)
	NHFOV	1 (0.2%)
Type of interface	Nasal cannula	277 (55.4%)
	RAM cannula	38 (7.6%)
	Nasopharyngeal tube	8 (1.6%)
	Nasal mask	177 (35.4%)
Type of interface - nasal	Double	260 (93.9%)
	Single	17 (6.1%)
Duration of surfactant instillation (min:s)	Number of observations	500
	Mean (SD)	1 min 45 s (1 min 18 s)
	Median	1 min 30 s
	IQR	1 min – 2min
	Range	10 s – 10 min
Number of attempts to insert a catheter into the trachea	Number of observations	500
	Mean (SD)	1.14 (0.4)
	Median	1
	IQR	1 - 1
	Range	1 - 4

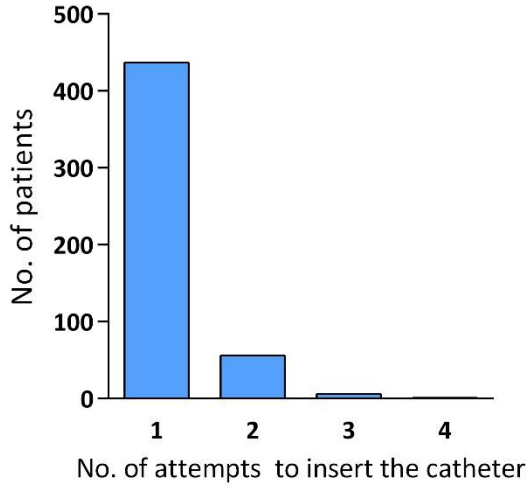
NIPPV = Nasal intermittent positive pressure ventilation
HFNC = High Flow Nasal Cannula
NHFOV = Non-invasive High Frequency Oscillatory Ventilation

Figure 3. Distribution of duration of surfactant instillation (minutes)



Bin Center (min)	# values
0.0	4
0.5	64
1.0	121
1.5	94
2.0	105
2.5	30
3.0	65
3.5	4
4.0	0
4.5	0
5.0	4
5.5	1
6.0	0
6.5	1
7.0	0
7.5	0
8.0	0
8.5	1

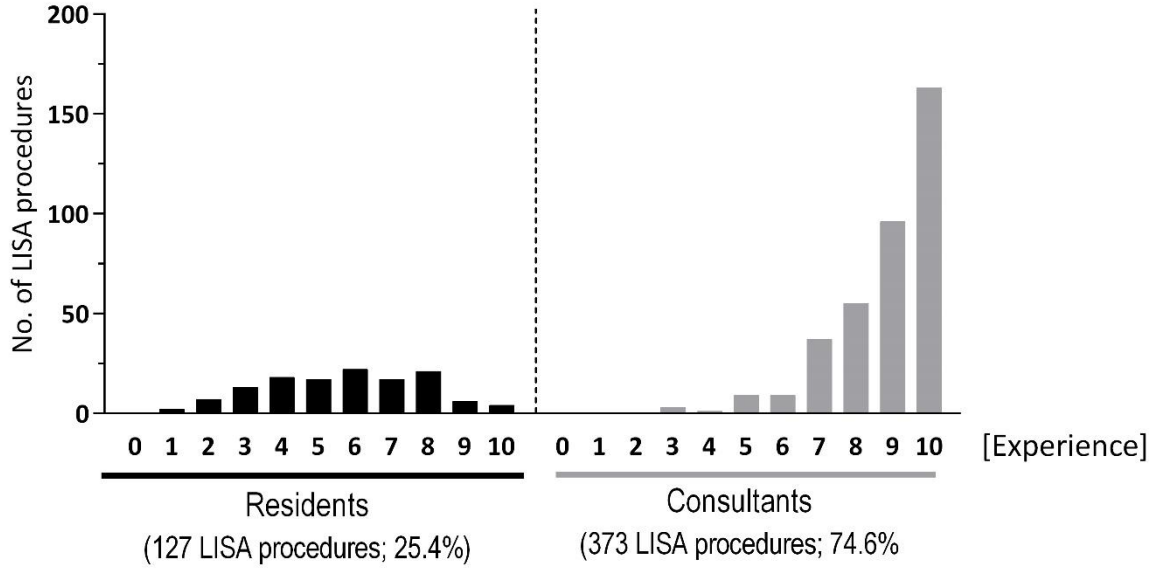
Figure 4. Distribution of number of attempts to insert intratracheal catheter



# attempts	# infants	% frequency
1	437	87.4%
2	56	11.2%
3	6	1.2%
4	1	0.2%

Figure 5. Experience in intubation by proceduralist's qualifications (consultants vs residents).

Experience was self-assessed in the scale of 0-10, where 0=no experience and 10=expert



10. Surfactant (SF)

In almost all procedures (98.2%) poractant alfa was used (Curosurf®, Chiesi Farmaceutici S.p.A.), at a median dosage of 192 mg/kg body weight (BW). Beractant (Survanta®, AbbVie) was applied to nine infants (1.8%) and its median dosage was 99 mg/kg BW.

Surfactant was administered on average 2.12 hours post birth (median), with 90% of all applications in the first 24h of life.

The median time of SF instillation was 1 minute 30 seconds (minimal time was 10 seconds, maximal 10 minutes).

Median FiO_2 level prior to SF was 0.4, and median SpO_2 was 90%.

Seventy-six infants (15.2%) required SF redosing. Of those infants who required 2 doses of SF, 26 (41%) received the second dose using LISA again. Of those babies who required 3 doses, LISA was used in 6 infants (50%) on the first re-treatment and 1 infant (8%) on the second re-treatment.

Figure 6. Methods of surfactant administration in infants (N=63) requiring second dose

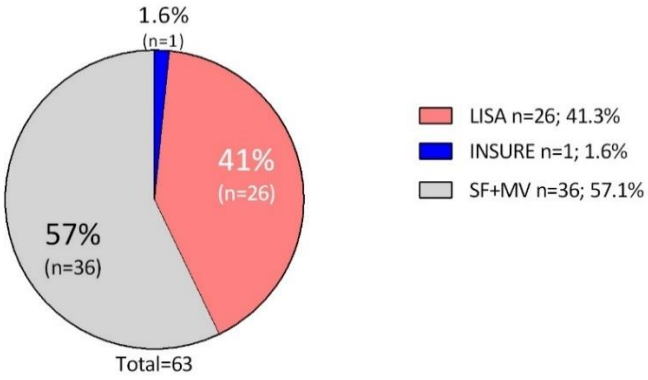


Figure 7. Methods of surfactant administration in infants (N=12) requiring 3 doses

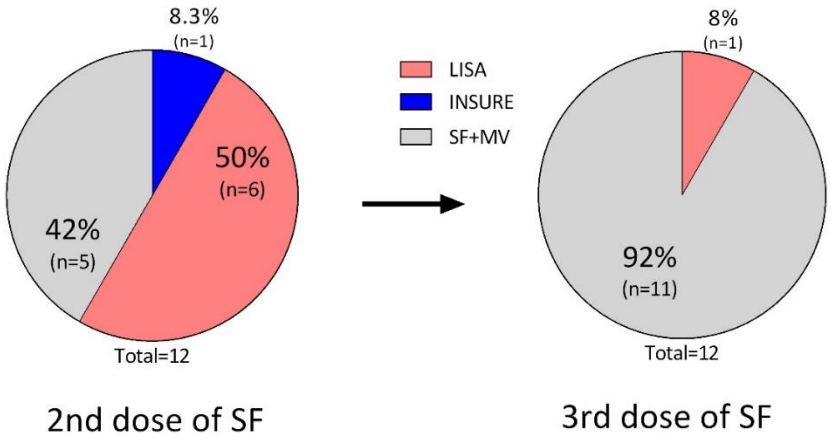
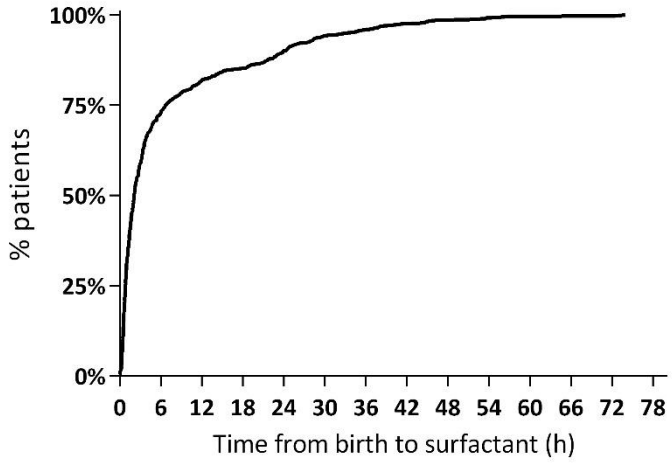


Table 6. Surfactant administration

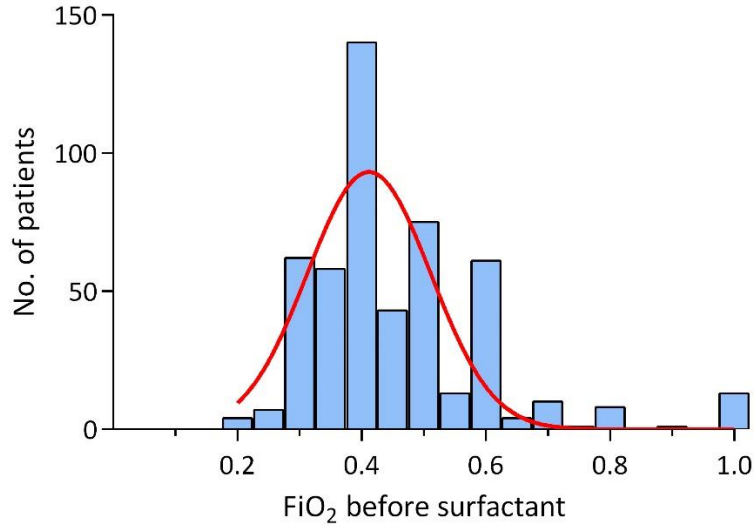
Variable	Parameter	Total
Surfactant generic name	Poractant alfa	491 (98.2%)
	Beractant	9 (1.8%)
Dose of poractant alfa [mg/kg BW]	Number of observations	491
	Mean (SD)	174.83 (40.4)
	Median	192.51
	IQR	157.96 - 200
	Range	40.68 - 266.67
Dose of beractant [mg/kg BW]	Number of observations	9
	Mean (SD)	96.27 (6.63)
	Median	98.87
	IQR	92.17 - 101.88
	Range	83.49 - 103.45
Time from birth to surfactant [hours]	Number of observations	500
	Mean (SD)	7.19 (11.59)
	Median	2.12
	IQR	0.83 - 6.68
	Range	0 - 73.92
Time from birth to surfactant		
<15 min	N (%)	15 (3%)
15 min – 2 h	N (%)	226 (45.2%)
2 h – 24 h	N (%)	209 (41.8%)
>24 h	N (%)	50 (10%)
No. of surfactant doses; N (%)	1 dose	423 (84.6%)
	2 doses	63 (12.6%)
	3 doses	12 (2.4%)
	4 doses	1 (0.2%)
	Missing	1 (0.2%)
FiO_2 prior to surfactant	Number of observations	500
	Mean (SD)	0.46 (0.15)
	Median	0.4
	IQR	0.35 - 0.5
	Range	0.21 - 1
SpO_2 prior to surfactant	Number of observations	500
	Mean (SD)	88.87 (7.13)
	Median	90
	IQR	87 - 93
	Range	40 - 100

Figure 8. Cumulated histogram of time from birth to surfactant (hours)



Time to SF (h)	% frequency (cumulated)
0	0.4
4	66.6
8	77.2
12	81.8
16	84.8
20	86.4
24	90.0
28	92.8
32	94.6
36	95.8
40	97.2
44	97.8
48	98.6
52	98.8
56	99.4
60	99.6
76	100.0

Figure 9. Distribution of FiO2 prior to surfactant



Bin Center	# values
0.20	4
0.25	7
0.30	62
0.35	58
0.40	140
0.45	43
0.50	75
0.55	13
0.60	61
0.65	4
0.70	10
0.75	1
0.80	8
0.85	0
0.90	1
0.95	0
1.00	13

11. Caffeine citrate

All but 4 infants received caffeine citrate. On average, caffeine treatment was initiated at 1.3 h of life (median). Majority of infants 309/496 (63%) received caffeine before surfactant or concomitantly with surfactant.

Table 7. Caffeine citrate

Variable	Parameter	Total
Caffeine citrate	Yes	496 (99.2%)
	No	4 (0.8%)
Time from birth to caffeine (h)	Number of observations	493
	Mean (SD)	8.32 (59.49)
	Median	1.3
	IQR	0.73 - 2.42
	Range	0 - 910.23

12. Assessment of difficulty of LISA procedure

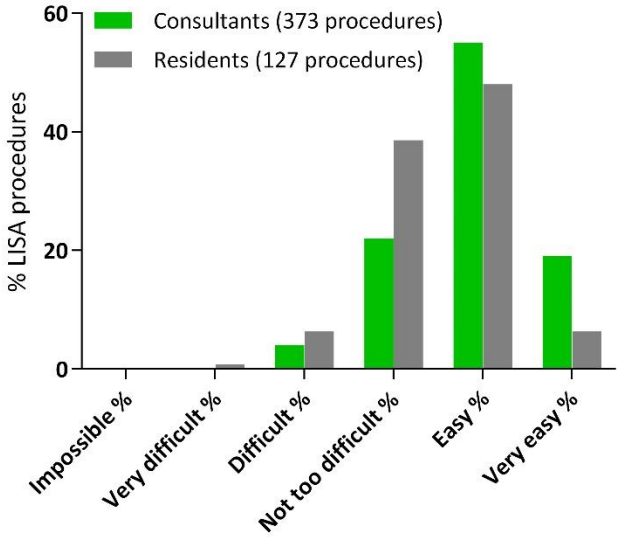
LISA procedure was self-assessed by the performer on a 6-point scale: “very easy”, “easy”, “somewhat difficult”, “difficult” and “impossible to perform”,

LISA was regarded as “very easy” or “easy” in 69.0% infants. In no case was it assessed as “impossible to perform”, and only in 1 infant as “very difficult”.

Table 8. Difficulty of performing LISA – proceduralist’s assessment

Variable	Parameter	Total (N=500)
Difficulty of LISA procedure: self-assessment (ordinal scale)	Impossible to perform	0 (0%)
	Very difficult	1 (0.2%)
	Difficult	23 (4.6%)
	Somewhat difficult	131 (26.2%)
	Easy	266 (53.2%)
	Very easy	79 (15.8%)

Figure 10. Comparison of difficulty of LISA: neonatology consultants vs. neonatology residents



	Consultants	Residents
Impossible %	0.00	0.00
Very difficult %	0.00	0.80
Difficult %	4.00	6.30
Not too difficult %	22.00	38.60
Easy %	55.00	48.00
Very easy %	19.00	6.30

Physicians' qualifications (consultants vs residents) had a significant impact on the assessment of difficulty of LISA.

Taking the degree of difficulty as a numerical variable from 1 (very easy procedure) to 6 (impossible to perform), in the linear mixed effect model with intercepts for investigators included as a random effect, the mean difficulty score was 2.18 for a specialist and 2.50 for a resident (least-square means). The difference between the groups was significant ($p<0.0001$).

In summary, residents rated LISA more difficult.

13. Treatment outcomes

13.1. CPAP failure

CPAP failure was defined as the need for invasive ventilation in the first 72 h of life. Overall, 114 infants (22.8%) needed intubation and mechanical ventilation by 72 h of life.

13.2. Mechanical ventilation

Overall, less than one third of newborns were subject to mechanical ventilation (MV) during hospitalization (31.0%). Majority of those patients (73.5%) required MV within 72h since birth. Median duration of MV was 6 days. High Frequency Oscillatory Ventilation (HFOV) was used in 21.9% of cases.

Table 9. Treatment outcomes – mechanical ventilation

Variable	Parameter	Total
Need for intubation and mechanical ventilation during hospitalization	Yes	155 (31%)
	No	344 (68.8%)
	Missing data	1 (0.2%)
Duration of mechanical ventilation [days]	Number of observations	155
	Mean (SD)	9.5 (11.34)
	Median	6
	IQR	2 - 11.5
	Range	0.08 - 67
Use of HFOV in mechanically ventilated patients	Yes	34 (21.9%)
	No	121 (78.1%)

HFOV = High Frequency Oscillatory Ventillation

13.3. Non-invasive respiratory support

As far as non-invasive ventilation techniques are concerned, nCPAP was most common. Overall, it was used in 77.8% of infants during hospitalization. An average exposure to non-invasive ventilation was 7 days (median).

Table 10. Treatment outcomes – non-invasive ventilation

Variable	Parameter	Total
Non-invasive ventilation technique	nCPAP	389 (77.8%)
	Biphasic positive airway pressure (BiPAP)	257 (51.4%)
	NIPPV/synchronized NIPPV	154 (30.8%)
	High-flow nasal cannulas (HFNC)	78 (15.6%)
Duration of non-invasive ventilation [days]	Number of observations	500
	Mean (SD)	13.8 (15.15)
	Median	7
	IQR	4 - 21
	Range	0 - 87

13.4. In-hospital mortality and typical complications of prematurity

Of 500 included infants, 23 have died, which gives a rate of 4.6%. It must be however considered that 53 (10.6%) infants have been transferred to another hospital or department and were lost to follow up, hence the actual in-hospital mortality rate might be higher.

Severe bronchopulmonary dysplasia occurred in cases of 4.2% of subjects, moderate in 10.4% and mild in 17.0%.

About 9.2% of infants required treatment due to retinopathy.

Frequency of intraventricular hemorrhage was 18.8%, and severe IVH 4%.

A little lower was the frequency of persistent ductus arteriosus (14.0%), which was usually treated pharmacologically (94.3% of cases).

Periventricular leukomalacia was a far less frequent complication (3.8%).

Table 11. Results of treatment – complications

Variable	Parameter	Total
BPD	No	341 (68.2%)
	Mild	85 (17%)
	Moderate	52 (10.4%)
	Severe	21 (4.2%)
	Missing data	1 (0.2%)
Retinopathy requiring treatment	Yes	46 (9.2%)
	No	453 (90.6%)
	Missing data	1 (0.2%)
Intraventricular hemorrhage (IVH)	Yes	94 (18.8%)
	No	405 (81%)
	Missing data	1 (0.2%)
Severe IVH	Yes	20 (4%)
	No	479 (96%)
Periventricular leukomalacia	Yes	19 (3.8%)
	No	480 (96%)
	Missing data	1 (0.2%)
Persistent ductus arteriosus requiring treatment	Yes	70 (14%)
	No	429 (85.8%)
	Missing data	1 (0.2%)
	Pharmacological treatment	63 (90%)
	Ligation	4 (5.7%)
	Both	3 (4.3%)

13.5. Termination of hospitalization

Of 500 enrolled infants, 423 (84.6%) were discharged home (survivors), after a median of 46 days of hospitalization.

Fifty-three babies were transferred to another hospital/ward after a median of 41 days treatment (range 0 – 109 days).

A median duration of hospitalization was 44 days overall, and 46 days in survivors.

Table 12. Termination of hospitalization

Variable	Parameter	Total
Reason for hospital discharge	Completion of treatment	423 (84.6%)
	Transfer to other ward/hospital	53 (10.6%)
	Death	23 (4.6%)
	Missing data	1 (0.2%)
Overall duration of hospitalization (days)	Number of observations	499
	Mean (SD)	46.79 (26.23)
	Median	44
	IQR	29 - 64
	Range	0 - 136
	Missing data	1

Table 13. Comparison of duration of hospitalization (days)

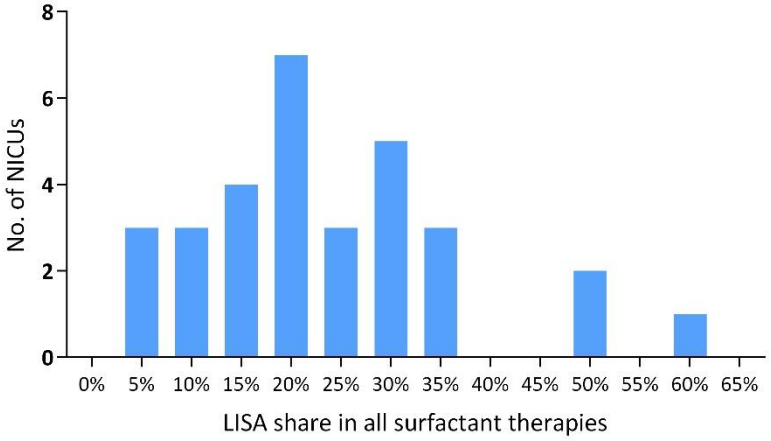
	Discharged home	Transferred to another hospital/department	Died
Number of values	423	53	23
Minimum	7	0	0.39
25% Percentile	31	20	1.35
Median	46	41	3.17
75% Percentile	65	67	9.25
Maximum	136	109	31.26
Mean	49.11	45.36	7.36
Std. Deviation	24.28	32.13	9.60
Std. Error of Mean	1.181	4.413	2.00

13.6. Percentage share of LISA compared to other administration methods

The percentage of LISA use out of other administration methods in the participating study sites were calculated. Sales volumes of Curosurf at investigational sites during the study conduct were used to obtain data on use of other administration methods.

The percentage of LISA use compared to other administration methods was of 24% and ranged from a minimum of 3.5% to a maximum of 61%.

Figure 11. LISA percentage share in 31 NICUs participating in START study



	LISA share (% all SF)
Minimum	3.5
25% Percentile	14.6
Median	20.6
75% Percentile	32.3
Maximum	60.6
Mean	24.0
Std. Deviation	13.4

14. Safety and tolerability of LISA

Safety and tolerability of LISA was evaluated with the rate of Adverse Events (AEs) during the procedure, as well as changes of the oxygenation status. The latter was assessed by the lowest SpO_2 and highest FiO_2 during LISA, as compared to baseline values recorded directly before LISA.

The pre-defined AEs of special interest (AESIs) were:

- surfactant reflux;
- clinically relevant bradycardia, desaturation, apnea;
- need for rescue intubation;
- unilateral surfactant deposition.

The investigators were free to record also other AEs occurring during LISA procedure, apart from the AESI listed above.

The investigators reported severity of AESI and other AEs, as well as their relatedness to the pharmacological effects of pulmonary surfactant (poractant alfa or beractant). The assessment of relatedness was not applicable to surfactant reflux and unilateral surfactant deposition. Both were regarded technical errors of the drug administration procedure.

14.1. Adverse Events during LISA procedure

There were altogether 255 adverse events (AEs) reported in START study, affecting 184 patients in total.

Most common AEs were oxygen desaturation (22%) and surfactant reflux (18.8%).

Table 14. Adverse events during LISA procedure

AE during LISA procedure	**Total=500 n (%)**
Oxygen desaturation	110 (22%)
Surfactant reflux	94 (18.8%)
Bradycardia	21 (4.2%)
Apnea	19 (3.8%)
Need for rescue intubation	6 (1.2%)
Unilateral surfactant deposition	2 (0.4%)
Other	3 (0.6%)

Table 15. Summary of patients with AEs during LISA procedure as reported by the investigators

Patients	**Total=500 n(%)**
Patients with AEs	184 (36.8%)
Patients with AESIs	183 (36.6%)
Patients with SAEs	6 (1.2%)
Patients with ADRs to surfactant	101 (20.2%)
Patients with SADRs to surfactant	6 (1.2%)

AE = Adverse Event ADR = Adverse Drug Reaction, SAE = Serious Adverse Event,
AESI = Adverse Event of Special Interest, SADR = Serious Adverse Drug Reaction

Table 16. AESI and other AEs by relatedness to surfactant

Variable	Total pts=500	
Oxygen desaturation	**110 (22%)**	
Relatedness to surfactant	Unrelated	16 (3.2%)
	Possibly related	42 (8.4%)
	Probably related	39 (7.8%)
	Definitely related	13 (2.6%)
Bradycardia	**21 (4.2%)**	
Relatedness to surfactant	Unrelated	3 (0.6%)
	Possibly related	6 (1.2%)
	Probably related	9 (1.8%)
	Definitely related	3 (0.6%)
Apnea	**19 (3.8%)**	
Relatedness to surfactant	Unrelated	6 (1.2%)
	Possibly related	5 (1.0%)
	Probably related	6 (1.2%)
	Definitely related	2 (0.4%)
Need for rescue intubation	**6 (1.2%)**	
Relatedness to surfactant	Unrelated	3 (0.6%)
	Possibly related	1 (0.2%)
	Probably related	2 (0.4%)
	Definitely related	0
Other adverse events	**3 (0.6%)**	
Left pneumothorax	2 (0.4%)	
Relatedness to surfactant	Unrelated	1 (0.2%)
	Possibly related	0
	Probably related	1 (0.2%)
	Definitely related	0
Bilateral pneumothorax	1 (0.2%)	
Relatedness to surfactant	Unrelated	0
	Possibly related	0
	Probably related	1 (0.2%)
	Definitely related	0

Table 17. AESI and other AEs by severity of symptoms

Variable	Total pts=500	
Oxygen desaturation	**110 (22%)**	
Symptoms severity	Mild	68 (13.6%)
	Moderate	32 (6.4%)
	Severe	10 (2.0%)
Bradycardia	**21 (4.2%)**	
Symptoms severity	Mild	8 (1.6%)
	Moderate	11 (2.2%)
	Severe	2 (0.4%)
Apnea	**19 (3.8%)**	
Symptoms severity	Mild	8 (1.6%)
	Moderate	5 (1.0%)
	Severe	6 (1.2%)
Need for rescue intubation	**6 (1.2%)**	
Symptoms severity	Mild	0
	Moderate	1 (0.2%)
	Severe	5 (1.0%)
Other adverse events	**3 (0.6%)**	
Left pneumothorax	2 (0.4%)	
Symptoms severity	Mild	0
	Moderate	0
	Severe	2 (0.4%)
Bilateral pneumothorax	1 (0.2%)	
Symptoms severity	Mild	0
	Moderate	0
	Severe	1 (0.2%)

14.2. Adverse Drug Reactions to surfactant

All AEs with relatedness to surfactant (poractant alfa or beractant) indicated as “possibly related”, “probably related” or “definitely related” were classified as Adverse Drug Reactions (ADRs).

Of 255 AEs, 130 (51%) were classified as ADRs. ADRs included 9 serious and 121 non-serious cases.

All reported cases of oxygen desaturation, bradycardia and apnea were upgraded to Important Medical Events (IME) by the Study Sponsor.

Table 18. Adverse events according to surfactant type

Variable	All (N=500)	Poractant alfa (N=491)	Beractant (N=9)
Oxygen desaturation	110 (22%)	107 (21.8%)	3 (33.3%)
Surfactant reflux	94 (18.8%)	89 (18.1%)	5 (55.6%)
Bradycardia	21 (4.2%)	21 (4.3%)	0
Apnea	19 (3.8%)	18 (3.7%)	1 (11.1%)
Need for rescue intubation	6 (1.2%)	6 (1.2%)	0
Unilateral surfactant deposition	2 (0.4%)	2 (0.4%)	0
Other	3 (0.6%)	3 (0.6%)	0

14.2.1. Adverse Drug Reactions to poractant alfa (Curosurf)

One hundred twenty-seven ADRs to Curosurf were recorded during the study, affecting 98 of 491 (19.9%) patients treated with Curosurf.

Of 98 patients affected, Serious Adverse Drug Reactions (SADRs) occurred in 6 infants.

The below table presents distribution of the number of ADRs and SADRs to Curosurf, based on seriousness as reported by the investigators.

Table 19. Summary of ADRs to Curosurf as reported by the investigators.

	Curosurf patients=491	
Oxygen desaturation	**92 (18.7%)**	
Seriousness of ADR	Serious	4 (0.8%)
	Non-serious	88 (17.9%)
Bradycardia	**18 (3.7%)**	
Seriousness of ADR	Serious	1 (0.2%)
	Non-serious	17 (3.5%)
Apnea	**12 (2.4%)**	
Seriousness of ADR	Serious	1 (0.2%)
	Non-serious	11 (2.2%)
Need for rescue intubation	**3 (0.6%)**	
Seriousness of ADR	Serious	2 (0.4%)
	Non-serious	1 (0.2%)
Other (pneumothorax)	**2 (0.4%)**	
Seriousness of ADR	Serious	1 (0.2%)
	Non-serious	1 (0.2%)
All	**127 (19.9%)**	
Seriousness of ADR	Serious	9 (1.2%)
	Non-serious	118 (18.7%)

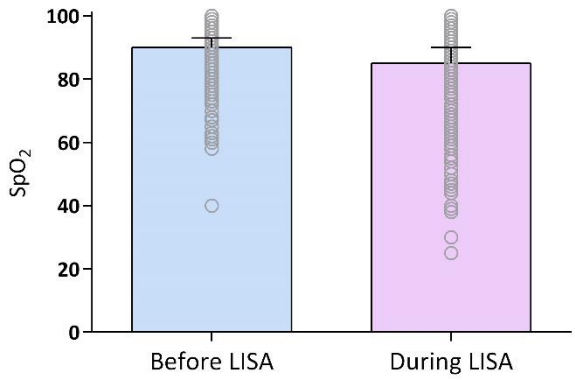
Bolded figures represent no. of ADRs (% pts. affected). Percentages calculated relative to the number of patients treated with Curosurf (n = 491)

14.3. Oxygenation status during LISA procedure

Oxygen saturation significantly decreased, from baseline median value of 90% (before LISA) to 85% during LISA ($p<0.0001$, Wilcoxon signed rank test).

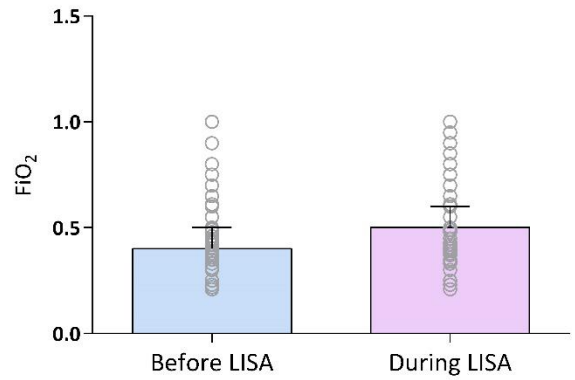
Also, maximum level of FiO_2 was significantly higher during LISA, compared to before LISA (median value of 0.50 vs. 0.40; $p<0.0001$, Wilcoxon signed rank test)

Figure 12. Change of SpO2 during LISA procedure (lowest SpO_2 vs. baseline value recorded directly before LISA)



	Before LISA	During LISA	During LISA - Before LISA
Number of values	500	500	500
Minimum	40.00	25.00	-70.00
25% Percentile	87.00	77.00	-11.75
Median	90.00	85.00	-4.000
75% Percentile	93.00	90.00	0.0
Maximum	100.0	100.0	40.00
Mean	88.87	81.14	-7.730
Std. Deviation	7.131	12.29	12.60
Std. Error of Mean	0.3189	0.5495	0.5636
Lower 95% CI	88.25	80.06	-8.837
Upper 95% CI	89.50	82.22	-6.623

Figure 13. Change of FiO2 during LISA procedure (lowest FiO_2 vs. baseline value recorded directly before LISA)



	Before LISA	During LISA	During LISA - Before LISA
Number of values	500	500	500
Minimum	0.2100	0.2100	-0.1500
25% Percentile	0.3500	0.4000	0.0
Median	0.4000	0.5000	0.0
75% Percentile	0.5000	0.6000	0.1000
Maximum	1.000	1.000	0.6500
Mean	0.4573	0.5267	0.06942
Std. Deviation	0.1450	0.1910	0.1399
Std. Error of Mean	0.006487	0.008542	0.006258
Lower 95% CI	0.4445	0.5099	0.05712
Upper 95% CI	0.4700	0.5435	0.08172

15. LISA vs INSURE

Neonatal outcomes in the START cohort were compared to the historical cohort of infants who received surfactant with INSURE (intubation-surfactant-extubation) technique. The study protocol presumed that the comparison will be based on the INSURE data from the non-interventional study conducted in Poland between 2014 and 2015 (Borszewska-Kornacka MK et al. PLoS One. 2017 Dec 20;12(12):e0189152).

As newer Polish data on the efficacy of INSURE became available during the conduct of this study, an additional comparison was also made, using the newer cohort from 2016-2018 (Gulczyńska E et al. Neonatology 2019 116(2):171-178]).

15.1. Pre-planned comparison (vs 2014-2015 cohort)

15.1.1. Clinical characteristics of LISA and INSURE cohorts

Comparison of baseline characteristics between the LISA cohort and the INSURE cohort of 2014-2015 showed significant differences regarding gestational age, birth weight, 5 min Apgar score, antenatal steroid therapy and rate of cesarean deliveries.

To compensate for the imbalance of baseline characteristics, propensity score matching (PSM) was used. After PSM, 269 LISA infants were matched with 269 INSURE infants with similar characteristics (Table 20).

Table 20. Baseline characteristics before and after propensity-score matching

	Before matching			After matching		
	INSURE (N=302)	LISA (N=500)	p-value	INSURE (N=269)	LISA (N=269)	p-value
Gender (male)	159 (53)	274 (54.8)	0.6735	147 (54.6)	149 (55.4)	0.9309
Gestational age (weeks)	29 [27.4-30.3]	30 [28-32]	<0.0001	29 [27.7-30.7]	29 [27.4-31]	0.7237
Birth weight (g)	1200 [950-1442]	1330 [990-1721]	<0.0001	1205 [950-1480]	1160 [940-1480]	0.5315
Birth weight <1000g,	85 (28.3)	127 (25.4)	0.4080	77 (28.6)	82 (30.5)	0.7055
Antenatal steroids,	256 (85.9)	392 (78.4)	0.0114	230 (85.5)	236 (87.7)	0.5266
Apgar 5 min	8 [7-8]	8 [7-8]	0.0213	8 [7-8]	8 [7-8]	0.7298
Cesarean delivery	248 83.2)	453 [90.6]	0.0029	234 (87)	237 (88.1)	0.7940
Multiparity	92 [31.2]	153 [30.6]	0.9255	87 (33)	88 (32.7)	1

Data are n (%) or median [IQR]

15.1.2. Comparison of neonatal outcomes

In the propensity-matched cohorts LISA was associated with significantly lower rate of IVH compared to INSURE cohort (24.2% vs 33.7%; p=0.0201) and a trend towards lower need for MV (36.4% vs 45%; p=0.0535).

However, in infants who required MV, its median duration was significantly longer in the LISA cohort (7 days vs 3.2 days; p=0.0001), which might contribute to the higher rate of BPD (40.9% vs 28.2%; p=0.0344). Also, PDA was more frequent in infants treated with LISA (20.1% vs 12.8%; p=0.0345).

The neonatal outcomes before and after PSM are summarized in Table 21.

Table 21. Neonatal outcomes in the LISA and INSURE cohorts

	Before matching			After matching		
	INSURE (N=302)	LISA (N=500)	p-value	INSURE (N=269)	LISA (N=269)	p-value
Death	9 (3)	23 (4.6)	0.3627	6 (2.3)	13 (4.8)	0.1686
BPD	87 (28.8)	158 (31.6)	0.8712	76 (28.2)	110 (40.9)	0.0344
Any MV	141 (46.7)	155 (31)	<0.0001	121 (45)	98 (36.4)	0.0535
Duration of MV (days)	4 [0.75-8.9]	6 [2-11.5]	0.0033	3.2 (0.5-8]	7 [2-13.5]	0.0001
IVH	103 (35.5)	94 (18.8)	<0.0001	87 (33.7)	65 (24.2)	0.0201
IVH grade 3 or 4	17 (5.9)	20 (4)	0.3110	14 (5.4)	13 (4.8)	0.9113
PDA	42 (14.5)	70 (14)	0.9285	33 (12.8)	54 (20.1)	0.0345
ROP	34 (11.8)	46 (9.2)	0.3009	30 (11.7)	35 (13)	0.7514
PVL	11 (3.9)	19 (3.8)	1	8 (3.2)	13 (4.8)	0.4545
Surfactant redosing	37 (13.2)	76 (15.2)	0.5088	32 (12.7)	46 (17.1)	0.2056

Data are n (%) or median [IQR]

15.2. Additional comparison (vs 2016-2018 cohort)

Additional analysis, not planned in the study protocol, included comparison of neonatal outcomes of the studied LISA cohort and infants treated with INSURE technique in the newer cohort (PICO study).

Age- and birth weight-adjusted odds for death and major neonatal morbidity were not significantly different in the LISA and INSURE groups, except for a trend towards lower rates of intraventricular hemorrhages in LISA-treated infants (19% vs 36%; p=0.067).

Table 22. Comparison of major neonatal morbidity and survival between the current study cohort (LISA) and the cohort of infants treated with INSURE in the previous year.

Variable	LISA (N=500)	INSURE (N=127)	LISA vs INSURE	
			Crude OR (95% CI)	Adjusted OR (95% CI)
Death	23 (4.6%)	9 (7.1%)	0.63 (0.29-1.41)	0.99 (0.45-2.37)
Death or BPD	180 (36.1%)	68 (54.4%)	0.47 (0.32-0.70)	1.37 (0.85-2.23)
BPD	127 (30%)	54 (49.1%)	0.44 (0.29-0.68)	1.52 (0.89-2.61)
MV <72 h	114 (22.8%)	31 (24.4%)	0.91 (0.58-1.44)	1.36 (0.85-2.22)
Any MV	155 (31%)	50 (39.4%)	0.69 (0.46-1.04)	1.22 (0.79-1.88)
IVH	94 (18.8%)	46 (36.2%)	0.41 (0.27-0.63)	0.66 (0.42-1.04)
IVH grade 3 or 4	20 (4%)	12 (9.4%)	0.40 (0.19-0.84)	0.63 (0.30-1.40)
ROP	46 (9.2%)	16 (12.8%)	0.69 (0.38-1.27)	1.19 (0.64-2.31)
PDA	70 (14%)	25 (19.7%)	0.67 (0.40-1.10)	1.02 (0.61-1.76)
SF redosing	76 (15.2%)	16 (12.6%)	1.25 (0.70-2.22)	1.57 (0.88-2.94)

16. Study conclusions

This naturalistic multicenter observational study aimed at evaluating the adoption of LISA in Poland reported a six-fold increase in the use of LISA in participating centers compared with previous years (24% of all surfactant therapies vs 4%). For most (77%) of the 500 premature infants, LISA was a successful treatment. The method has been shown to be relatively easy to perform as indicated by 69% of the procedures rated “easy” and “very easy”. The most frequent complications during the LISA procedure were oxygen desaturations (22%) and surfactant reflux (19%).

In summary, LISA is relatively easy to learn, but variable adoption rates in the study sites indicate that more time is needed until it becomes the dominant method of surfactant administration.

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List of tables

List of figures