

## 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. *JAMA*. doi:10.1001/jama.2023.15694

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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
<b>Cognitive or language impairment</b>	BSID-III <sup>a</sup> standard score <80 for either cognitive composite scale or language composite scale	PARCA-R <sup>b</sup> standard score <70 for either non-verbal cognition or language development	<5 words <sup>c</sup>
<b>Cerebral palsy</b>	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)
<b>Visual impairment</b>	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
<b>Hearing impairment</b>	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

<sup>a</sup>BSID-III data included if the assessment was performed between 12 and 36 months corrected age.

<sup>b</sup>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.<sup>1</sup> 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.

<sup>c</sup>Threshold of 5 words as per previous report.<sup>2</sup>

**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 <10 <sup>th</sup> 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 <sub>2</sub> O)		7 (6-8)	7 (6-8)	7 (6-8)	7 (6-8)
FiO <sub>2</sub> 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 <sub>2</sub> ≤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 Influenza		45/63 (71.4%) 34/62 (54.8%)	50/68 (73.5%) 35/68 (51.5%)	74/112 (66.1%) 57/111 (51.4%)	78/117 (66.7%) 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) <sup>a</sup>	Adjusted relative risk (95% CI) <sup>a</sup>
Death or neurodevelopmental disability <sup>b,c</sup>	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 <sup>b,c</sup>	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.

<sup>a</sup>Adjusted for gestation strata, birth weight <10th percentile, sex, mode of delivery, plurality, antenatal glucocorticoid exposure, and 5-minute Apgar score.

<sup>b</sup>Neurodevelopmental disability, defined as any of i) moderate-severe cognitive or language impairment; ii) cerebral palsy equivalent to Gross Motor Function Classification System  $\geq 2^3$ ; iii) visual impairment and iv) hearing impairment. See eTable 1 for further details.

<sup>c</sup>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<sup>a</sup>**

Outcome	MIST group		Control group		Adjusted relative risk (95% CI) <sup>c</sup>	P value
	N	Outcome incidence <sup>b</sup>	N	Outcome incidence <sup>b</sup>		
<b>Death or neurodevelopmental disability<sup>d</sup></b>	241	32.9%	244	32.3%	1.01 (0.77 to 1.34)	.92
<b>Neurodevelopmental disability<sup>d</sup></b>	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.

<sup>a</sup>Sensitivity analysis using only information collected in the parent questionnaire including PARCA-R assessment.

<sup>b</sup>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.

<sup>c</sup>Adjusted for gestation strata.

<sup>d</sup>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 <sup>a</sup>	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 <sup>b</sup>	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.

<sup>a</sup>Examples given: croup / pneumonia.

<sup>b</sup>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) <sup>a</sup>	P value for interaction <sup>b</sup>
Death or neurodevelopmental disability <sup>c</sup>	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 <sup>c</sup>	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.

<sup>a</sup>Adjusted for gestation.

<sup>b</sup>Interaction of gestation stratum with treatment allocation in the statistical model.

<sup>c</sup>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) <sup>a</sup>	P value for interaction <sup>b</sup>
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) <sup>a</sup>	P value for interaction <sup>b</sup>
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.

<sup>a</sup>Adjusted for gestation.

<sup>b</sup>Interaction of gestation stratum with treatment allocation in the statistical model.

## eReferences

- (1) Johnson S, Bountziouka V, Brocklehurst P et al. Standardisation of the Parent Report of Children's Abilities-Revised (PARCA-R): a norm-referenced assessment of cognitive and language development at age 2 years. *Lancet Child Adolesc Health* 2019;3:705-712.
- (2) BAPM/RCPCH Working Group. *Classification of Health Status at 2 Years as a Perinatal Outcome. Report of a BAPM/RCPCH Working Group*. London: British Association of Perinatal Medicine, 2008.
- (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.