Two-year outcomes after minimally invasive surfactant therapy in preterm infants: Follow-up of the OPTIMIST-A randomized clinical trial

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KEY POINTS

Question: For preterm infants with respiratory distress syndrome supported with continuous positive airway pressure (CPAP), does administration of surfactant via a thin catheter improve survival without moderate-severe neurodevelopmental disability (NDD) at 2 years of age compared with sham treatment?

Findings: In this follow-up of a randomized clinical trial of 486 infants at 25 to 28 weeks' gestation, the composite outcome of death or NDD at two years of age occurred in 36.3% receiving minimally invasive surfactant therapy compared with 36.1% receiving sham treatment.

Meaning: In preterm infants supported with CPAP, minimally invasive surfactant therapy did not lead to a reduction in the composite outcome of death or neurodevelopmental disability at 2 years of age.

ABSTRACT

Importance: The long-term effects of surfactant administration via a thin catheter (minimally invasive surfactant therapy, MIST) in preterm infants with respiratory distress syndrome remain to be definitively clarified.

Objective: To examine the effect of MIST on death or neurodevelopmental disability (NDD) at 2 years corrected age.

Design, Setting and Participants: Prospective follow-up study of a randomized clinical trial with blinding of clinicians and outcome assessors, conducted in 33 tertiary-level neonatal intensive care units in 11 countries. The trial included 486 infants with a gestational age of 25 to 28 weeks supported with continuous positive airway pressure (CPAP). Collection of follow up data at 2 years corrected age was completed on December 9, 2022.

Interventions: Infants assigned to MIST (n=242) received exogenous surfactant (200 mg/kg poractant alfa) via a thin catheter; those assigned to the control group (n=244) received sham treatment.

Main outcomes and measures: The key secondary outcome death or moderate-severe NDD was assessed at 2 years corrected age. Other secondary outcomes included components of this composite outcome, as well as hospitalizations for respiratory illness and parent-reported wheezing or breathing difficulty in the first 2 years.

Results: Among the 486 infants randomized, 453 had follow-up data available (median gestation 27.3 weeks; 228 [50.3%] female); data on the key secondary outcome were available in 434. Death or NDD occurred in 78 (36.3%) of infants in the MIST group and 79 (36.1%) in the control group (relative risk [RR], 1.0 [95% CI, 0.81–1.24]); components of this outcome did not differ significantly between groups.

Secondary respiratory outcomes favored the MIST group. Hospitalization with respiratory illness occurred in 49 (25.1%) infants in the MIST group vs 78 (38.2%) in the control group (RR, 0.66 [95% CI, 0.54–0.81]) and parent-reported wheezing or breathing difficulty in 73 (40.6%) vs 104 (53.6%) (RR, 0.76 [95% CI, 0.63–0.90]).

Conclusions and Relevance: In this follow-up study of a randomized clinical trial of preterm infants with respiratory distress syndrome supported with CPAP, MIST compared with sham treatment did not reduce the incidence of death or NDD by 2 years of age. However, infants who received MIST had lower rates of adverse respiratory outcomes during their first 2 years of life.

Trial registration: ACTRN12611000916943.

INTRODUCTION

Bronchopulmonary dysplasia (BPD), the chronic disease of the preterm lung, has lasting effects on respiratory health in infancy and childhood,[1] and may be associated with a greater risk of neurodevelopmental disability (NDD) throughout childhood and adolescence.[2] It has been posited that interventions to reduce BPD frequency could produce lasting benefit on neurodevelopment and/or respiratory health.

Delivery of surfactant via a thin catheter, an emerging technique for spontaneously breathing preterm infants with respiratory distress syndrome (RDS), is known to improve survival without BPD in preterm infants. A meta-analysis of data from 14 randomized controlled trials (RCTs) found surfactant delivery via thin catheter, compared with administration via endotracheal tube, to be associated with a lower frequency of the composite outcome of death or BPD [relative risk (RR) 0.59, 95% confidence interval (CI) 0.48 to 0.73], and of BPD in survivors (RR 0.57, 95% CI 0.45 to 0.74).[3] However, only one of these 14 studies specifically targeted infants less than 29 weeks' gestation, the group most at risk of BPD and other morbidities.[4] Only this study reported outcomes beyond the first hospitalization, finding a benefit of surfactant delivery via thin catheter in relation to neurodevelopment[5] but not respiratory function at 5-9 years.[6] Another RCT comparing surfactant delivery via a thin catheter with ongoing respiratory support with continuous positive airway pressure (CPAP) did not detect a difference in incidence of BPD,[7] nor was there a discernible effect on rate of NDD at 2 years of age.[8]

The OPTIMIST-A trial (one of cOllaborative Paired Trials Investigating Minimally Invasive Surfactant Therapy) compared surfactant delivery via thin catheter

(minimally invasive surfactant therapy, MIST) with sham treatment, and in relation to outcomes during first hospitalization, found no clear difference in the primary outcome of death or BPD, but a reduction in BPD in survivors to 36 weeks' postmenstrual age (RR 0.83, 95% CI 0.70-0.98).[9] We now report outcomes at 2 years corrected age in infants enrolled in the OPTIMIST-A trial, examining the hypothesis that application of MIST would reduce the incidence of the composite outcome of death or moderate-severe NDD, or its components.

METHODS

Study design and oversight

The trial was an investigator-initiated international multicenter, blinded randomized clinical trial, conducted in 33 tertiary level neonatal intensive care units in Australia, Canada, Israel, New Zealand, Qatar, Singapore, Slovenia, The Netherlands, Turkey, the United Kingdom and the United States. The human research ethics committees of all participating centers approved the Trial Protocol, which included description of the methodology for ascertainment of outcomes at 2 years corrected age[10] (Supplement 1). An independent Data and Safety Monitoring Committee (DSMC) reviewed interim analyses of in-hospital outcomes for safety and efficacy. Prospective written parental consent was obtained for participation in all aspects of the trial, including the 2 year follow-up study (OPTIMIST-A2).

A separate Statistical Analysis Plan (Supplement 2) was developed for the OPTIMIST-A2 study prior to any review or analysis of follow-up data, in which the follow-up outcomes and methodology of analysis originally outlined in the Trial Protocol were expanded upon. The composite outcome of death or NDD was selected

as the key secondary outcome of this follow-up study based on preferences for outcomes reported by parents of preterm infants.[11]

Participants

Infants were included in the trial if within the gestation range 25 weeks 0 days and 28 weeks 6 days, born at a study center, admitted to the neonatal intensive care unit and supported with CPAP (5-8 cm H_2O) or non-invasive positive pressure ventilation for respiratory insufficiency without prior intubation. Infants were eligible if needing $FiO_2 \geq 0.30$ in the first 6 hours from birth. Exclusion criteria were imminent need for intubation, respiratory disease other than RDS, or a serious congenital anomaly. All infants originally enrolled in the study were eligible to be included in the OPTIMIST-A2 study, including those that died during the first hospitalization. Follow-up data were gathered in all infants alive at 2 years corrected age unless they had been withdrawn, or if parents declined to participate or could not be contacted.

Intervention

The design of the intervention and the procedures for randomization and blinding have been described previously,[9] and are detailed in Supplement 1. The MIST intervention was administered using the Hobart method[12] whereby a dose of 200 mg/kg surfactant (poractant alfa, Chiesi Farmaceutici) was administered intra-tracheally. Infants in the control group received a sham treatment consisting only of transient repositioning without airway instrumentation. Treating clinicians, outcome assessors and parents were blinded to intervention group status. Non-invasive respiratory support continued in both groups post-intervention unless intubation

criteria were met, including $FiO_2 \geq 0.45$. Other aspects of management during hospitalization were at the discretion of treating clinicians.

Data collection

Outcome data collection for the OPTIMIST-A2 study commenced in February 2014, performed in all cases by individuals blinded to trial allocation (site trial or follow-up personnel, parents). At the outset, data collection was by face-to-face follow-up assessment at 2 years corrected age, including history-taking to gather post-hospital data on immunizations, family history of asthma, subsequent hospitalizations and respiratory health, along with a clinical examination and a Bayley Scales of Infant and Toddler Development Third Edition (BSID-III[13]) standardized assessment.

With the involvement of more international sites, an online questionnaire was developed in 2016 as an alternative means of follow-up, to be completed by parents and submitted electronically. This questionnaire allowed collection of the same post-hospital data, along with a detailed description of neurodevelopmental outcomes at two years corrected age, incorporating the Parent Report of Children's Abilities – Revised (PARCA-R[14;15]), a standardized assessment of children's cognitive and language development that has been validated against the BSID III[16] and has been used previously in RCTs in preterm infants.[17-19] For the OPTIMIST-A2 study the questionnaire including the PARCA-R was uploaded to an online survey platform and was translated into 8 languages. An electronic link was sent by study personnel to the parents, with periodic reminders if a response was not forthcoming. Where no data could be collected by either of these methods, an abbreviated questionnaire was

administered where possible, consisting of 6 questions related to NDD and respiratory hospitalisations.

Outcomes

The key secondary outcome in this follow-up study was the composite of death or moderate-severe NDD by 2 years corrected age, defined as any of i) moderate-severe cognitive or language impairment; ii) cerebral palsy (CP) equivalent to Gross Motor Function Classification System (GMFCS) level ≥2[20]; iii) visual impairment and iv) hearing impairment (see eTable 1 in Supplement 3 for details of the methodology for ascertainment of neurodevelopmental outcomes in the different domains and modalities of follow-up). Other outcomes included the components of the key secondary outcome, sub-components of the NDD outcome, requirement for at least 1, and 3 or more, hospitalizations in the first 2 years (any cause and for respiratory illness), measures of respiratory morbidity in the first 2 years (parent-reported wheezing or breathing difficulty, frequency of use of bronchodilator therapy, parental report of a physician diagnosis of asthma) and frequency of tube feeding beyond 1 year corrected age. See the Statistical Analysis Plan (Supplement 2) for further details.

Sample size calculation

The sample size was limited to that recruited for the inception cohort (486 infants correctly randomized). The original projected sample size for the trial was 606 infants, based on detection of a 13% absolute risk reduction in the primary outcome of death or BPD with 90% power.

Statistical analysis

For the key secondary outcome and its components, relative risk (RR) comparing active treatment with control, with 95% confidence interval (CI), was estimated according to randomization group using a generalized linear model (GLM), adjusting for gestational age strata and incorporating a cluster-robust standard error calculation to account for clustering by study site (Stata Statistical Software: Release 16, StataCorp LLC, College Station, USA). The GLM used the 'modified Poisson' approach of Zou[21] with a log link function. An extended GLM additionally adjusted for covariates likely to influence the death or NDD – birth weight <10th centile, sex, mode of delivery, plurality, antenatal glucocorticoid exposure, and 5-minute Apgar score. For other binary outcomes, RR was estimated using GLMs, adjusting for gestation strata only. Treatment effects were also estimated as risk difference (RD), using a GLM approach with Gaussian error distribution (to avert convergence difficulties with low-prevalence outcomes) and linear link function.[22] Because of the potential for type 1 error due to multiple comparisons, findings for the analyses of the follow-up outcomes were interpreted with caution.

A pre-planned exploratory subgroup analysis was performed for all binary outcomes by gestational age strata. Further, a pre-planned sensitivity analysis was conducted on the key secondary outcome and its second component of moderate-severe NDD using only information collected in the parent questionnaire, this being the predominant mode of follow-up. For this sensitivity analysis, data were included if the questionnaire was completed between 24 and 27 months corrected age, inclusive. Data in relation to those participants who did not complete the parent questionnaire, or completed the PARCA-R questionnaire outside the time frame of 24-27 months,

were handled using multiple imputation, using chained equations.[23;24] Within the chained equations algorithm, ordinal variables were imputed using ordinal regression and binary variables using logistic regression, and baseline variables were included as auxiliary variables in the imputation model. Imputation was carried out separately by treatment group, to ensure that any treatment effects were maintained, using 50 imputed datasets. Two-tailed *P* values <0.05 were labeled significant.

RESULTS

Study conduct

Infants were enrolled between December 16, 2011 and March 26, 2020, and ceased thereafter short of the recruitment target in the wake of the COVID-19 pandemic, with 488 infants enrolled, from 5187 infants screened in 33 participating centers (Figure 1). Collection of follow up data at 2 years corrected age was completed on December 9, 2022.

Study infants

Of the 486 infants randomized, 453 contributed data at 2 years corrected age to the OPTIMIST-A2 study (MIST: N=224 [29 deaths <2 years corrected age including 28 during first hospitalization; 195 survivors with follow-up data]; control: N=229 [24 deaths including 20 during first hospitalization; 205 survivors with follow-up data]) (Figure 1). Among 431 infants continuing in the study and surviving to 2 years corrected age, 400 (93%) had follow-up data available, and 381 (88%) had sufficient data for a full assessment of NDD (Figure 1), including 186 and 195 infants in the MIST and control groups, respectively.

For the 453 infants for whom data were included in the OPTIMIST-A2 study, median gestational age was 27.3 weeks (interquartile range 26.4-28.1 weeks); 228 (50.3%) were female. Baseline characteristics of the OPTIMIST-A2 study infants were similar between the groups overall (Table 1), although within the 25-26 week gestation stratum the frequency of male sex, incomplete or no steroid exposure and multiple birth were each 13-15% higher in the MIST group (eTable 2 in Supplement 3).

Key secondary outcome and components

Death or NDD assessed at 2 years corrected age occurred in 78 infants (36.3%) in the MIST group and 79 (36.1%) in the control group (RR, 1.00 [95% CI, 0.81-1.24]; *P* = .99; RD, 0.0% [95% CI, -7.6% to 7.7%]) (Table 2). Death before 2 years occurred in 29 infants (12.9%) in the MIST group and 24 infants (10.5%) in the control group (RR, 1.23 [95% CI, 0.69-2.19]; *P* = .48; RD, 2.4% [95% CI, -3.6% to 8.4%]). NDD in survivors at two years occurred in 49/186 (26.3%) of infants in the MIST group and 55/195 (28.2%) in the control group (RR, 0.94 [95% CI, 0.71–1.25]; *P* = .69; RD, -1.6% [95% CI, -9.4% to 6.2%]). These findings were not changed in an analysis using the extended GLM with additional covariates (eTable 3 in Supplement 3), nor in the sensitivity analysis solely using data collected with the parent questionnaire including PARCA-R between 24 and 27 months corrected age (eTable 4 in Supplement 3).

Other secondary outcomes

Sub-components of the NDD outcome were broadly similar between infants in the MIST and control groups (Table 3). There were benefits for the MIST group compared with the control group in relation to all secondary respiratory outcomes (Table 4, eTable 5 in Supplement 3). In particular, there was a relative reduction of

34% (MIST 25.1%, control 38.2%; RR, 0.66 [95% CI, 0.54–0.81]) in the frequency of 1 or more hospitalization for respiratory illness in the MIST group compared to control. The first respiratory hospitalization was related to RSV infection/bronchiolitis in over 70% of instances in both groups, and the median age at admission was 4.2 and 4.7 months corrected age in the MIST and control groups, respectively (eTable 5 in Supplement 3). The frequency of wheezing or breathing difficulty reported by parents showed a 24% relative reduction in the MIST group compared with controls (40.6% vs 53.6%; RR, 0.76 [95% CI, 0.63–0.90]), with a similar reduction in the frequency of bronchodilator use (Table 4). Reported use of inhaled relievers (beta-2 agonists) was: MIST (23.9%), control (38.7%), and of inhaled preventers (corticosteroids) was MIST (5.6%), control (15.5%) (eTable 5 in Supplement 3). Asthma diagnosed by a physician was reported in 4.4% and 11.9% of MIST and control group infants, respectively.

The incidence of tube feeding beyond 1 year corrected age was very low, with no observed difference between groups.

Subgroups

In the exploratory analysis by gestational age groups, for the outcome of death prior to 2 years there was evidence of an interaction between treatment group and gestational age group (lower proportion of the outcome in control group at lower gestation and lower proportion of the outcome in the MIST group at higher gestation, *P*-value for interaction 0.044) (eTable 6 in Supplement 3). Amongst other secondary outcomes, the treatment effect favoring the MIST group was more prominent in the 27-28 week gestation stratum for 1 or more hospitalization with respiratory and any

illness, and for parent reported wheezing or breathing difficulty (eTable 7 in Supplement 3).

No adverse events were reported in relation to outcomes beyond first hospitalization.

DISCUSSION

In this follow-up study of a multicenter randomized clinical trial in preterm infants supported with CPAP and exhibiting features of RDS, administration of surfactant via a thin catheter at a low oxygenation threshold, compared with sham treatment, did not significantly reduce the incidence of the composite outcome of death or NDD at 2 years corrected age, nor its components. The neurodevelopmental outcomes of the groups based on analysis of the sub-components of the NDD outcome were broadly similar. However, the MIST group had better outcomes than the control group in all secondary measures related to respiratory health in the first two years of life.

To our knowledge, the OPTIMIST-A2 study cohort is the largest to date to have follow-up assessment after an RCT of surfactant delivery via thin catheter, with any form of comparator. The importance of the follow-up component is emphasized when considering the RCT design, which in the first days of life resulted in there being a substantial difference between the MIST and control groups in the number of procedures involving laryngoscopy, which is known to be a major cause of hypoxemic and bradycardic episodes[25;26] that could have lasting neurodevelopmental consequences. Infants in the MIST group each had on average 1.37 such procedures (100% having laryngoscopy for thin catheter placement and 37% being intubated in the first 72 h[9]). For the control group the average number of procedures involving

laryngoscopy was 0.72 (72% being intubated <72 h). Reassuringly, the disparity in the rate of airway instrumentation between the groups was not followed by any discernible difference in the risk of NDD assessed at 2 years corrected age.

On the other hand, the lower incidence of BPD at 36 weeks' postmenstrual age that was noted in the MIST group[9] did not confer a reduction in NDD at 2 years corrected age. Although a diagnosis of BPD is a known risk factor for NDD in childhood and adolescence,[27] the mechanisms by which the these conditions are linked are complex, likely involving diverse intermediaries at play during the first hospitalization, and beyond.[1;28] A previous RCT in infants <27 weeks' gestation found surfactant administration via a thin catheter, compared with administration via endotracheal tube with delayed extubation, to be associated with a reduced incidence of severe intraventricular hemorrhage but not BPD during first hospitalization[4], and a lower rate of moderate-severe motor impairment at 2 years corrected age (22% versus 42%).[5] Another RCT with a similar comparator group to the OPTIMIST-A trial (continuation of CPAP) found no difference in incidence of BPD during first hospitalization,[7] nor was there a discernible effect on rate of NDD using the BSID-II assessment.[8] The smaller inception cohorts in each of these trials (N=211 and N=220, respectively) limits the impact of these follow-up data.

In exploratory subgroup analysis for the outcome of death prior to 2 years corrected age, there was some evidence of an interaction suggesting a higher mortality risk in the 25-26 weeks' gestation stratum associated with allocation to the MIST group (eTable 6), in parallel with findings this study team reported previously for death prior to 36 weeks post-menstrual age.[9] This finding may have been due in part to a chance

imbalance in risk profile in this subgroup, but behooves caution in application of MIST at 25-26 weeks' gestation. Subgroup analysis also suggested that the benefits of MIST in relation to longer term respiratory outcomes (eTable 7) may be more prominent above 26 weeks' gestation. The influence of gestation on the effect of MIST on respiratory outcomes after first hospitalization warrants further study.

Notwithstanding some differences in definitions of NDD and modalities of data capture, the neurodevelopmental outcomes in our follow-up cohort are comparable with those reported previously in preterm infants of similar gestational age. Our finding of an overall rate of cognitive or language impairment of 23.5% was similar to that reported for preterm infants <29 weeks' gestation enrolled in an RCT of docosahexaenoic acid supplementation, in which the overall rate of general cognitive impairment assessed at 5 years was approximately 29%.[29] Another RCT examining oxygen saturation targets in preterm infants born before 28 weeks' gestation reported the overall language or cognitive score on BSID-III assessment to be <85 in around 27% of infants surviving to 2 years corrected age.[30]

As with other investigations of respiratory health in preterm infants after first hospital discharge, this study observed a high rate of hospitalization for respiratory illness in the first 2 years (32% overall), compared with 31% overall between 6 and 22 months corrected age in a large RCT involving extremely preterm infants,[31] and approximately 31% in registry data including infants at 22-26 weeks' gestation.[32] The frequency of parent-reported wheezing and breathing difficulty (46% overall) also matched that of other studies.

The effects of MIST on respiratory health in infancy appeared to be greater than on the outcome of BPD at 36 weeks' postmenstrual age. This finding bespeaks the difficulty of accurately quantifying the degree of lung injury in early life after preterm birth, with the current metrics of BPD being overly reductionist for this purpose.[1;33;34] We speculate that many infants in this study cohort without a diagnosis of BPD had a lasting lung injury that manifested in early life with respiratory symptoms and rendered them vulnerable to respiratory infection. Rates of respiratory symptoms and hospitalizations observed in other studies in the first 2 years in preterm infants without a BPD diagnosis would support this contention.[33] Further, the application of MIST on the first day of life appears to have attenuated lung injury. This is likely related to the lessening of exposure to positive pressure ventilation in the critical first days of life,[35] with the rate of intubation <72 h being nearly halved in the MIST group compared with controls (37% vs 72%).[9]

Limitations

This study has several limitations. First, this was a follow-up study of a clinical trial that was not specifically designed to detect differences in 2-year outcomes and analysis of the follow-up data involved multiple additional comparisons beyond those reported previously. Second, the sample size was limited by the early closure of recruitment due to the COVID-19 pandemic. Third, several methods of data capture were used, with the dominant method being an online questionnaire rather than a face-to-face assessment. However, the PARCA-R assessment involved a parent report (blinded to group assignment) of their child's language and non-verbal cognitive ability, the totality of which may be difficult to elicit completely in a single face-to-face BSID III assessment.

CONCLUSION

In this follow-up of a randomized clinical trial of preterm infants with respiratory distress syndrome supported with CPAP, MIST compared with sham treatment did not reduce the incidence of death or NDD by two years of age. However, infants who received MIST had lower rates of adverse respiratory outcomes during their first 2 years of life.

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Author contributions

Prof. Dargaville and Ms. Orsini had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The trial coordinating center and data management and statistics center were led by Prof. Dargaville and Prof. Carlin, respectively.

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(Principle Investigators for the OPTIMIST-A2 study at each of the participating centers, who supervised the local conduct of the trial and vouch for its integrity).

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Conflict of interest disclosures

Prof. Dargaville reports receipt of support for attending meetings and/or travel from Chiesi Farmaceutici, consultancies on advisory boards established by Chiesi Farmaceutici and Abbvie, and holds (without royalty claims) a design patent for a catheter for surfactant instillation (US D752,215S).

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Group information – OPTIMIST-A trial investigative team

See Supplement 4.

Data sharing statement:

See Supplement 5.

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TABLES

	Minimally invasive surfactant therapy (N=224)	Control treatment (N=229)
Demographic characteristics		
Gestation, weeks	27.3 (26.3–28.1)	27.3 (26.4–28.0)
Birth weight (g)	932 (780–1065)	905 (777-1070)
Birth weight <10th centile	32/224 (14.3%)	31/229 (13.5%)
Female sex	108/224 (48.2%)	120/229 (52.4%)
Male sex	116/224 (51.8%)	109/229 (47.6%)
Plurality, birth order		
Singleton	140/224 (62.5%)	158/229 (69.0%)
First of multiples	40/224 (17.8%)	30/229 (13.1%)
Second or subsequent multiple	44/224 (19.6%)	41/229 (17.9%)
Peripartum details		
Exposure to antenatal glucocorticoids		
2 or more doses prior to delivery	144/224 (64.3%)	162/229 (70.7%)
1 dose prior to delivery	60/224 (26.8%)	48/229 (21.0%)
None	20/224 (8.9%)	19/229 (8.3%)
Delivery mode		
Vaginal delivery	40/224 (17.9%)	49/229 (21.4%)
Cesarean delivery with labour	91/224 (40.6%)	75/229 (32.8%)
Cesarean delivery, no labour	93/224 (41.5%)	105/229 (45.9%)
Apgar score at 5 min[a]	8 (7–9)	8 (7–9)
Apgar score <7 at 5 min	28/224 (12.5%)	30/229 (13.1%)
Clinical state at randomization		
Age (hrs)	2.7 (1.6–4.0)	2.6 (1.7–3.6)
CPAP level at randomization (cm H_2O)	7 (6–8)	7 (6–8)
FiO_2 at randomization	0.35 (0.30–0.40)	0.35 (0.30–0.40)

FiO_2 ≤0.35	141/224 (62.9%)	141/229 (61.6%)
Data gathered after first hospital discharge		
Oxygen therapy at home	24/195 (12.3%)	46/205 (22.4%)
Immunized against **RSV** **Influenza**	 119/175 (68.0%) 91/173 (52.6%)	 128/185 (69.2%) 104/184 (56.5%)
Family history of asthma (in parents or siblings)	50/177 (28.2%)	53/188 (28.2%)
Corrected age at 2 year assessment (years)	2.05 (2.00–2.15)	2.04 (2.00–2.18)

Table 1. Baseline characteristics for infants contributing data to the follow-up study

n/N (%) or median (interquartile range). Complete data available for all pre- and peri-randomization variables; post-discharge data shown for survivors with follow-up data available. Abbreviations: CPAP, continuous positive airway pressure; RSV, respiratory syncytial virus.

[a]Indicates success of transition at birth. The score range is 0 to 10. A score of 0 to 2 is given for each of the following: heart rate, respiratory effort, reflex irritability, muscle tone, and skin color. An Apgar score of 7 or greater at 5 minutes after birth generally indicates a satisfactory transition for a preterm infant.

Outcome	Minimally invasive surfactant therapy (N=224)	Control treatment (N=229)	Risk difference, % (95% CI)[a]	Relative risk (95% CI)[a]	*P* value[b]
Death or neurodevelopmental disability[c,d,e]	78/215 (36.3%)	79/219 (36.1%)	0.0 (-7.6 to 7.7)	1.00 (0.81 to 1.24)	.99
Death prior to 2 years corrected age	29/224 (12.9%)	24/229 (10.5%)	2.4 (-3.6 to 8.4)	1.23 (0.69 to 2.19)	.48
Neurodevelopmental disability[c,d,e]	49/186 (26.3%)	55/195 (28.2%)	-1.6 (-9.4 to 6.2)	0.94 (0.71 to 1.25)	.69

Table 2. Key secondary outcome analysis

n/N (%). Abbreviations: CI, confidence interval.

[a]Adjusted for gestation strata.

[b]P value for relative risk derived from generalized linear model.

[c]Neurodevelopmental disability, defined as any of i) moderate-severe cognitive or language impairment; ii) cerebral palsy equivalent to Gross Motor Function Classification System ≥2[20]; iii) visual impairment and iv) hearing impairment. See eTable 1 in Supplement 3 for further details of the approach to outcome ascertainment with the different modalities of data capture.

[d]Key secondary outcome not determinable from available follow-up data in 9 of 224 infants in the minimally invasive surfactant therapy group and 10 of 229 infants in the control group.

[e]NDD assessment at two years was by online questionnaire including Parent Report of Children's Abilities – Revised in 315 infants (minimally invasive surfactant therapy 152, control 163), including 64 and 69 cases, respectively, in which the questionnaire was administered using a translated version. Other modes of follow-up were face to face assessment including Bayley Scales of Infant and Toddler Development III in 38 infants (minimally invasive surfactant therapy 19, control 19), abbreviated questionnaire in 25 (minimally invasive surfactant therapy 14, control 11) and a combination of modalities in 3 (minimally invasive surfactant therapy 1, control 2).

Outcome	Minimally invasive surfactant therapy	Control treatment	Risk difference, % (95% CI)[a]	Relative risk (95% CI)[a]	*P* value[b]
Cognitive or language impairment	42/183 (23.0%)	47/195 (24.1%)	-0.9 (-7.5 to 5.6)	0.96 (0.73 to 1.27)	.77
Cognitive impairment	26/171 (15.2%)	34/183 (18.6%)	-3.3 (-10.7 to 4.1)	0.82 (0.54 to 1.27)	.38
BSID III cognitive composite standard score[c]	(n=18) 95 (80-95)	(n=19) 95 (85-105)	–	–	–
PARCA-R non-verbal cognitive scale standard score[d]	(n=153) 91 (78-107)	(n=164) 92 (75-106)	–	–	–
Language impairment	29/170 (17.1%)	25/180 (13.9%)	3.5 (-2.6 to 9.6)	1.25 (0.85 to 1.85)	.25
BSID III language composite standard score[c]	(n=18) 81 (74-106)	(n=18) 93 (83-103)	–	–	–
PARCA-R language scale standard score[d]	(n=152) 89 (77-99)	(n=162) 88 (79-97)	–	–	–
Cerebral palsy	9/195 (4.6%)	15/204 (7.4%)	-2.7 (-6.3 to 0.9)	0.63 (0.36 to 1.11)	.11
Visual impairment	0/193 (0.0%)	5/204 (2.5%)	-2.5 (-4.4 to -0.6)	Not estimable	–
Hearing impairment	4/194 (2.1%)	4/205 (2.0%)	0.1 (-2.3 to 2.6)	1.06 (0.31 to 3.61)	.93

Table 3. Indices of neurodevelopment assessed at two years

n/N (%) or median (interquartile range). Abbreviations: BSID III, Bayley Scales of Infant and Toddler Development Third Edition; CI, confidence interval; PARCA-R, Parent Report of Children's Abilities – Revised.

[a]Adjusted for gestation strata.

[b]P value for relative risk derived from generalized linear model.

[c]Bayley III composite scores: population mean 100 (standard deviation 15); range, 47-153, with higher scores indicating better performance. A score <80 was indicative of moderate-severe disability.

[d]PARCA-R standard scores: population mean 100 (standard deviation 15); range, 10-147, with higher scores indicating better performance. A score <70 was indicative of moderate-severe disability.

Outcome	Minimally invasive surfactant therapy	Control treatment	Risk difference, % (95% CI)[a]	Relative risk (95% CI)[a]	*P* value[b]
One or more hospitalizations with any illness	77/194 (39.7%)	104/204 (51.0%)	-11.2 (-18.2 to -4.3)	0.78 (0.66 to 0.92)	.003
Three or more hospitalizations with any illness	22/194 (11.3%)	39/204 (19.1%)	-7.8 (-13.7 to -1.8)	0.59 (0.40 to 0.87)	.008
One or more hospitalizations with respiratory illness	49/195 (25.1%)	78/204 (38.2%)	-13.1 (-19.5 to -6.7)	0.66 (0.54 to 0.81)	<.001
Three or more hospitalizations with respiratory illness	14/195 (7.2%)	23/204 (11.3%)	-4.1 (-8.6 to 0.4)	0.63 (0.41 to 0.98)	.042
Parent reported wheeze or breathing difficulty	73/180 (40.6%)	104/194 (53.6%)	-13.1 (-20.1 to -6.1)	0.76 (0.63 to 0.90)	.002
Use of any bronchodilator therapy	57/180 (31.7%)	83/194 (42.8%)	-11.2 (-20.0 to -2.4)	0.74 (0.57 to 0.96)	.026
Parent report of a physician diagnosis of asthma	8/180 (4.4%)	23/194 (11.9%)	-7.6 (-13.7 to -1.5)	0.37 (0.19 to 0.73)	.004

Table 4. Hospitalizations and respiratory health in the first two years

n/N (%) or median (interquartile range). Abbreviations: CI, confidence interval.

[a]Adjusted for gestation strata.

[b]P value for relative risk derived from generalized linear model.

FIGURES

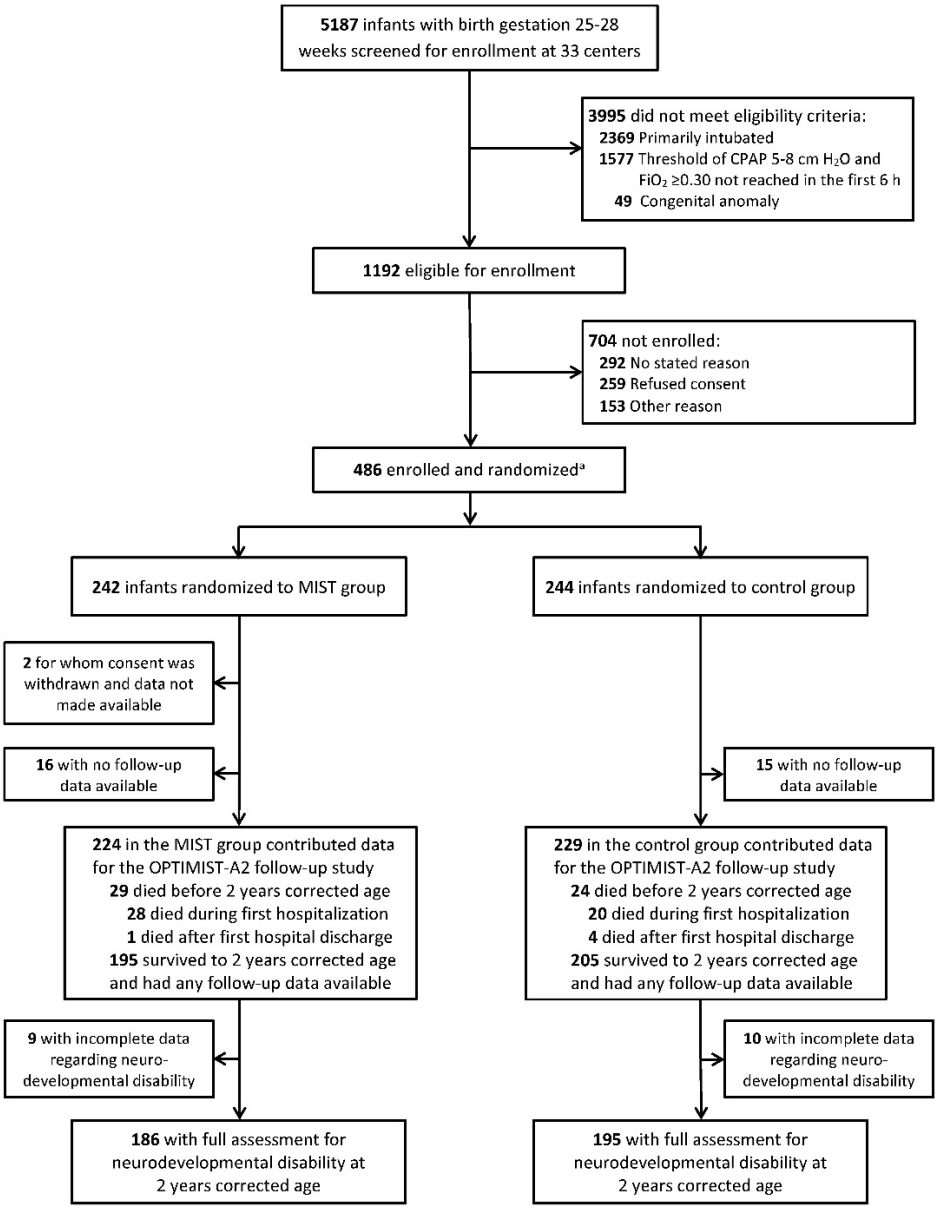

Figure 1. Screening, enrollment, randomization and follow-up

Abbreviations: CPAP, continuous positive airway pressure; MIST, minimally invasive surfactant therapy.

[a]An additional 2 infants were enrolled but randomization failed in one case and in another was performed when the infant was ineligible (FiO_2 = 0.24). Treatment allocation was not revealed in either case.

SUPPLEMENT 3

SUPPLEMENTARY ONLINE CONTENT

Dargaville PA, Kamlin COF, Orsini F et al; OPTIMIST-A trial investigators. Two-year outcomes after minimally invasive surfactant therapy in preterm infants: Follow-up of the OPTIMIST-A randomized clinical trial.

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Definitions of moderate-severe neurodevelopmental disability by components and form of data capture

Component	Form of data capture		
	Face-to-face assessment and BSID-III	**Parent questionnaire including PARCA-R assessment**	**Abbreviated questionnaire**
Cognitive or language impairment	BSID-III[a] standard score <80 for either cognitive composite scale or language composite scale	PARCA-R[b] standard score <70 for either non-verbal cognition or language development	<5 words[c]
Cerebral palsy	GMFCS level ≥2 on clinical assessment	"Walks only with help", or "doesn't walk" (± diagnosis of CP)	"Walks only with help", or "doesn't walk" (± diagnosis of CP)
Visual impairment	Sees close-up objects at best, even with glasses	Sees close-up objects at best, even with glasses	Sees close-up objects at best, even with glasses
Hearing impairment	No useful hearing without amplification, or deaf	No useful hearing without amplification, or deaf	No useful hearing without amplification, or deaf

Abbreviations: BSID-III, Bayley Scales of Infant Development Third Edition; CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; PARCA-R, Parent Report of Children's Abilities – Revised

[a]BSID-III data included if the assessment was performed between 12 and 36 months corrected age.

[b]All PARCA-R data received in the age range 24-30 months corrected age were included. Normative data for the PARCA-R cognitive and language scales are reported from 24-27 months corrected age.[1] For questionnaires received between 28 and 30 months corrected age, the raw score thresholds used for standard score determination in males and females at 27 months were applied. For PARCA-R questionnaires received beyond 30 months corrected age, if the raw cognitive or language score was below the 27 month threshold for impairment, the data were included; otherwise the data were treated as missing.

[c]Threshold of 5 words as per previous report.[2]

eTable 2. Baseline characteristics by gestation strata

		Gestation stratum 25-26 weeks		Gestation stratum 27-28 weeks	
		MIST group (N=84)	**Control group (N=83)**	**MIST group (N=140)**	**Control group (N=146)**
Gestation, weeks		26.0 (25.6–26.4)	26.1 (25.9–26.6)	28.0 (27.4–28.4)	27.9 (27.3–28.4)
Birth weight (g)		813 (675-931.5)	810 (730-910)	1003 (863-1150)	990 (810-1140)
Birth weight <10th centile		13 (15.5%)	9 (10.8%)	19 (13.6%)	22 (15.1%)
Female sex		41 (48.8%)	53 (63.9%)	67 (47.9%)	67 (45.9%)
Male sex		43 (51.2%)	30 (36.1%)	73 (52.1%)	79 (54.1%)
Plurality, birth order	**Singleton**	44 (52.4%)	54 (65.1%)	96 (68.6%)	104 (71.2%)
	First of multiples	16 (19.0%)	12 (14.5%)	24 (17.1%)	18 (12.3%)
	Second or subsequent multiple	24 (28.6%)	17 (20.5%)	20 (14.3%)	24 (16.4%)
Exposure to antenatal glucocorticoids	**2 or more doses prior to delivery**	50 (59.5%)	61 (73.5%)	94 (67.1%)	101 (69.2%)
	1 dose prior to delivery	30 (35.7%)	20 (24.1%)	30 (21.4%)	28 (19.2%)
	None	4 (4.8%)	2 (2.4%)	16 (11.4%)	17 (11.6%)
Delivery mode	**Vaginal delivery**	23 (27.4%)	21 (25.3%)	17 (12.1%)	28 (19.2%)
	Cesarean delivery with labour	37 (44.0%)	29 (34.9%)	54 (38.6%)	46 (31.5%)
	Cesarean delivery, no labour	24 (28.6%)	33 (39.8%)	69 (49.3%)	72 (49.3%)
Apgar score at 5 min		8 (7–8)	8 (7–9)	8 (7–9)	8 (7–9)
Apgar score <7 at 5 min		10 (11.9%)	10 (12.0%)	18 (12.9%)	20 (13.7%)
Age at randomization (hrs)		2.3 (1.5-3.5)	2.7 (1.9-3.7)	3.0 (1.8-4.1)	2.4 (1.6-3.6)
CPAP level at randomization (cm H_2O)		7 (6-8)	7 (6-8)	7 (6-8)	7 (6-8)
FiO_2 at randomization		0.35 (0.30-0.40)	0.35 (0.30-0.40)	0.35 (0.30-0.39)	0.35 (0.30-0.39)
FiO_2 ≤0.35		48 (57.1%)	51 (61.4%)	93 (66.4%)	90 (61.6%)
Oxygen therapy at home		10/68 (14.7%)	23/75 (30.7%)	14/127 (11.0%)	23/130 (17.7%)
Immunized against					
RSV		45/63 (71.4%)	50/68 (73.5%)	74/112 (66.1%)	78/117 (66.7%)
Influenza		34/62 (54.8%)	35/68 (51.5%)	57/111 (51.4%)	69/116 (59.5%)
Family history of asthma (in parents or siblings)		14/62 (22.6%)	18/71 (25.4%)	36/115 (31.3%)	35/117 (29.9%)
Corrected age at 2 year assessment (years)		2.07 (2.01-2.25)	2.04 (2.00-2.25)	2.03 (2.00-2.11)	2.03 (2.00-2.17)

n (%), n/N (%) or median (interquartile range). Includes infants contributing data to the follow-up study. Complete data available for all pre- and peri-randomization variables; post-discharge data shown for survivors with follow-up data available. Abbreviations: CPAP, continuous positive airway pressure; MIST, minimally invasive surfactant therapy; RSV, respiratory syncytial virus.

eTable 3. Key secondary outcome and its components: estimated effect with additional adjustments

Outcome	MIST group	Control group	Adjusted risk difference (%) (95% CI)[a]	Adjusted relative risk (95% CI)[a]
Death or neurodevelopmental disability[b,c]	78/215 (36.3%)	79/219 (36.1%)	-0.3 (-7.7 to 7.1)	0.99 (0.81 to 1.21)
Death prior to 2 years corrected age	29/224 (12.9%)	24/229 (10.5%)	1.7 (-4.4 to 7.8)	1.14 (0.65 to 1.98)
Neurodevelopmental disability[b,c]	49/186 (26.3%)	55/195 (28.2%)	-1.4 (-8.6 to 5.8)	0.95 (0.73 to 1.23)

n/N (%). Abbreviations: CI, confidence interval; MIST, minimally invasive surfactant therapy.
[a]Adjusted for gestation strata, birth weight <10th percentile, sex, mode of delivery, plurality, antenatal glucocorticoid exposure, and 5-minute Apgar score.
[b]Neurodevelopmental disability, defined as any of i) moderate-severe cognitive or language impairment; ii) cerebral palsy equivalent to Gross Motor Function Classification System ≥2[3]; iii) visual impairment and iv) hearing impairment. See eTable 1 for further details.
[c]Key secondary outcome not determinable from available follow-up data in 9 of 224 infants in the MIST group and 10 of 229 infants in the control group.

eTable 4. Key secondary outcome and neurodevelopmental disability component: sensitivity analysis[a]

Outcome	MIST group		Control group		Adjusted relative risk (95% CI)[c]	*P* value
	N	Outcome incidence[b]	N	Outcome incidence[b]		
Death or neurodevelopmental disability[d]	241	32.9%	244	32.3%	1.01 (0.77 to 1.34)	.92
Neurodevelopmental disability[d]	212	23.7%	220	24.9%	0.96 (0.67 to 1.36)	.81

n/N (%). Abbreviations: CI, confidence interval; MIST, minimally invasive surfactant therapy.
[a]Sensitivity analysis using only information collected in the parent questionnaire including PARCA-R assessment.
[b]Incidence estimate from sensitivity analysis, solely using data collected with the parent questionnaire including Parent Report of Children's Abilities – Revised assessment between 24 and 27 months corrected age, with missing data handled using multiple imputation. See Methods for further details.
[c]Adjusted for gestation strata.
[d]Neurodevelopmental disability defined as per eTable 1 and eTable 3.

eTable 5. Hospitalizations and respiratory health in the first two years - categorical and continuous outcomes

Outcome		MIST group	Control group
Number of hospitalizations with any illness in first two years	0	117/194 (60.3%)	100/204 (49.0%)
	1	40/194 (20.6%)	41/204 (20.1%)
	2	15/194 (7.7%)	24/204 (11.8%)
	3	7/194 (3.6%)	18/204 (8.8%)
	4	5/194 (2.6%)	5/204 (2.5%)
	5	1/194 (0.5%)	3/204 (1.5%)
	>5	9/194 (4.6%)	13/204 (6.4%)
Number of hospitalizations with respiratory illness in first two years	0	146/195 (74.9%)	126/204 (61.8%)
	1	30/195 (15.4%)	31/204 (15.2%)
	2	5/195 (2.6%)	24/204 (11.8%)
	3	3/195 (1.5%)	10/204 (4.9%)
	4	2/195 (1.0%)	4/204 (2.0%)
	5	8/195 (4.1%)	9/204 (4.4%)
	>5	1/195 (0.5%)	0/204 (0.0%)
Corrected age at first hospitalization with respiratory illness (months)		(n=45) 4.2 (0.6-10.7)	(n=72) 4.7 (1.5-8.9)
Diagnosis at first hospitalization with respiratory illness	RSV / bronchiolitis	35/49 (71.4%)	56/78 (71.8%)
	Other respiratory problem[a]	14/49 (28.6%)	22/78 (28.2%)
Frequency of parent-reported wheezing or breathing difficulty in first two years	No episodes	107/180 (59.4%)	90/191 (47.1%)
	Less than once a month	55/180 (30.6%)	75/191 (39.3%)
	1-4 times per month	11/180 (6.1%)	16/191 (8.4%)
	1-6 times per week	2/180 (1.1%)	6/191 (3.1%)
	Daily	5/180 (2.8%)	4/191 (2.1%)
Use of bronchodilator therapy in first few years[b]	No medication	123/180 (68.3%)	111/194 (57.2%)
	Relievers, inhaled	43/180 (23.9%)	75/194 (38.7%)
	Preventers, inhaled	10/180 (5.6%)	30/194 (15.5%)
	Preventers, oral	10/180 (5.6%)	17/194 (8.8%)
	Other medication	9/180 (5.0%)	10/194 (5.2%)

n/N (%) or median (interquartile range). Percentages may not add up to 100% due to rounding. Abbreviations: CI, confidence interval; MIST, minimally invasive surfactant therapy; RSV; respiratory syncytial virus.
[a]Examples given: croup / pneumonia.
[b]More than one medication could be selected.

eTable 6. Key secondary outcome and its components by gestation strata

Outcome	Gestation stratum	MIST group	Control group	Adjusted relative risk (95% CI)[a]	*P* value for interaction[b]
Death or neurodevelopmental disability[c]	**25-26 weeks**	38/80 (47.5%)	34/79 (43.0%)	1.11 (0.86 to 1.42)	.29
	27-28 weeks	40/135 (29.6%)	45/140 (32.1%)	0.93 (0.74 to 1.17)	
Death prior to 2 years corrected age	**25-26 weeks**	16/84 (19.0%)	8/83 (9.6%)	1.95 (0.85 to 4.45)	.044
	27-28 weeks	13/140 (9.3%)	16/146 (11.0%)	0.86 (0.51 to 1.45)	
Neurodevelopmental disability[c]	**25-26 weeks**	22/64 (34.4%)	26/71 (36.6%)	0.95 (0.65 to 1.41)	.98
	27-28 weeks	27/122 (22.1%)	29/124 (23.4%)	0.96 (0.69 to 1.33)	

n/N (%). Abbreviations: CI, confidence interval; MIST, minimally invasive surfactant therapy.
[a]Adjusted for gestation.
[b]Interaction of gestation stratum with treatment allocation in the statistical model.
[c]Neurodevelopmental disability defined as per eTable 1 and eTable 3.

eTable 7. Other secondary outcomes by gestation strata

Outcome	Gestation stratum	MIST group	Control group	Adjusted relative risk (95% CI)[a]	*P* value for interaction[b]
Cognitive or language impairment	**25-26 weeks**	21/ 64 (32.8%)	23/ 71 (32.4%)	1.03 (0.67 to 1.57)	.74
	27-28 weeks	21/119 (17.6%)	24/124 (19.4%)	0.90 (0.64 to 1.26)	
Cognitive impairment	**25-26 weeks**	13/ 60 (21.7%)	15/ 67 (22.4%)	0.98 (0.49 to 1.94)	.55
	27-28 weeks	13/111 (11.7%)	19/116 (16.4%)	0.70 (0.38 to 1.29)	
Language impairment	**25-26 weeks**	18/ 59 (30.5%)	12/ 67 (17.9%)	1.76 (0.99 to 3.10)	.14
	27-28 weeks	11/111 (9.9%)	13/113 (11.5%)	0.86 (0.52 to 1.40)	
Cerebral palsy	**25-26 weeks**	3/ 68 (4.4%)	9/ 75 (12.0%)	0.37 (0.11 to 1.17)	.16
	27-28 weeks	6/127 (4.7%)	6/129 (4.7%)	1.03 (0.54 to 1.96)	
Visual impairment	**25-26 weeks**	0/ 68 (0.0%)	1/ 75 (1.3%)	Not estimable	.46
	27-28 weeks	0/125 (0.0%)	4/129 (3.1%)	Not estimable	
Hearing impairment	**25-26 weeks**	1/ 68 (1.5%)	2/ 75 (2.7%)	0.55 (0.13 to 2.25)	.45
	27-28 weeks	3/126 (2.4%)	2/130 (1.5%)	1.51 (0.22 to 10.60)	
One or more hospitalizations with any illness	**25-26 weeks**	33/ 68 (48.5%)	35/ 75 (46.7%)	1.04 (0.73 to 1.48)	.040
	27-28 weeks	44/126 (34.9%)	69/129 (53.5%)	0.67 (0.54 to 0.83)	
Three or more hospitalizations with any illness	**25-26 weeks**	7/ 68 (10.3%)	15/ 75 (20.0%)	0.51 (0.22 to 1.20)	.66
	27-28 weeks	15/126 (11.9%)	24/129 (18.6%)	0.64 (0.43 to 0.96)	
One or more hospitalizations with respiratory illness	**25-26 weeks**	20/ 68 (29.4%)	26/ 75 (34.7%)	0.85 (0.59 to 1.22)	.041
	27-28 weeks	29/127 (22.8%)	52/129 (40.3%)	0.59 (0.48 to 0.72)	
Three or more hospitalizations with respiratory illness	**25-26 weeks**	3/ 68 (4.4%)	8/ 75 (10.7%)	0.41 (0.13 to 1.31)	.38
	27-28 weeks	11/127 (8.7%)	15/129 (11.6%)	0.78 (0.47 to 1.29)	
Parent reported wheeze or breathing difficulty	**25-26 weeks**	29/ 63 (46.0%)	34/ 72 (47.2%)	0.97 (0.72 to 1.32)	.039
	27-28 weeks	44/117 (37.6%)	70/122 (57.4%)	0.67 (0.54 to 0.83)	

eTable 7. Other secondary outcomes by gestation strata (continued)

Outcome	Gestation stratum	MIST group	Control group	Adjusted relative risk (95% CI)[a]	*P* value for interaction[b]
Use of any bronchodilator therapy	**25-26 weeks**	24/63 (38.1%)	25/ 72 (34.7%)	1.10 (0.75 to 1.60)	.083
	27-28 weeks	33/117 (28.2%)	58/122 (47.5%)	0.61 (0.40 to 0.92)	
Parent report of a physician diagnosis of asthma	**25-26 weeks**	1/ 63 (1.6%)	4/ 72 (5.6%)	0.29 (0.04 to 2.37)	.79
	27-28 weeks	7/117 (6.0%)	19/122 (15.6%)	0.38 (0.20 to 0.72)	
Tube feeding beyond 1 year corrected age	**25-26 weeks**	4/ 68 (5.9%)	1/ 75 (1.3%)	4.39 (0.53 to 36.53)	.21
	27-28 weeks	3/126 (2.4%)	4/130 (3.1%)	0.76 (0.16 to 3.66)	

n/N (%). Abbreviations: CI, confidence interval; MIST, minimally invasive surfactant therapy.
[a]Adjusted for gestation.
[b]Interaction of gestation stratum with treatment allocation in the statistical model.

eReferences

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(3) Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-223.