The efficacy and mechanism of surfactant therapy for critically ill infants with bronchiolitis:
The **B**ronchiolitis **E**ndotracheal **S**urfactant **S**tudy (BESS)

EudraCT No. 2018-001169-18

Final Analysis Report v5.0

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Change Control

Updated version no.	Shell section changed	Description of change	Date changed	Initials
Prior to 1.0	6.8.1.2	6.8.1.2.1 Added as per SAP, missed in error from shell	18/12/2024	RC
	6.7.4.1	Profile plots updated to just a panel per outcome. Joint model Estimate, 95%CI and p-value for both longitudinal and survival element	19/02/2025 12/03/2025	RC
	6.7.4.2	Model estimates updated to present Mean, Standard error and 95% CI for each arm rather than N and mean.	19/02/2025	RC
	7.1	Added as discussed with Lead Statistician to perform safety outcomes on the safety set	19/02/2025	RC
	7.2 and 7.3	Added as requested by the Chief Investigator	03/2025	RC
	8 and 9	Section 8 Listing Shell and 9 Plots and Graphs have been removed. Section 9 has been covered in the appendix	05/03/2025	RC
1.1	Change control	Column heading updated to removed 'shell'.	09/05/2025	AJ/RC
	6.7.1	Table 6-19 updated to clarify unobtainable data	09/05/2025	AJ/RC
	6.7.2	Table 6-25 updated to clarify those that did not meet the SBT criteria	09/05/2025	AJ/RC
	Throughout	Adjusted column width in order for header row to be one row for the following tables: Table 6-1, Table 6-2, Table 6-3, Table 6-45, Table 7-5 and Table 7-6. Ensured required borders on tables are present	09/05/2025	RC
	6.3	Add bottom border to table (Table 6-7)	09/05/2025	AJ/RC
	6.6.5	Remove blank column from Table 6-17	13/05/2025	RC
V2.0	7.4	Ethnicity table added	12/06/2025	RC
	3	Update 'Lost to follow-up' to 'Withdrawn' in CONSORT diagram. Add extra category to 'Eligible not randomised' to account for patient with an incomplete screening log.	12/06/2025	RC
	Appendix 1: Mapping report contents to SAP	Correction to formatting	23/06/2025	RC
	6.7.1.2.1	Rename table and heading to distinguish sensitivity from main primary outcome	23/06/2025	RC
	6.7.9	Remove duplicated text	12/06/2025	RC
	7.2	Correct typo	12/06/2025	RC
V3.0	7.5	Added additional summary of gestational age and primary outcome sensitivity using gestational age categories as requested by reviewer	24/10/2025	RC
V4.0	7.5	Amend gestational age to remove implausible values	11/03/2026	RC

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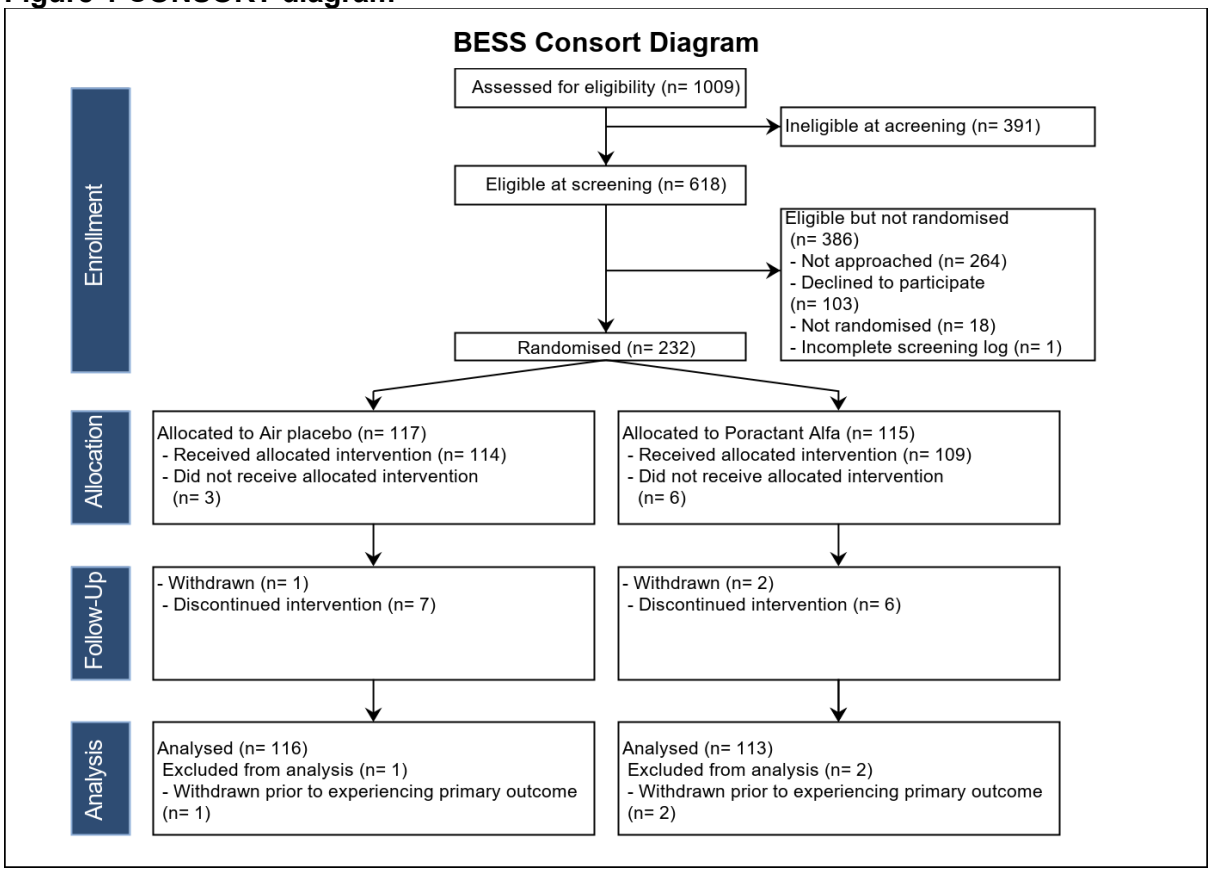
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3. CONSORT diagram

Figure 1 CONSORT diagram



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4. Randomisation checking

4.1 Missing or out of sequence randomisation numbers

Table 4-1 Randomisation checks

	Endotracheal poractant alfa	Sham Intervention group	Overall
Randomisation numbers are not sequential by date randomised	0	0	0
Missing randomisation number	0	0	0
Randomisation number is duplicated	0	0	0

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4.2 Balance across strata

Table 4-2 Check of balance across strata

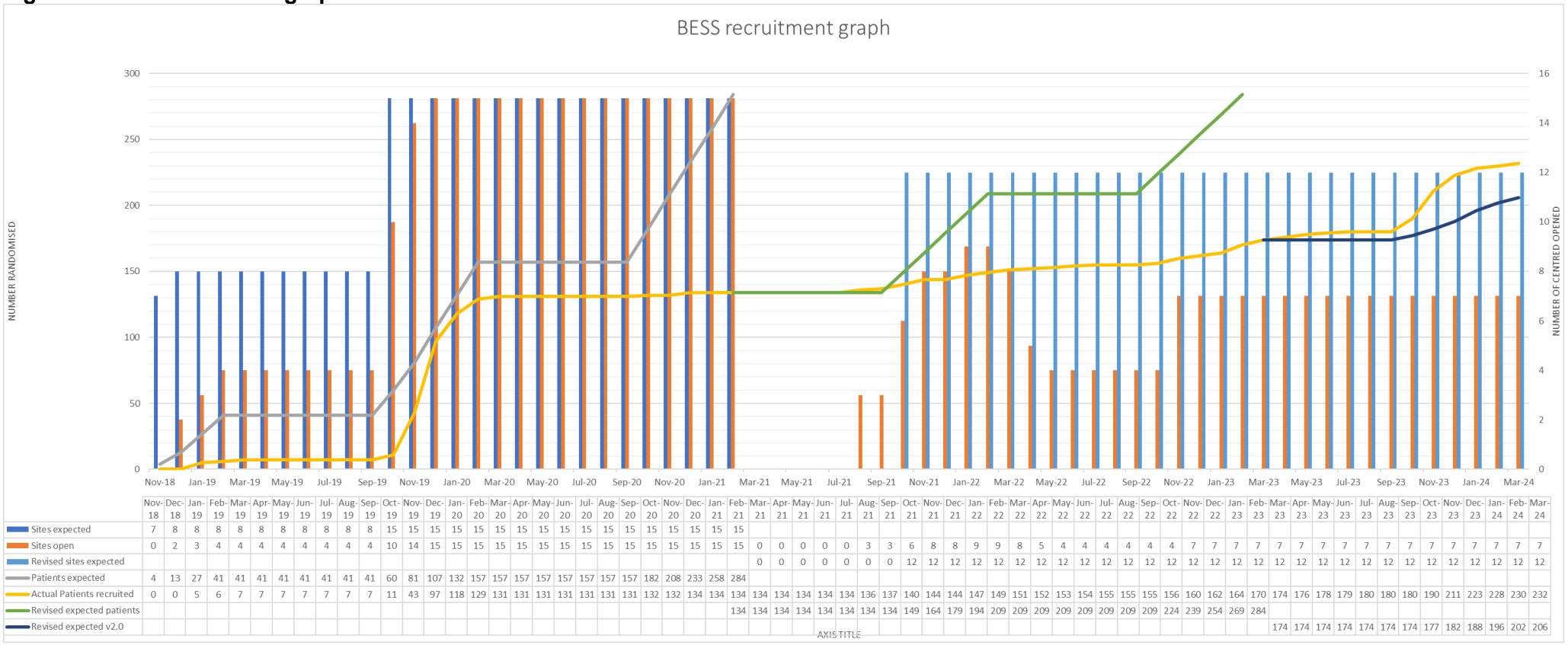
Strata Time on MV prior to randomisation	Allocation n (Col %, Row %)	
	Endotracheal poractant alfa	Sham Intervention group
< 24 hours	35 (30.43, 48.61)	37 (31.62, 51.39)
≥ 24 hours	80 (69.57, 50.00)	80 (68.38, 50.00)

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5. Recruitment

5.1 Randomisation summary

Figure 2 Final recruitment graph



| | Nov-18 | Dec-18 | Jan-19 | Feb-19 | Mar-19 | Apr-19 | May-19 | Jun-19 | Jul-19 | Aug-19 | Sep-19 | Oct-19 | Nov-19 | Dec-19 | Jan-20 | Feb-20 | Mar-20 | Apr-20 | May-20 | Jun-20 | Jul-20 | Aug-20 | Sep-20 | Oct-20 | Nov-20 | Dec-20 | Jan-21 | Feb-21 | Mar-21 | Apr-21 | May-21 | Jun-21 | Jul-21 | Aug-21 | Sep-21 | Oct-21 | Nov-21 | Dec-21 | Jan-22 | Feb-22 | Mar-22 | Apr-22 | May-22 | Jun-22 | Jul-22 | Aug-22 | Sep-22 | Oct-22 | Nov-22 | Dec-22 | Jan-23 | Feb-23 | Mar-23 | Apr-23 | May-23 | Jun-23 | Jul-23 | Aug-23 | Sep-23 | Oct-23 | Nov-23 | Dec-23 | Jan-24 | Feb-24 | Mar-24 |
|---|---|---

Table 5-1 Summary of randomisation

Hospital (code)	site opening	Closed to recruitment	Endotracheal poractant alfa Randomisation details			Sham Intervention group Randomisation details			Total
			First	Last	Total	First	Last	Total	
Alder Hey Children's Hospital (001)	18/12/2018	31/03/2024	16FEB2019	18DEC2023	15	02JAN2019	09DEC2023	14	29
Royal London Hospital (013)	19/12/2018	31/03/2024	10JAN2019	13NOV2023	11	02JAN2019	02JAN2024	13	24
Royal Hospital for Sick Children (Yorkhill) (004)	04/01/2019	31/03/2024	12NOV2019	15DEC2019	5	12NOV2019	07FEB2024	5	10
Royal Hospital for Sick Children Edinburgh (003)	19/02/2019	28/02/2020	12DEC2019	12DEC2019	1	.	.	0	1
Bristol Royal Hospital for Children (011)	01/10/2019	31/03/2024	21NOV2019	02JAN2024	9	24NOV2019	19MAR2024	11	20
Royal Stoke University Hospital (009)	03/10/2019	31/03/2024	27OCT2019	16MAR2024	12	14NOV2019	16JAN2020	12	24
John Radcliffe Hospital (014)	24/10/2019	22/01/2021	08JAN2020	09JAN2020	2	09DEC2019	17DEC2019	2	4
Royal Manchester Children's Hospital (007)	28/10/2019	31/03/2024	13NOV2019	15NOV2023	12	26NOV2019	11DEC2023	12	24
Birmingham Children's Hospital (010)	29/10/2019	17/08/2023	05DEC2019	30SEP2021	3	17DEC2019	26OCT2022	4	7
Royal Belfast Hospital for Sick Children (005)	31/10/2019	31/03/2024	11NOV2019	24NOV2023	14	11NOV2019	10NOV2023	14	28
Leeds Children's Hospital (008)	05/11/2019	28/02/2022	09DEC2019	27FEB2020	2	20DEC2019	20DEC2019	1	3
Queens Medical Centre Nottingham (015)	08/11/2019	28/02/2022	27DEC2019	27DEC2019	1	22NOV2019	13DEC2019	3	4
Leicester Royal Infirmary (016)	12/11/2019	22/01/2021	13NOV2019	01DEC2020	3	05DEC2019	03MAR2020	2	5
Southampton Children's Hospital (002)	21/11/2019	31/03/2024	28NOV2019	19DEC2023	16	27NOV2019	19DEC2023	13	29
Great North Children's Hospital (006)	16/12/2019	31/01/2024	08JAN2020	22JAN2024	9	21DEC2019	02JAN2024	11	20
				Total	**115**		**Total**	**117**	**232**

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Note: Ordered by date of site opening.

5.2 Screening summary

Table 5-2 Summary of screening logs

Hospital (code)	No. screened *[N]* **N**	Eligible *[a]* **n (%)**	Ineligible *[b]* **n (%)**	Approached *[c]* **n (%)**	Not Approached *[d]* **n (%)**	Consent provided *[e]* **n (%)**	Did not provide consent *[f]* **n (%)**	Not Randomised *[g]* **n (%)**	Randomised *[h]* **n (%)**
Total	1009	618 (61.2)	391 (38.8)	354* (57.3)	264 (42.7)	250 (70.6)	103 (29.1)	18 (7.2)	232 (92.8)
Alder Hey Children's Hospital, (001)	149	68 (45.6)	81 (54.4)	45 (66.2)	23 (33.8)	33 (73.3)	12 (26.7)	4 (12.1)	29 (87.9)
Southampton Children's Hospital, (002)	176	115 (65.3)	61 (34.7)	38 (33)	77 (67)	31 (81.6)	7 (18.4)	2 (6.5)	29 (93.5)
Paediatric Critical Care Unit, Royal Hospital for Children and Young People, NHS Lothian, (003)	14	9 (64.3)	5 (35.7)	2 (22.2)	7 (77.8)	1 (50)	1 (50)	0 (0)	1 (100)
Royal Hospital for Children, NHS Greater Glasgow and Clyde, (004)	35	25 (71.4)	10 (28.6)	15 (60)	10 (40)	11 (73.3)	4 (26.7)	1 (9.1)	10 (90.9)
Royal Belfast Hospital for Sick Children, (005)	85	40 (47.1)	45 (52.9)	35* (87.5)	5 (12.5)	29 (82.9)	5 (14.3)	1 (3.4)	28 (96.6)
Great North Children's Hospital, (006)	111	82 (73.9)	29 (26.1)	28 (34.1)	54 (65.9)	21 (75)	7 (25)	1 (4.8)	20 (95.2)
Royal Manchester Children's Hospital, (007)	94	73 (77.7)	21 (22.3)	46 (63)	27 (37)	26 (56.5)	20 (43.5)	2 (7.7)	24 (92.3)
Leeds Children's Hospital, (008)	15	7 (46.7)	8 (53.3)	4 (57.1)	3 (42.9)	3 (75)	1 (25)	0 (0)	3 (100)
Royal Stoke University Hospital, (009)	44	38 (86.4)	6 (13.6)	29 (76.3)	9 (23.7)	25 (86.2)	4 (13.8)	1 (4)	24 (96)
Birmingham Children's Hospital, (010)	59	32 (54.2)	27 (45.8)	14 (43.8)	18 (56.3)	9 (64.3)	5 (35.7)	2 (22.2)	7 (77.8)
Bristol Royal Hospital for Children, (011)	65	51 (78.5)	14 (21.5)	37 (72.5)	14 (27.5)	22 (59.5)	15 (40.5)	2 (9.1)	20 (90.9)
Royal London Hospital, (013)	73	45 (61.6)	28 (38.4)	38 (84.4)	7 (15.6)	25 (65.8)	13 (34.2)	1 (4)	24 (96)
John Radcliffe Hospital, (014)	33	9 (27.3)	24 (72.7)	6 (66.7)	3 (33.3)	4 (66.7)	2 (33.3)	0 (0)	4 (100)
Queens Medical Centre Nottingham, (015)	45	18 (40)	27 (60)	12 (66.7)	6 (33.3)	5 (41.7)	7 (58.3)	1 (20)	4 (80)
Leicester Royal Infirmary, (016)	11	6 (54.5)	5 (45.5)	5 (83.3)	1 (16.7)	5 (100)	0 (0)	0 (0)	5 (100)

**One patient was approached however, the screening log is incomplete following this.*

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Calculating percentages for Table 5-2:

Percentages	Equation
Percent eligible	a/N
Percent ineligible	b/N
Percent approached	c/a
Percent not approached	d/a
Percent consent provided	e/c
Percent consent not provided	f/c
Percent not randomised	g/e
Percent randomised	h/e

Table 5-3 Summary of ineligible patients

Hospital (code)	No. of ineligible patients	Reasons for ineligibility [a,b]									
		R1 n (%)	R2 n (%)	R3 n (%)	R4 n (%)	R5 n (%)	R6 n (%)	R7 n (%)	R8 n (%)	R9 n (%)	R10 n (%)
Total [c]	391	98 (25.1)	6 (1.5)	71 (18.2)	12 (3.1)	1 (0.3)	128 (32.7)	0 (0)	73 (18.7)	3 (0.8)	15 (3.8)
Alder Hey Children's Hospital, (001)	81	18 (22.2)	0 (0)	7 (8.6)	5 (6.2)	0 (0)	34 (42)	0 (0)	24 (29.6)	0 (0)	4 (4.9)
Southampton Children's Hospital, (002)	61	24 (39.3)	1 (1.6)	29 (47.5)	1 (1.6)	0 (0)	3 (4.9)	0 (0)	4 (6.6)	0 (0)	0 (0)
Paediatric Critical Care Unit, Royal Hospital for Children and Young People, NHS Lothian, (003)	5	0 (0)	0 (0)	5 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Royal Hospital for Children, NHS Greater Glasgow and Clyde, (004)	10	2 (20)	0 (0)	1 (10)	0 (0)	0 (0)	4 (40)	0 (0)	2 (20)	0 (0)	1 (10)
Royal Belfast Hospital for Sick Children, (005)	45	10 (22.2)	0 (0)	2 (4.4)	0 (0)	0 (0)	22 (48.9)	0 (0)	9 (20)	1 (2.2)	3 (6.7)
Great North Children's Hospital, (006)	29	2 (6.9)	4 (13.8)	1 (3.4)	0 (0)	1 (3.4)	16 (55.2)	0 (0)	5 (17.2)	1 (3.4)	0 (0)
Royal Manchester Children's Hospital, (007)	21	10 (47.6)	0 (0)	0 (0)	0 (0)	0 (0)	8 (38.1)	0 (0)	1 (4.8)	0 (0)	2 (9.5)
Leeds Children's Hospital, (008)	8	0 (0)	0 (0)	1 (12.5)	0 (0)	0 (0)	2 (25)	0 (0)	5 (62.5)	0 (0)	0 (0)
Royal Stoke University Hospital, (009)	6	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (83.3)	0 (0)	0 (0)	0 (0)	1 (16.7)
Birmingham Children's Hospital, (010)	27	21 (77.8)	0 (0)	1 (3.7)	1 (3.7)	0 (0)	3 (11.1)	0 (0)	0 (0)	1 (3.7)	0 (0)
Bristol Royal Hospital for Children, (011)	14	2 (14.3)	0 (0)	1 (7.1)	0 (0)	0 (0)	5 (35.7)	0 (0)	5 (35.7)	0 (0)	1 (7.1)
Royal London Hospital, (013)	28	2 (7.1)	0 (0)	6 (21.4)	3 (10.7)	0 (0)	12 (42.9)	0 (0)	5 (17.9)	0 (0)	0 (0)
John Radcliffe Hospital, (014)	24	3 (12.5)	0 (0)	10 (41.7)	2 (8.3)	0 (0)	7 (29.2)	0 (0)	2 (8.3)	0 (0)	0 (0)
Queens Medical Centre Nottingham, (015)	27	4 (14.8)	1 (3.7)	5 (18.5)	0 (0)	0 (0)	6 (22.2)	0 (0)	11 (40.7)	0 (0)	1 (3.7)
Leicester Royal Infirmary, (016)	5	0 (0)	0 (0)	2 (40)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	2 (40)

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[a] Patients may ineligible for 1 or more reasons. Percentages based on number of ineligible patients per site.

[b] Reasons for ineligibility 1-10:

R1 Major congenital anomalies

R2 Congenital neuromuscular disease

R3 Already intubated MV for > 48 hours or likely to have been intubated for MV for > 48 hours by randomisation

R4 Having received or are receiving extracorporeal member oxygenation (ECMO) or oscillation during episode of bronchiolitis

R5 Have received or are receiving intratracheal administration of any surfactant during this episode of bronchiolitis

R6 Receiving MV for primary apnoea rather than respiratory failure

R7 A known hypersensitivity to the active substance or excipients of poractant alpha (Curosurf ®)

R8 A decision to wean to extubation has already been made

R9 Clinical judgement of futility

R10 No reason provided (queried with site)

[c] Only sites that have screened at least one ineligible patient are included in table.

Table 5-4 Summary of eligible patients not approached for consent

Hospital (code)	No. not approached	Reasons for not being approached [a,b]			
		R1 n (%)	R2 n (%)	R3 n (%)	R4 n (%)
Total [c]	264	26 (9.8)	122 (46.2)	8 (3)	117 (44.3)
Alder Hey Children's Hospital, (001)	23	7 (30.4)	8 (34.8)	1 (4.3)	13 (56.5)
Southampton Children's Hospital, (002)	77	0 (0)	43 (55.8)	1 (1.3)	33 (42.9)
Paediatric Critical Care Unit, Royal Hospital for Children and Young People, NHS Lothian, (003)	7	2 (28.6)	0 (0)	0 (0)	6 (85.7)
Royal Hospital for Children, NHS Greater Glasgow and Clyde, (004)	10	5 (50)	4 (40)	1 (10)	0 (0)
Royal Belfast Hospital for Sick Children, (005)	5	1 (20)	3 (60)	0 (0)	1 (20)
Great North Children's Hospital, (006)	54	0 (0)	48 (88.9)	0 (0)	8 (14.8)
Royal Manchester Children's Hospital, (007)	27	6 (22.2)	2 (7.4)	1 (3.7)	18 (66.7)
Leeds Children's Hospital, (008)	3	0 (0)	1 (33.3)	0 (0)	2 (66.7)
Royal Stoke University Hospital, (009)	9	0 (0)	0 (0)	1 (11.1)	8 (88.9)
Birmingham Children's Hospital, (010)	18	3 (16.7)	5 (27.8)	1 (5.6)	9 (50)
Bristol Royal Hospital for Children, (011)	14	0 (0)	2 (14.3)	0 (0)	12 (85.7)
Royal London Hospital, (013)	7	2 (28.6)	4 (57.1)	0 (0)	1 (14.3)
John Radcliffe Hospital, (014)	3	0 (0)	0 (0)	1 (33.3)	2 (66.7)
Queens Medical Centre Nottingham, (015)	6	0 (0)	1 (16.7)	1 (16.7)	4 (66.7)
Leicester Royal Infirmary, (016)	1	0 (0)	1 (100)	0 (0)	0 (0)

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[a] Parents/ person with parental responsibility may not be approached for 1 or more reasons. Percentages based on number of not approached patients per site.

[b] Reasons for not approaching for consent 1-4:

R1 GCP trained staff not available

R2 Limited resource capacity

R3 Not an appropriate time to approach the family

R4 Other reason (please specify) *

[c] Only sites that have screened at least one patient and parent/ person with parental responsibility who were not approached are included in table

Table 5-5 Summary of declined consent

Hospital (code)	No. of non-consenting parents/ person with parental responsibility	Reasons for consent not being provided [a,b]			
		R1 n (%)	R2 n (%)	R3 n (%)	R4 n (%)
Total	103	18 (17.5)	44 (42.7)	10 (9.7)	34 (33)
Alder Hey Children's Hospital, (001)	12	0 (0)	1 (8.3)	3 (25)	8 (66.7)
Southampton Children's Hospital, (002)	7	0 (0)	4 (57.1)	1 (14.3)	2 (28.6)
Paediatric Critical Care Unit, Royal Hospital for Children and Young People, NHS Lothian, (003)	1	0 (0)	1 (100)	0 (0)	0 (0)
Royal Hospital for Children, NHS Greater Glasgow and Clyde, (004)	4	0 (0)	3 (75)	2 (50)	0 (0)
Royal Belfast Hospital for Sick Children, (005)	5	0 (0)	2 (40)	0 (0)	3 (60)
Great North Children's Hospital, (006)	7	3 (42.9)	1 (14.3)	1 (14.3)	2 (28.6)
Royal Manchester Children's Hospital, (007)	20	0 (0)	12 (60)	1 (5)	7 (35)
Leeds Children's Hospital, (008)	1	0 (0)	1 (100)	0 (0)	0 (0)
Royal Stoke University Hospital, (009)	4	0 (0)	3 (75)	0 (0)	1 (25)
Birmingham Children's Hospital, (010)	5	3 (60)	1 (20)	0 (0)	1 (20)
Bristol Royal Hospital for Children, (011)	15	2 (13.3)	5 (33.3)	2 (13.3)	6 (40)
Royal London Hospital, (013)	13	6 (46.2)	6 (46.2)	0 (0)	2 (15.4)
John Radcliffe Hospital, (014)	2	0 (0)	1 (50)	0 (0)	1 (50)
Queens Medical Centre Nottingham, (015)	7	4 (57.1)	3 (42.9)	0 (0)	1 (14.3)

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\03 - Screening summary V1.0.sas

[a] Non-consented patients may fail on 1 or more reasons. Percentages based on number of non-consented patients per site.

[b] Reasons for not consenting 1-4:

R1 Parent/person with parental responsibility does not want infant to receive porcine surfactant

R2 Does not want to take part in research

R3 Unwilling to provide a reason

R4 Other reason (please specify) *

[c] Only sites that have screened at least one patient for whom consent was not obtained are included in table.

Table 5-6 Summary of patients not randomised

Hospital (code)	No. not randomised	Reasons for consent not being provided [a,b]							
		R1 n (%)	R2 n (%)	R3 n (%)	R4 n (%)	R5 n (%)	R6 n (%)	R7 n (%)	R8 n (%)
Total	18	0 (0)	0 (0)	0 (0)	10 (55.6)	1 (5.6)	0 (0)	7 (38.9)	0 (0)
Alder Hey Children's Hospital, (001)	4	0 (0)	0 (0)	0 (0)	3 (75)	0 (0)	0 (0)	1 (25)	0 (0)
Southampton Children's Hospital, (002)	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)
Royal Hospital for Children, NHS Greater Glasgow and Clyde, (004)	1	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Royal Belfast Hospital for Sick Children, (005)	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Great North Children's Hospital, (006)	1	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Royal Manchester Children's Hospital, (007)	2	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	1 (50)	0 (0)
Royal Stoke University Hospital, (009)	1	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Birmingham Children's Hospital, (010)	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)
Bristol Royal Hospital for Children, (011)	2	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Royal London Hospital, (013)	1	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Queens Medical Centre Nottingham, (015)	1	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\03 - Screening summary V1.0.sas

[a] Non-randomised patients may fail on 1 or more reasons. Percentages based on number of non-randomised patients per site.

[b] Reasons not randomised 1-8:

R1	No longer possible to start treatment within 2 hours of randomisation
R2	Infant mechanically ventilated for more than 48 hours
R3	Futility
R4	Decision made to extubate
R5	No delegated staff available to randomise
R6	Technical issue with randomisation system
R7	Other (please specify) *
R8	No reason provided

[c] Only sites that have screened at least one patient for whom consent was not obtained are included in table.

6. Tables

6.1 Baseline characteristics

6.1.1 Demographic details

Table 6-1 Demographic details

Demographics	Endotracheal poractant alfa	Sham Intervention group	Overall
Premature (yes/ no), n (%)			
n	115	117	232
Yes	66 (57.4%)	61 (52.1%)	127 (54.7%)
No	49 (42.6%)	56 (47.9%)	105 (45.3%)
Age corrected for prematurity (weeks)			
N	115	117	232
Mean (S.D.)	5.0 (6.5)	4.8 (5.9)	4.9 (6.2)
Median (IQR)	4.0 (0.0 to 8.0)	3.0 (1.0 to 7.0)	3.5 (1.0 to 8.0)
Range	-5.0 to 25.0	-4.0 to 23.0	-5.0 to 25.0
Chronological age- not corrected for premature birth			
n	115	117	232
Mean (S.D.)	9.1 (7.5)	9.2 (7.0)	9.1 (7.2)
Median (IQR)	6.0 (5.0 to 12.0)	8.0 (4.0 to 12.0)	7.0 (4.0 to 12.0)
Range	1.0 to 42.0	1.0 to 37.0	1.0 to 42.0
Age (EudraCT categories) corrected for gestation, n (%)			
n	115	117	232
Preterm newborn – gestational age 0-<37 weeks	4 (3.5%)	2 (1.7%)	6 (2.6%)
Newborn – 0-27days	53 (46.1%)	57 (48.7%)	110 (47.4%)
Infants and toddlers – 28days - 23months	58 (50.4%)	58 (49.6%)	116 (50.0%)
Weight (Kg)			
n	115	116	231
Mean (S.D.)	4.2 (1.5)	4.2 (1.5)	4.2 (1.5)
Median (IQR)	4.0 (3.0 to 5.0)	4.0 (3.1 to 5.0)	4.0 (3.0 to 5.0)
Range	2.0 to 8.9	2.0 to 8.8	2.0 to 8.9
Data unobtainable	0	1	1
Sex: n (%)			
n	115	117	232
Male	63 (54.8%)	67 (57.3%)	130 (56.0%)
Female	52 (45.2%)	50 (42.7%)	102 (44.0%)

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\05 - Baseline V3.0.sas

Table 6-2 Age sub-group summaries

Demographics	Endotracheal poractant alfa	Sham Intervention group	Overall
Number of patients randomised	115	117	232
Adjusted age pre-term (weeks)			
n	66	61	127
Mean (S.D.)	2.5 (5.4)	2.6 (5.2)	2.6 (5.3)
Median (IQR)	1.0 (-1.0 to 5.0)	2.0 (-1.0 to 4.0)	1.0 (-1.0 to 5.0)
Range	-5.0 to 25.0	-4.0 to 21.0	-5.0 to 25.0
Data unobtainable	0	0	0
Age full-term (weeks)			
n	49	56	105
Mean (S.D.)	8.3 (6.4)	7.1 (5.7)	7.7 (6.0)
Median (IQR)	6.0 (4.0 to 11.0)	6.0 (3.0 to 10.0)	6.0 (3.0 to 10.0)
Range	1.0 to 24.0	1.0 to 23.0	1.0 to 24.0
Data unobtainable	0	0	0

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\05 - Baseline V3.0.sas

6.1.2 Baseline disease characteristics

Table 6-3 Baseline disease characteristics

Summary	Endotracheal poractant alfa	Sham Intervention group	Overall
Intubated on arrival to PICU (yes/ no), n (%)			
n	115	117	232
Yes	90 (78.3%)	97 (82.9%)	187 (80.6%)
No	25 (21.7%)	20 (17.1%)	45 (19.4%)
O_2 supplementation on arrival to PICU (yes/ no), n (%)			
n	115	117	232
Yes	113 (98.3%)	115 (98.3%)	228 (98.3%)
No	1 (0.9%)	2 (1.7%)	3 (1.3%)
Data unobtainable	1 (0.9%)	0 (0.0%)	1 (0.4%)
Time on mechanical ventilator prior to arrival at PICU (hours)			
n	111	116	227
Mean (S.D.)	29.4 (9.4)	29.4 (10.4)	29.4 (9.9)
Median (IQR)	30.1 (22.7 to 37.0)	29.9 (21.3 to 37.1)	30.0 (22.1 to 37.0)
Range	9.1 to 47.5	4.1 to 47.6	4.1 to 47.6
Data unobtainable	4	1	5
Underlying viral infection identified: n (%)			
n	115	117	232
Yes	101 (87.8%)	111 (94.9%)	212 (91.4%)
No infection identified	8 (7.0%)	5 (4.3%)	13 (5.6%)
No sample	4 (3.5%)	0 (0.0%)	4 (1.7%)
Data unobtainable	2 (1.7%)	1 (0.9%)	3 (1.3%)
Underlying bacterial infection identified: n (%)			
n	115	117	232
Yes	29 (25.2%)	31 (26.5%)	60 (25.9%)
No infection identified	79 (68.7%)	82 (70.1%)	161 (69.4%)
No sample	4 (3.5%)	2 (1.7%)	6 (2.6%)
Data unobtainable	3 (2.6%)	2 (1.7%)	5 (2.2%)

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\05 - Baseline V3.0.sas

6.2 Study population

6.2.1 Data sets analysed

Table 6-4 Data sets analysed

Population	Endotracheal poractant alfa	Sham Intervention group	Overall
Screened			1009
Randomised	115 (100.0%)	117 (100.0%)	232 (100.0%)
Intention-to-treat	115 (100.0%)	117 (100.0%)	232 (100.0%)
Safety	109 (94.8%)	114 (97.4%)	223 (96.1%)
Primary outcome	113 (98.3%)	116 (99.1%)	229 (98.7%)

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\13 - Study population and premature discontinuation V1.0.sas

6.2.2 Protocol deviations

Table 6-5 Protocol deviations

Protocol deviations: n (%)	Endotracheal poractant alfa	Sham Intervention group	Overall
Any protocol deviation, n(%)	90 (78.3%)	96 (82.1%)	186 (80.2%)
At least one major	16 (13.9%)	14 (12.0%)	30 (12.9%)
Recruitment of patients already in process of weaning from MV	1 (0.9%)	0 (0.0%)	1 (0.4%)
Patient does not receive allocated intervention*	6 (5.2%)	2 (1.7%)*	8 (3.4%)
Premature discontinuation of trial treatment	6 (5.2%)	7 (6.0%)	13 (5.6%)
Premature discontinuation from trial treatment	1 (0.9%)	1 (0.9%)	2 (0.9%)
Tracheal toilet not completed prior to administration	4 (3.5%)	5 (4.3%)	9 (3.9%)
At least one minor	90 (78.3%)	94 (80.3%)	184 (79.3%)
Patient is not given scheduled dose (Missed dose)	12 (10.4%)	5 (4.3%)	17 (7.3%)
Intervention administered outside of specified time window**	34 (29.6%)	32 (27.4%)	66 (28.4%)
Physical examination not completed in specified time frame (prior to intervention)**	30 (26.1%)	30 (25.6%)	60 (25.9%)
BAL not completed prior to administration (to dose 1 and dose 3 at all sites)	15 (13.0%)	23 (19.7%)	38 (16.4%)
BAL not completed prior to administration (to dose 2 from season 2 at Alder Hey and Southampton)	19 (16.5%)	21 (17.9%)	40 (17.2%)
Post intervention examination not completed or completed outside specified time frame	56 (48.7%)	52 (44.4%)	108 (46.6%)

PD27 – Blood gas and ventilator readings not taken or taken at incorrect timepoints has not been provided due to known issues with the data collection, see secondary outcome 3 regarding the data collection for these.

PD28 – LRSQ not administered or administered at incorrect timepoint not provided.

**One patient is unknown for receiving allocated intervention as no treatment form received, these have been removed from the safety set and classified as not received allocation in the CONSORT diagram.*

***Interdependence between two events. If the intervention is outside the time window, the physical exam may also be outside the time window due to this.*

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\13 - Study population and premature discontinuation V1.0.sas

6.3 Completion of treatment course

Table 6-6 Completion of treatment course (three doses)

	Endotracheal poractant alfa	Sham Intervention group	Overall
Number randomised	115	117	232
Intervention 1			
Number of patients expected to receive dose	114 (99.1%)	117 (100.0%)	231 (99.6%)
Intervention completed	107 (93.9%)	114 (97.4%)	221 (95.7%)
Intervention not completed	2 (1.8%)	0 (0.0%)	2 (0.9%)
Intervention not done	5 (4.4%)	2 (1.7%)	7 (3.0%)
CRF not returned	0 (0.0%)	1 (0.9%)	1 (0.4%)
Reason intervention dose not completed or done*	7	3	10**
SBT criteria met and deemed ready for SBT	1 (14.3%)	1 (33.3%)	2 (20.0%)
Adverse Event	1 (14.3%)	0 (0.0%)	1 (10.0%)
Adverse Event during preparatory processes e.g. Tracheal Toilet	1 (14.3%)	0 (0.0%)	1 (10.0%)
Other	4 (57.1%)	1 (33.3%)	5 (50.0%)
CRF not returned	0 (0.0%)	1 (33.3%)	1 (10.0%)
Intervention 2			
Number of patients expected to receive dose	113 (98.3%)	117 (100.0%)	230 (99.1%)
Intervention completed	89 (78.8%)	104 (88.9%)	193 (83.9%)
Intervention not completed	3 (2.7%)	0 (0.0%)	3 (1.3%)
Intervention not done	20 (17.7%)	11 (9.4%)	31 (13.5%)
Data unobtainable	0 (0.0%)	1 (0.9%)	1 (0.4%)
CRF not returned	1 (0.9%)	1 (0.9%)	2 (0.9%)
Reason intervention dose not completed or done*	24	12	36**
SBT criteria met and deemed ready for SBT	12 (50.0%)	8 (66.7%)	20 (55.6%)
Adverse Event during preparatory processes e.g. Tracheal Toilet	1 (4.2%)	0 (0.0%)	1 (2.8%)
Serious Adverse Event	1 (4.2%)	0 (0.0%)	1 (2.8%)
Other	9 (37.5%)	3 (25.0%)	12 (33.3%)
CRF not returned	1 (4.2%)	1 (8.3%)	2 (5.6%)
Intervention 3			
Number of patients expected to receive dose	106 (92.2%)	105 (89.7%)	211 (90.9%)
Intervention completed	80 (75.5%)	82 (78.1%)	162 (76.8%)
Intervention not completed	3 (2.8%)	2 (1.9%)	5 (2.4%)
Intervention not done	20 (18.9%)	19 (18.1%)	39 (18.5%)
Data unobtainable	2 (1.9%)	1 (1.0%)	3 (1.4%)
CRF not returned	1 (0.9%)	1 (1.0%)	2 (0.9%)

	Endotracheal poractant alfa	Sham Intervention group	Overall
Number randomised	115	117	232
Reason intervention dose not completed or done*	24	22	46**
SBT criteria met and deemed ready for SBT	15 (62.5%)	16 (72.7%)	31 (67.4%)
Other	8 (33.3%)	5 (22.7%)	13 (28.3%)
CRF not returned	1 (4.2%)	1 (4.5%)	2 (4.3%)

**Note: Only reasons experienced by at least one patient will be presented.*

***Patients classified as 'Data unobtainable' have not been included in reason intervention dose not completed or done.*

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\ 09 - Treatment Compliance V1.0.sas

Table 6-7 Post randomisation discontinuations

	Endotracheal poractant alfa	Sham Intervention group	Overall
Premature discontinuation			
n	115	117	232
Yes	6 (5.2%)	7 (6.0%)	13 (5.6%)
No	109 (94.8%)	109 (93.2%)	218 (94.0%)
Data unobtainable	0 (0.0%)	1 (0.9%)	1 (0.4%)
Reason*			
Clinical information - new subsequently discussed Chief Investigator CI - protocol deviation; Clinical deterioration intervention replaced by unblinded dose of surfactant as per treating team	0 (0.0%)	1 (14.3%)	1 (7.7%)
No access - CVL being inserted. Not minimal handling out of + 1 hours for intervention	1 (16.7%)	0 (0.0%)	1 (7.7%)
Patient improving discussed with principle investigator	0 (0.0%)	1 (14.3%)	1 (7.7%)
Patient on SBT	0 (0.0%)	1 (14.3%)	1 (7.7%)
baby transferred	1 (16.7%)	0 (0.0%)	1 (7.7%)
discontinuation discussed BESS	1 (16.7%)	0 (0.0%)	1 (7.7%)
no staff available	1 (16.7%)	0 (0.0%)	1 (7.7%)
no surfactant to be able to do intervention	1 (16.7%)	0 (0.0%)	1 (7.7%)
patient extubated - self ventilating	0 (0.0%)	1 (14.3%)	1 (7.7%)
patient extubated to room air	0 (0.0%)	1 (14.3%)	1 (7.7%)
patient presentation greatly improving, MDT decision that BESS intervention would likely delay weaning progress and extubation	0 (0.0%)	1 (14.3%)	1 (7.7%)
see file note dated [date removed] confirming the patient didn't receive 2nd and 3rd intervention as mum didn't want her child to have further study interventions however happy for data to be collected and followed up	1 (16.7%)	0 (0.0%)	1 (7.7%)
withdrawal from third intervention	0 (0.0%)	1 (14.3%)	1 (7.7%)

**All reasons have been provided under the other category; therefore, verbatim reasons have been provided. Where multiple reasons have been provided (discontinued more than one dose) then multiple reasons have been given where they are not exactly the same. SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\13 - Study population and premature discontinuation V1.0.sas and 17 - Premature discontinuation reasons V1.0.sas*

6.4 Unblinding

Table 6-8 Unblinding details

	Endotracheal poractant alfa	Sham Intervention group	Overall
Number randomised	115	117	232
Number unblinded	4 (3.5%)	2 (1.7%)	6 (2.6%)
Timepoint of unblinding (days since randomisation)			
n	4	2	6
Mean (S.D.)	0.5 (0.6)	2.0 (1.4)	1.0 (1.1)
Median (IQR)	0.5 (0.0 to 1.0)	2.0 (1.0 to 3.0)	1.0 (0.0 to 1.0)
Range	0.0 to 1.0	1.0 to 3.0	0.0 to 3.0
Accidental			
Yes	1 (25.0%)	1 (50.0%)	2 (33.3%)
No	3 (75.0%)	1 (50.0%)	4 (66.7%)
Reason*			
Verbal information between non blinded and blinded team	1 (25.0%)	0 (0.0%)	1 (16.7%)
Written information between non blinded and blinded team	2 (50.0%)	1 (50.0%)	3 (50.0%)
Clinical need to know for management	1 (25.0%)	0 (0.0%)	1 (16.7%)
Blinded staff observe intervention process	0	0	0
Blinded staff observe intervention drug in ET tube	0	0	0
Other	2 (50.0%)	1 (50.0%)	3 (50.0%)

**Reasons are not mutually exclusive*

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\08 - Withdrawals and Unblinding V1.0.sas

6.5 Withdrawals

Table 6-9 Withdrawals

Row*	Arm	Site	Time from randomisation to withdrawal (days)	Decision	Reason for withdrawal
3	Endotracheal poractant alfa	Royal Stoke University Hospital	9	Parent/Person with parental responsibility	No reason provided
2	Endotracheal poractant alfa	Royal Stoke University Hospital	0	Parent/Person with parental responsibility	No reason provided
1	Sham Intervention group	John Radcliffe Hospital	0	Clinician	Other - Felt parents too upset with clinical picture to be able to continue making informed decisions about BESS.

*Row number to be assigned rather than randomisation number.

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\08 - Withdrawals and Unblinding V1.0.sas

6.6 Safety data

6.6.1 Adverse events

There were a total of 26 non-serious adverse events/reactions reported by 22 of the 223 patients in the safety population (all patients who received at least one dose).

- A total of 17 non-serious adverse events/reactions were reported by 14 of the 109 patients in Endotracheal poractant alfa.
- A total of 9 non-serious adverse events/reactions were reported by 8 of the 114 patients in Sham Intervention group.

Table 6-10 Adverse events overall

Adverse event		**Endotracheal poractant alfa**		**Sham Intervention group**		**Overall**	
System organ Class (SOC)	**Preferred term (PT)**	Events: n	Patients: n(%)	Events: n	Patients: n(%)	Events: n	Patients: n(%)
Total		**17**	**14 (12.84%)**	**9**	**8 (7.02%)**	**26**	**22 (9.87%)**
Cardiac disorders	Bradycardia	4	4 (3.67%)	0	0 (0.00%)	4	4 (1.79%)
Ear and labyrinth disorders	Otorrhoea	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
General disorders and administration site conditions	Perforation	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Pyrexia	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Total	0	0 (0.00%)	2	2 (1.75%)	2	2 (0.90%)
Infections and infestations	Bronchiolitis	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Pneumonia	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total	1	1 (0.92%)	1	1 (0.88%)	2	2 (0.90%)
Injury, poisoning and procedural complications	Endotracheal intubation complication	1	1 (0.92%)	1	1 (0.88%)	2	2 (0.90%)
	Sedation complication	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total	2	2 (1.83%)	1	1 (0.88%)	3	3 (1.35%)
Investigations	Oxygen saturation decreased	5	4 (3.67%)	0	0 (0.00%)	5	4 (1.79%)
Metabolism and nutrition disorders	Hypokalaemia	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
Nervous system disorders	Epilepsy	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
Reproductive system and breast disorders	Genital discharge	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
Respiratory, thoracic and mediastinal disorders	Atelectasis	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Hypoxia	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Respiratory depth decreased	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total	1	1 (0.92%)	2	2 (1.75%)	3	3 (1.35%)
Surgical and medical procedures	Extubation	2	2 (1.83%)	1	1 (0.88%)	3	3 (1.35%)

Table 6-11 Adverse events by severity

Adverse event			Endotracheal poractant alfa		Sham Intervention group		Overall	
System organ Class (SOC)	**Preferred term (PT)**	**Severity**	Events: n	Patients: n(%)	Events: n	Patients: n(%)	Events: n	Patients: n(%)
Total		Mild	9	7 (6.42%)	6	5 (4.39%)	15	12 (5.38%)
		Moderate	7	6 (5.50%)	3	3 (2.63%)	10	9 (4.04%)
		Severe	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
		Total	17	14 (12.84%)	9	8 (7.02%)	26	22 (9.87%)
Cardiac disorders	Bradycardia	Mild	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
		Moderate	2	2 (1.83%)	0	0 (0.00%)	2	2 (0.90%)
		Severe	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total		4	4 (3.67%)	0	0 (0.00%)	4	4 (1.79%)
Ear and labyrinth disorders	Otorrhoea	Mild	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Total		0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
General disorders and administration site conditions	Perforation	Mild	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Pyrexia	Mild	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Total		0	0 (0.00%)	2	2 (1.75%)	2	2 (0.90%)
Infections and infestations	Bronchiolitis	Moderate	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Pneumonia	Mild	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total		1	1 (0.92%)	1	1 (0.88%)	2	2 (0.90%)
Injury, poisoning and procedural complications	Endotracheal intubation complication	Moderate	1	1 (0.92%)	1	1 (0.88%)	2	2 (0.90%)
	Sedation complication	Mild	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total		2	2 (1.83%)	1	1 (0.88%)	3	3 (1.35%)
Investigations	Oxygen saturation decreased	Mild	3	2 (1.83%)	0	0 (0.00%)	3	2 (0.90%)
		Moderate	2	2 (1.83%)	0	0 (0.00%)	2	2 (0.90%)
	Total		5	4 (3.67%)	0	0 (0.00%)	5	4 (1.79%)
Metabolism and nutrition disorders	Hypokalaemia	Mild	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total		1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
Nervous system disorders	Epilepsy	Mild	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Total		0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
Reproductive system and breast disorders	Genital discharge	Mild	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total		1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Atelectasis	Mild	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)

Adverse event			Endotracheal poractant alfa		Sham Intervention group		Overall	
System organ Class (SOC)	**Preferred term (PT)**	**Severity**	Events: n	Patients: n(%)	Events: n	Patients: n(%)	Events: n	Patients: n(%)
Respiratory, thoracic and mediastinal disorders	Hypoxia	Moderate	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Respiratory depth decreased	Mild	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total		1	1 (0.92%)	2	2 (1.75%)	3	3 (1.35%)
Surgical and medical procedures	Extubation	Mild	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
		Moderate	2	2 (1.83%)	0	0 (0.00%)	2	2 (0.90%)
	Total		2	2 (1.83%)	1	1 (0.88%)	3	3 (1.35%)

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Note: Where patients have experienced more than one adverse event and more than one severity, they have been reported in the most severe category for patient total columns.

6.6.1.1 Adverse reactions

Table 6-12 Adverse reaction by causality

Adverse event			Endotracheal poractant alfa		Sham Intervention group		Overall	
System organ Class (SOC)	**Preferred term (PT)**	**Causality**	Events: n	Patients: n(%)	Events: n	Patients: n(%)	Events: n	Patients: n(%)
	Total	Possibly	7	6 (5.50%)	1	1 (0.88%)	8	7 (3.14%)
		Probably	4	3 (2.75%)	0	0 (0.00%)	4	3 (1.35%)
		Almost certainly	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
		Total	12	10 (9.17%)	1	1 (0.88%)	13	11 (4.93%)
Cardiac disorders	Bradycardia	Possibly	3	3 (2.75%)	0	0 (0.00%)	3	3 (1.35%)
		Probably	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total	Total	4	4 (3.67%)	0	0 (0.00%)	4	4 (1.79%)
Infections and infestations	Bronchiolitis	Possibly	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Pneumonia	Possibly	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total	Total	1	1 (0.92%)	1	1 (0.88%)	2	2 (0.90%)
Injury, poisoning and procedural complications	Endotracheal intubation complication	Possibly	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total	Total	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
Investigations	Oxygen saturation decreased	Almost Certainly	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
		Possibly	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
		Probably	3	2 (1.83%)	0	0 (0.00%)	3	2 (0.90%)
	Total	Total	5	4 (3.67%)	0	0 (0.00%)	5	4 (1.79%)
Respiratory, thoracic and mediastinal disorders	Respiratory depth decreased	Possibly	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total	Total	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)

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Note: Where patients have experienced more than one adverse reaction and more than one causality, they have been reported in the highest relationship category for the patients columns.

6.6.2 Adverse events by use of muscle relaxants

Table 6-13 Adverse events by use of muscle relaxant

Muscle relaxants use	Adverse event		Endotracheal poractant alfa		Sham Intervention group		Overall	
	System organ Class (SOC)	Preferred term (PT)	Events: n	Patients: n(%)	Events: n	Patients: n(%)	Events: n	Patients: n(%)
Yes	**Total**		16	15 (13.76%)	9	9 (7.89%)	25	24 (10.76%)
	Cardiac disorders	Bradycardia	3	3 (2.75%)	0	0 (0.00%)	3	3 (1.35%)
	Ear and labyrinth disorders	Otorrhoea	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	General disorders and administration site conditions	Perforation	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
		Pyrexia	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
		Total	0	0 (0.00%)	2	2 (1.75%)	2	2 (0.90%)
	Infections and infestations	Bronchiolitis	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
		Pneumonia	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
		Total	1	1 (0.92%)	1	1 (0.88%)	2	2 (0.90%)
	Injury, poisoning and procedural complications	Endotracheal intubation complication	1	1 (0.92%)	1	1 (0.88%)	2	2 (0.90%)
		Sedation complication	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
		Total	2	2 (1.83%)	1	1 (0.88%)	3	3 (1.35%)
	Investigations	Oxygen saturation decreased	5	4 (3.67%)	0	0 (0.00%)	5	4 (1.79%)
	Metabolism and nutrition disorders	Hypokalaemia	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Nervous system disorders	Epilepsy	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Reproductive system and breast disorders	Genital discharge	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Respiratory, thoracic and mediastinal disorders	Atelectasis	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
		Hypoxia	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
		Respiratory depth decreased	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
		Total	1	1 (0.92%)	2	2 (1.75%)	3	3 (1.35%)
	Surgical and medical procedures	Extubation	2	2 (1.83%)	1	1 (0.88%)	3	3 (1.35%)
No	**Total**		1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Cardiac disorders	Bradycardia	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)

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6.6.3 Serious adverse events

There were a total of 13 serious adverse events/reactions reported by 12 of the 223 patients in the safety population (all patients who received at least one dose).

- A total of 7 serious adverse events/reactions were reported by 6 of the 109 patients in Endotracheal poractant alfa.
- A total of 6 serious adverse events/reactions were reported by 6 of the 114 patients in Sham Intervention group.

Table 6-14 Serious adverse events

Adverse event		**Endotracheal poractant alfa**		**Sham Intervention group**		**Overall**	
System organ Class (SOC)	**Preferred term (PT)**	Events: n	Patients: n(%)	Events: n	Patients: n(%)	Events: n	Patients: n(%)
Total		7	6 (5.50%)	6	6 (5.26%)	13	12 (5.38%)
Cardiac disorders	Bradycardia	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Cardiac arrest	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total	1	1 (0.92%)	1	1 (0.88%)	2	2 (0.90%)
Infections and infestations	Adenovirus infection	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Bronchiolitis	2	2 (1.83%)	0	0 (0.00%)	2	2 (0.90%)
	Parainfluenzae virus infection	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Pneumonia	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Total	3	3 (2.75%)	2	2 (1.75%)	5	5 (2.24%)
Injury, poisoning and procedural complications	Endotracheal intubation complication	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
Respiratory, thoracic and mediastinal disorders	Hypoxia	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Obliterative bronchiolitis	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Pneumothorax	1	1 (0.92%)	1	1 (0.88%)	2	2 (0.90%)
	Pulmonary haemorrhage	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total	3	3 (2.75%)	2	2 (1.75%)	5	5 (2.24%)

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Table 6-15 Serious adverse event by severity

Adverse event			Endotracheal poractant alfa		Sham Intervention group		Overall	
System organ Class (SOC)	**Preferred term (PT)**	**Severity**	Events: n	Patients: n(%)	Events: n	Patients: n(%)	Events: n	Patients: n(%)
Total		Mild	0	0	0	0	0	0
		Moderate	2	2 (1.83%)	4	4 (3.51%)	6	6 (2.69%)
		Severe	5	4 (3.67%)	2	2 (1.75%)	7	6 (2.69%)
		Total	7	6 (5.50%)	6	6 (5.26%)	13	12 (5.38%)
Cardiac disorders	Bradycardia	Severe	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Cardiac arrest	Severe	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total	**Total**	**1**	**1 (0.92%)**	**1**	**1 (0.88%)**	**2**	**2 (0.90%)**
Infections and infestations	Adenovirus infection	Severe	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Bronchiolitis	Severe	2	2 (1.83%)	0	0 (0.00%)	2	2 (0.90%)
	Parainfluenzae virus infection	Moderate	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Pneumonia	Moderate	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Total	**Total**	**3**	**3 (2.75%)**	**2**	**2 (1.75%)**	**5**	**5 (2.24%)**
Injury, poisoning and procedural complications	Endotracheal intubation complication	Moderate	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
Respiratory, thoracic and mediastinal disorders	Hypoxia	Severe	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Obliterative bronchiolitis	Moderate	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Pneumothorax	Moderate	1	1 (0.92%)	1	1 (0.88%)	2	2 (0.90%)
	Pulmonary haemorrhage	Severe	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Total	**Total**	**3**	**3 (2.75%)**	**2**	**2 (1.75%)**	**5**	**5 (2.24%)**

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6.6.4 Serious adverse events by use of muscle relaxants

Table 6-16 Serious adverse events by use of muscle relaxant

Muscle relaxants use	Adverse event		Endotracheal poractant alfa		Sham Intervention group		Overall	
	System organ Class (SOC)	Preferred term (PT)	Events: n	Patients: n(%)	Events: n	Patients: n(%)	Events: n	Patients: n(%)
Yes	**Total**		6	6 (5.50%)	6	6 (5.26%)	12	12 (5.38%)
	Cardiac disorders	Bradycardia	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
		Cardiac arrest	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
		Total	1	1 (0.92%)	1	1 (0.88%)	2	2 (0.90%)
	Infections and infestations	Adenovirus infection	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
		Bronchiolitis	2	2 (1.83%)	0	0 (0.00%)	2	2 (0.90%)
		Parainfluenzae virus infection	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
		Pneumonia	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
		Total	3	3 (2.75%)	2	2 (1.75%)	5	5 (2.24%)
	Injury, poisoning and procedural complications	Endotracheal intubation complication	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
	Respiratory, thoracic and mediastinal disorders	Obliterative bronchiolitis	0	0 (0.00%)	1	1 (0.88%)	1	1 (0.45%)
		Pneumothorax	1	1 (0.92%)	1	1 (0.88%)	2	2 (0.90%)
		Pulmonary haemorrhage	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
		Total	2	2 (1.83%)	2	2 (1.75%)	4	4 (1.79%)
No	**Total**		1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)
	Respiratory, thoracic and mediastinal disorders	Hypoxia	1	1 (0.92%)	0	0 (0.00%)	1	1 (0.45%)

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6.6.5 Serious adverse reactions

There were a total of 4 serious adverse events reported by 4 of the 223 patients in the safety population (all patients who received at least one dose).

- A total of 2 serious adverse reactions were reported by 2 of the 109 patients in Endotracheal poractant alfa.
- A total of 2 serious adverse reactions were reported by 2 of the 114 patients in Sham Intervention group.

Table 6-17 Serious adverse reactions

SOC	PT	Doses of intervention	Serious criteria	Severity	Relationship (CI / PI)	Expectedness (CI)	Outcome	Allocation
Infections and infestations	Pneumonia	Three doses	Prolonged existing hospitalisation	Moderate	Unrelated/ Possibly	Unexpected	Resolved	Sham Intervention group
Respiratory, thoracic and mediastinal disorders	Hypoxia	One dose	Immediately life-threatening	Severe	Possibly/ Probably	Expected	Resolved	Curosurf (Endotracheal poractant alfa)
	Pneumothorax	Three doses	Required hospitalisation; Prolonged existing hospitalisation; Medically significant / important	Moderate	Possibly/ Probably	Expected	Resolved	Curosurf (Endotracheal poractant alfa)
			Medically significant / important	Moderate	Possibly/ Possibly	Unexpected	Resolved	Sham Intervention group

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6.6.6 Serious adverse events line listing

Table 6-18 SAE line listing

System organ class (SOC)	Preferred term (PT)	Doses of intervention	SAE no	Serious criteria	Severity	Relationship (CI/PI)	Expectedness (CI)	Outcome	Treatment
Cardiac disorders	Bradycardia	One dose	005	Immediately life-threatening	Severe	Unrelated/ Unrelated	Unexpected	Resolved	Sham Intervention group
	Cardiac arrest	Three doses	004	Immediately life-threatening; Prolonged existing hospitalisation	Severe	Unrelated/ Unlikely	Unexpected	Resolved	Curosurf (Endotracheal poractant alfa)
Infections and infestations	Adenovirus infection	One dose	009	Immediately life-threatening; Prolonged existing hospitalisation; Medically significant / important	Severe	Unrelated/ Unrelated	Unexpected	Resolved with sequelae	Sham Intervention group
	Bronchiolitis	One dose	006	Required hospitalisation	Severe	Unrelated/ Unrelated	Unexpected	Resolved	Curosurf (Endotracheal poractant alfa)
		Three doses	010	Prolonged existing hospitalisation	Severe	Unlikely/ Unrelated	Unexpected	Resolved	Curosurf (Endotracheal poractant alfa)
	Parainfluenzae virus infection	Three doses	013	Required hospitalisation	Moderate	Unrelated/ Unrelated	Unexpected	Resolved	Curosurf (Endotracheal poractant alfa)
	Pneumonia	Three doses	012	Prolonged existing hospitalisation	Moderate	Unrelated/ Possibly	Unexpected	Resolved	Sham Intervention group
Injury, poisoning and procedural complications	Endotracheal intubation complication	One dose	002	Immediately life-threatening; Medically significant / important	Moderate	Unlikely/ Unrelated	Unexpected	Resolved	Sham Intervention group

System organ class (SOC)	Preferred term (PT)	Doses of intervention	SAE no	Serious criteria	Severity	Relationship (CI/PI)	Expectedness (CI)	Outcome	Treatment
Respiratory, thoracic and mediastinal disorders	Hypoxia	One dose	001	Immediately life-threatening	Severe	Possibly/ Probably	Expected	Resolved	Curosurf (Endotracheal poractant alfa)
	Obliterative bronchiolitis	Three doses	008	Prolonged existing hospitalisation	Moderate	Unrelated/ Unlikely	Unexpected	Ongoing at final follow up	Sham Intervention group
	Pneumothorax	Three doses	003	Required hospitalisation; Prolonged existing hospitalisation; Medically significant / important	Moderate	Possibly/ Probably	Expected	Resolved	Curosurf (Endotracheal poractant alfa)
			011	Medically significant / important	Moderate	Possibly/ Possibly	Unexpected	Resolved	Sham Intervention group
	Pulmonary haemorrhage	Three doses	007	Immediately life-threatening; Prolonged existing hospitalisation	Severe	Unrelated/ Unlikely	Unexpected	Resolved	Curosurf (Endotracheal poractant alfa)

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\07 - Safety - 06 - SAE line listing tables v1_0.sas

6.7 Efficacy outcomes

6.7.1 Primary outcome – Total duration of mechanical ventilation in hours

Table 6-19 Summary of time on mechanical ventilator in hours

	Endotracheal poractant alfa n=115	**Sham Intervention group** n=117	**Overall** n=232
Time to successful extubation			
n	113	116	229
Median (Q1 to Q3)	64.9 (43.2 to 92.1)	62.0 (39.3 to 95.1)	63.6 (40.6 to 94.4)
Range	1.9 to 500.3	12.6 to 1631.6	1.9 to 1631.6
Unobtainable due to withdrawal	2	1	3
Time off mechanical ventilator due to failed extubation			
n	3	3	6
Median (Q1 to Q3)	28.2 (25.2 to 36.7)	1.7 (0.3 to 37.0)	26.7 (1.7 to 36.7)
Range	25.2 to 36.7	0.3 to 37.0	0.3 to 37.0

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\06 - 01 Primary outcome v1.0.sas

6.7.1.1 Primary outcome – two sample t-test

Table 6-20 Results of two-sample t-test for log time on MV in hours

Allocation	**Mean**	**95% CL Mean**	**Exponential**		**T Value**	**Pr > |t|**
			Mean	**95% CL Mean**		
Endotracheal poractant alfa	4.14	(4.01, 4.28)	63.06	(55.00, 72.30)	-	-
Sham Intervention group	4.13	(3.99, 4.27)	61.98	(53.80, 71.41)	-	-
Difference (Endotracheal poractant alfa- Sham Intervention group)	0.02	(-0.18, 0.21)	1.02	(0.84, 1.24)	0.17	0.8625

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\06 - 01 Primary outcome v1.0.sas

6.7.1.2 Primary outcome – Fixed effects model

Table 6-21 Solutions for Fixed Effects for log time on MV (hours) mixed model

Effect	Variable Level	Estimate (95% CI)	Standard Error	Exp Estimate (95% CI)	DF	t Value	Pr > |t|
Intercept	-	4.34 (4.07, 4.60)	0.12	76.51 (58.75, 99.66)	14	35.20	<.0001
Adjusted Age	-	-0.02 (-0.03, 0.00)	0.01	0.98 (0.97, 1.00)	210	-2.43	0.0158
Time on MV (prior to randomisation)	1 (≥24 hours)	-0.28 (-0.49, -0.08)	0.10	0.75 (0.61, 0.92)	210	-2.78	0.0059
	0 (<24 hours)	0.00	.	.	.	.	.
Sex	Female	0.19 (0.00, 0.38)	0.10	1.20 (1.00, 1.46)	210	1.93	0.0545
	Male	0.00	.	.	.	.	.
Allocation	Endotracheal poractant alfa	0.01 (-0.17, 0.20)	0.09	1.01 (0.84, 1.22)	210	0.15	0.8806
	Sham Intervention group	0.00	.	.	.	.	.

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\06 - 01 Primary outcome v1.0.sas

The estimated treatment effect for Endotracheal poractant alfa is 0.01 (with an exponential of 1.01) with a p-value of 0.8806.

6.7.1.2.1 Primary outcome – Fixed effects model sensitivity analysis

Time of last observation on the outcomes and observation form has been used for patients with failed extubations (n=3). Where patients have withdrawn the same day as randomisation and no observation and outcome forms have been completed post randomisation then the time has been assumed to be one hour.

Table 6-22 Solutions for Fixed Effects for log time on MV (hours) mixed model sensitivity analysis

Effect	Variable Level	Estimate (95% CI)	Standard Error	Exp Estimate (95% CI)	DF	t Value	Pr > |t|	Alpha
Intercept	-	4.23 (3.83, 4.63)	0.19	68.89 (46.20, 102.70)	14	22.73	<.0001	0.05
Adjusted Age	-	-0.02 (-0.04, 0.00)	0.01	0.98 (0.96, 1.00)	213	-1.66	0.0975	0.05
Time on MV (prior to randomisation)	1 (≥24 hours)	-0.26 (-0.55, 0.03)	0.15	0.77 (0.58, 1.03)	213	-1.76	0.0792	0.05
	0 (<24 hours)	0.00	.	.	.	.	.	.
Sex	Female	0.15 (-0.11, 0.41)	0.13	1.16 (0.90, 1.50)	213	1.15	0.2531	0.05
	Male	0.00	.	.	.	.	.	.
Allocation	Endotracheal poractant alfa	0.03 (-0.22, 0.29)	0.13	1.03 (0.80, 1.33)	213	0.26	0.7931	0.05
	Sham Intervention group	0.00	.	.	.	.	.	.

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\06 - 02 Primary outcome sensitivity v1.0.sas

The estimated treatment effect for Endotracheal poractant alfa is 0.03 (with an exponential of 1.03) with a p-value of 0.7931.

6.7.1.3 Primary outcome – sensitivity analysis 1 cox regression

Table 6-23 Maximum likelihood estimates for cox proportional hazards model

Effect	Variable Level	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Time on MV (prior to randomisation)	1 (≥24 hours)	0.140	0.15	0.9750	0.3233	1.155
	0 (<24 hours)	0	.	.	.	.
Allocation	Endotracheal poractant alfa	-0.010	0.13	0.0110	0.9182	0.986
	Sham Intervention group	0	.	.	.	.

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\06 - 02 Primary outcome sensitivity v1.0.sas

6.7.1.4 Primary outcome – sensitivity analysis 2 subgroup analysis

Subgroup analysis recommended by the TSC.

Table 6-24 Solutions for Fixed Effects for log time on MV (hours) mixed model

Effect	Variable Level	Estimate (95%CI)	Standard Error	Exp Estimate (95%CI)	DF	t Value	Pr > |t|	Alpha
Intercept	-	4.20 (3.88, 4.52)	0.15	66.71 (48.36, 92.01)	14	28.01	<.0001	0.05
Adjusted Age	-	-0.02 (-0.03, 0.00)	0.01	0.99 (0.97, 1.00)	208	-1.76	0.0792	0.05
Time on MV (prior to randomisation)	1 (≥24 hours)	-0.16 (-0.37, 0.06)	0.11	0.85 (0.69, 1.06)	208	-1.43	0.1529	0.05
	0 (<24 hours)	0.00	-		-	-	-	-
Sex	Female	0.18 (-0.01, 0.37)	0.10	1.20 (0.99, 1.45)	208	1.83	0.0681	0.05
	Male	0.00	-		-	-	-	-
Premature	Yes	0.07 (-0.21, 0.35)	0.14	1.07 (0.81, 1.42)	208	0.47	0.6399	0.05
	No	0.00	-		-	-	-	-
Premature*Allocation	Sham Intervention group*Premature Y	0.00	-		-	-	-	-
	Sham Intervention group*Premature N	0.00	-		-	-	-	-
	Endotracheal poractant alfa *Premature Y	0.16 (-0.23, 0.54)	0.19	1.17 (0.80, 1.71)	208	0.81	0.4205	0.05
	Endotracheal poractant alfa *Premature N	0.00	-		-	-	-	-
Allocation	Endotracheal poractant alfa	-0.07 (-0.35, 0.21)	0.14	0.93 (0.70, 1.23)	208	-0.52	0.6024	0.05
	Sham Intervention group	0	-		-	-	-	-

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\06 - 02 Primary outcome sensitivity v1.0.sas

The estimated treatment effect for Endotracheal poractant alfa is -0.07 (with an exponential of 0.93) with a p-value of 0.6024.

6.7.2 Secondary outcome 1 – Readiness for SBT

Table 6-25 Summary of time to readiness for SBT in hours

	Endotracheal poractant alfa n=115	Sham Intervention group n=117	Overall n=232
Time to readiness for SBT*			
n	98	104	202
Median (Q1 to Q3)	57.3 (32.4 to 75.6)	37.2 (25.6 to 81.4)	49.3 (28.0 to 80.5)
Range	0.2 to 496.6	6.7 to 1569.1	0.2 to 1569.1

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 01 Readiness for SBT v1.0.sas

* First occurrence where senior clinician agrees with numerical criteria for SBT, where date only is provided this has been used as midnight that day. If a participant did not meet the criteria for SBT then they were not included in this analysis. A break down of total occurrences can be seen in Table 6-26.

Table 6-26 Frequency of the SBT criteria being met per participant

Total occurrences of SBT readiness	Endotracheal poractant alfa	Sham Intervention group	Overall
n	115	117	232
0	17 (14.8%)	13 (11.1%)	30 (12.9%)
1	71 (61.7%)	63 (53.8%)	134 (57.8%)
2	20 (17.4%)	25 (21.4%)	45 (19.4%)
3	4 (3.5%)	8 (6.8%)	12 (5.2%)
4	1 (0.9%)	5 (4.3%)	6 (2.6%)
5	2 (1.7%)	3 (2.6%)	5 (2.2%)

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 01 Readiness for SBT v1.0.sas

Table 6-27 Result for two-sample t-test for time to SBT in hours

Allocation	Mean	95% CL Mean	Exponential		T Value	Pr > |t|
			Mean	95% CL Mean		
Endotracheal poractant alfa	3.78	(3.55, 4.00)	43.70	(34.97, 54.62)	-	-
Sham Intervention group	3.79	(3.61, 3.97)	44.20	(36.94, 52.89)	-	-
Difference (Endotracheal poractant alfa- Sham Intervention group)	-0.01	(-0.29, 0.27)	0.99	(0.75, 1.31)	-0.08	0.9373

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 01 Readiness for SBT v1.0.sas

6.7.2.1 Secondary outcome 1 – sensitivity analysis: First SBT criteria

A sensitivity analysis was conducted using the first time a patient meets the numerical criteria for SBT.

Table 6-28 Result for two-sample t-test for time to SBT: sensitivity analysis

Allocation	Mean	95% CL Mean	Exponential		T Value	Pr > |t|
			Mean	95% CL Mean		
Endotracheal poractant alfa	3.78	(3.55, 4.00)	43.70	(34.97, 54.62)	-	-
Sham Intervention group	3.80	(3.61, 3.98)	44.51	(37.15, 53.32)	-	-
Difference (Endotracheal poractant alfa- Sham Intervention group)	-0.02	(-0.30, 0.27)	0.98	(0.74, 1.30)	-0.13	0.8994

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 01 Readiness for SBT v1.0.sas

6.7.3 Secondary outcome 2 – Number of trial interventions

Table 6-29 Frequency of trial interventions

Total trial interventions	Endotracheal poractant alfa	Sham Intervention group	Overall	Chi Square/Fishers exact*	
				Test statistic	P-value
0; n (%)	6 (5.2%)	3 (2.6%)	9 (3.9%)	3.6240	0.3166
1; n (%)	17 (14.8%)	10 (8.5%)	27 (11.6%)		
2; n (%)	17 (14.8%)	21 (17.9%)	38 (16.4%)		
3; n (%)	75 (65.2%)	83 (70.9%)	158 (68.1%)		
Total	115	117	232		

**Pearsons Chi-square to be used if at least 5 in each category, Fisher exact test p-value given but Chi-Square test statistic provided*

. SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 02 Number of trial interventions v1.0.sas

6.7.4 Secondary outcome 3 – Change over time in blood/ gas measurements

Table 6-30 Blood/ gas summaries

Measure	Timepoint (hours)*	Endotracheal poractant alfa		Sham Intervention group		Overall	
		n	mean (Std Dev)	n	mean (Std Dev)	n	mean (Std Dev)
VI	0 (+/-2)	79	29.8 (15.4)	83	30.9 (14.5)	162	30.4 (14.9)
	6 (+/-2)	73	25.9 (9.4)	87	29.3 (14.9)	160	27.8 (12.8)
	12 (+/-2)	75	28.1 (11.4)	81	28.9 (13.5)	156	28.5 (12.5)
	24 (+/-2)	64	27.0 (10.8)	63	29.1 (15.8)	127	28.0 (13.5)
	36 (+/-2)	52	23.6 (10.2)	51	29.0 (20.1)	103	26.3 (16.1)
	48 (+/-2)	40	26.2 (11.4)	30	28.9 (14.8)	70	27.4 (13.0)
	72**	20	32.3 (14.8)	26	29.9 (18.4)	46	31.0 (16.8)
	96**	14	24.4 (8.5)	15	29.0 (14.1)	29	26.8 (11.7)
	120**	10	31.1 (19.1)	11	27.7 (13.3)	21	29.3 (16.0)
	144*	4	33.4 (17.3)	5	34.3 (19.5)	9	33.9 (17.4)
	168**	2	27.7 (4.6)	4	31.0 (12.0)	6	29.9 (9.7)
	192**	2	39.0 (18.7)	6	36.6 (16.2)	8	37.2 (15.4)
	216**	1	26.7 (.)	3	28.8 (12.6)	4	28.3 (10.4)
	240**	1	39.8 (.)	3	18.5 (6.6)	4	23.8 (11.9)
OI	0 (+/-2)	74	1032.7 (638.1)	80	1014.3 (488.4)	154	1023.2 (563.5)
	6 (+/-2)	73	936.3 (498.4)	91	965.7 (584.5)	164	952.7 (546.4)
	12 (+/-2)	74	920.8 (836.8)	78	854.3 (406.0)	152	886.7 (650.9)
	24 (+/-2)	65	951.3 (565.6)	58	880.8 (682.6)	123	918.0 (621.9)
	36 (+/-2)	53	765.5 (488.7)	47	840.1 (667.6)	100	800.5 (577.9)
	48 (+/-2)	45	744.7 (570.9)	33	801.9 (563.6)	78	768.9 (564.9)
	72**	23	804.8 (448.9)	23	1142.5 (1214.8)	46	973.7 (921.5)
	96**	16	712.4 (420.8)	17	636.3 (448.7)	33	673.2 (430.3)
	120**	10	810.7 (433.8)	11	709.6 (426.3)	21	757.7 (422.2)
	144*	5	733.8 (198.5)	6	686.0 (296.1)	11	707.8 (245.4)
	168**	4	1062.5 (570.0)	5	747.6 (429.8)	9	887.5 (491.7)
	192**	3	2604.9 (1543.7)	6	1114.5 (666.4)	9	1611.3 (1195.2)
	216**	3	1279.6 (484.2)	3	802.1 (289.4)	6	1040.8 (442.4)
	240**	2	1349.4 (164.2)	3	612.6 (105.2)	5	907.3 (418.5)
OSI	0 (+/-2)	79	527.6 (316.8)	82	513.9 (235.9)	161	520.6 (277.8)
	6 (+/-2)	77	492.3 (270.6)	93	494.9 (277.0)	170	493.7 (273.3)

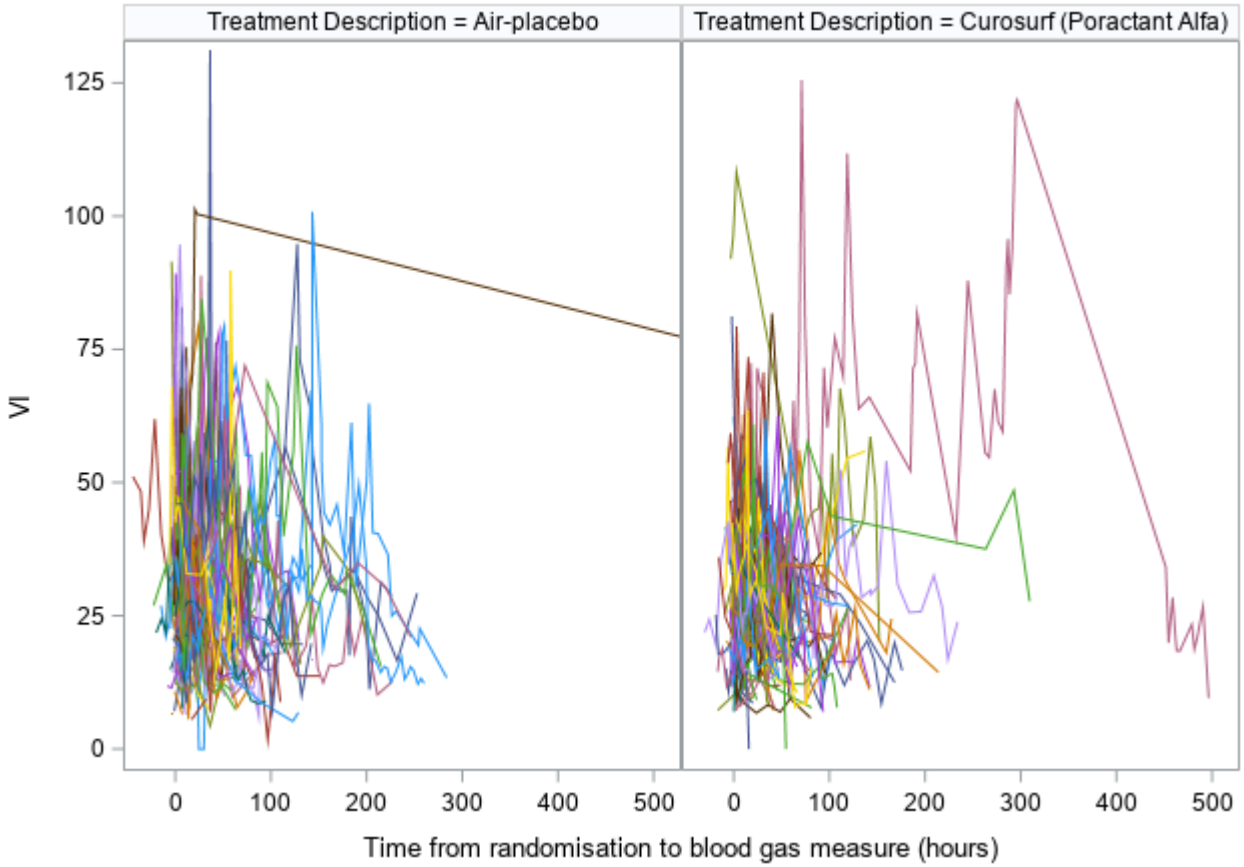
Measure	Timepoint (hours)*	Endotracheal poractant alfa		Sham Intervention group		Overall	
		n	mean (Std Dev)	n	mean (Std Dev)	n	mean (Std Dev)
	12 (+/-2)	77	479.6 (314.6)	80	452.0 (175.6)	157	465.5 (253.1)
	24 (+/-2)	68	482.6 (223.1)	59	461.6 (407.5)	127	472.9 (321.0)
	36 (+/-2)	54	404.5 (263.8)	49	423.8 (293.8)	103	413.7 (277.3)
	48 (+/-2)	46	406.2 (287.6)	35	419.1 (304.6)	81	411.7 (293.3)
	72**	26	397.1 (197.2)	24	604.8 (678.3)	50	496.8 (496.8)
	96**	18	414.6 (208.9)	20	351.2 (189.3)	38	381.2 (198.7)
	120**	10	415.9 (189.1)	12	395.9 (232.9)	22	405.0 (209.4)
	144*	5	439.4 (177.4)	6	487.2 (249.1)	11	465.5 (210.3)
	168**	4	602.4 (487.5)	5	396.1 (227.2)	9	487.8 (356.1)
	192**	4	1165.4 (1039.7)	6	531.8 (231.8)	10	785.3 (705.2)
	216**	3	826.3 (305.1)	3	562.4 (243.7)	6	694.3 (286.1)
	240**	2	760.7 (46.0)	4	357.2 (61.9)	6	491.7 (214.8)

**Data categorised as per protocol. **After 48 hours, data from the routine blood gases will be used if collected between 9:00-15:00 in subsequent 24 hour windows. Time calculated from randomisation.*

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 03 Blood Gases v2.0.sas and 11 - Secondary outcome - 03 Blood Gases - format output table v1.0.sas

6.7.4.1 Joint modelling for blood/ gas measure recorded while on MV

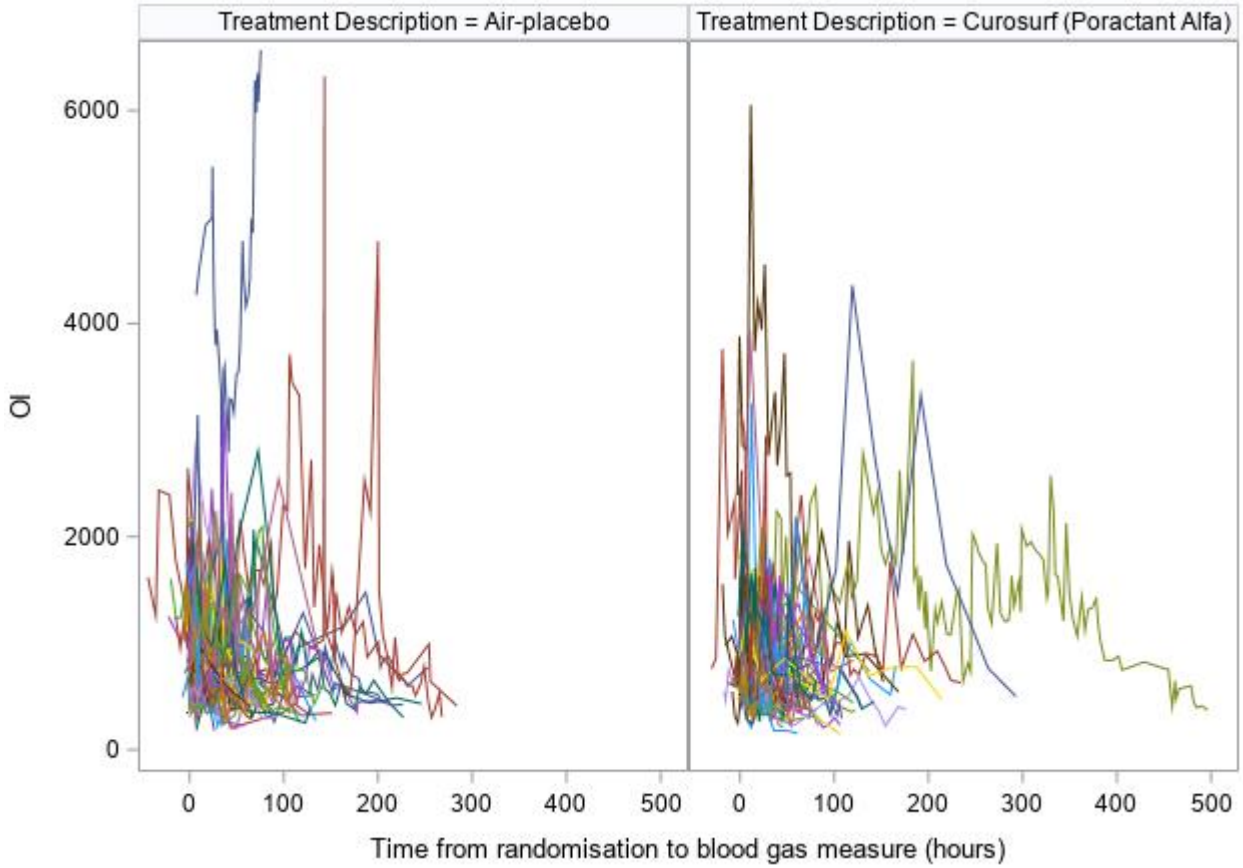
Figure 3 Profile plot for VI by arm



*1 patient capped at 500 hours, 55 observations post this time.

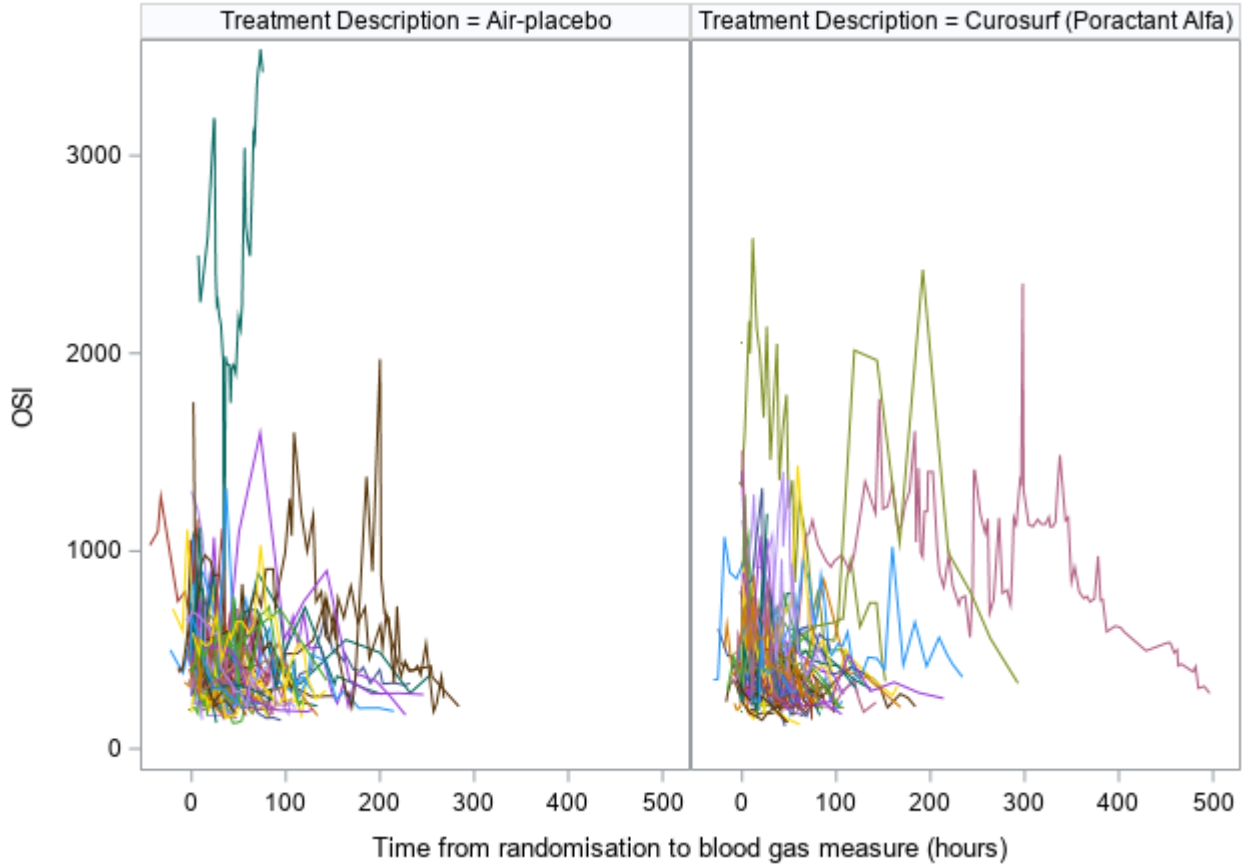
SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 03 Blood Gases v2.0.sas

Figure 4 Profile plot for OI by arm



SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 03 Blood Gases v2.0.sas

Figure 5 Profile plot for OSI by arm



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Table 6-31 Results of joint modelling

	Longitudinal		Survival	
Blood/ gas measure	**Estimated treatment effect (95% CI)**	**p-value**	**Estimated treatment effect (95% CI)**	**p-value**
VI	-1.19 (-3.76, 1.64)	0.3859	0.05 (-0.32, 0.39)	0.7763
OI	-27.67 (-155.12, 93.24)	0.6549	0.02 (-0.34, 0.44)	0.9326
OSI	6.21 (-59.17, 62.85)	0.8402	0.05 (-0.36, 0.51)	0.8011

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Table 6-32 Results of joint modelling adjusted for prematurity

	Longitudinal		Survival	
Blood/ gas measure	**Estimated treatment effect (95% CI)**	**p-value**	**Estimated treatment effect (95% CI)**	**p-value**
VI	-1.26 (-4.01, 1.46)	0.3607	0.05 (-0.34, 0.37)	0.7896
OI	-31.00 (-151.44, 80.53)	0.5978	0.01 (-0.39, 0.42)	0.9417
OSI	5.54 (-52.72, 57.54)	0.8524	0.05 (-0.31, 0.45)	0.7925

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 03 Blood Gases v2.0.sas and 11 - Secondary outcome - 03 Blood Gases Joint modelling v1.0.R and 11 - Secondary outcome - 03 Blood Gases Joint modelling - p values v1.0.R

6.7.4.2 Longitudinal model for SF ratio

The measurements required for the SF ratio are independent of being on MV so there was no drop out of this outcome due to successful extubation (i.e. this outcome is measured after participant was successfully extubated).

Table 6-33 Solutions for Fixed Effects for SF ratio

Effect	Variable Level	Estimate (95% CI)	Standard Error	DF	t Value	Pr > |t|
Intercept	-	1.83 (1.54, 2.12)	0.15	186	12.50	<.0001
Baseline SF ratio*	-	0.40 (0.31, 0.49)	0.05	1883	8.71	<.0001
Time (hours)*	-	0.00 (0.00, 0.00)	0	1883	5.33	<.0001
Time on MV (prior to randomisation)	1 (≥24 hours)	-0.08 (-0.22, 0.07)	0.07	1883	-1.07	0.2852
	0 (<24 hours)	0	-	-	-	-
Allocation	Endotracheal poractant alfa	-0.03 (-0.16, 0.11)	0.07	1883	-0.37	0.7150
	Sham Intervention group	0	-	-	-	-

**Time calculated from randomisation, baseline SF ratio taken as those prior to first intervention rather than 0 (+/-2 hr window).*
SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 03 Blood Gases v2.0.sas

Table 6-34 Mean estimated differences in result

Time (hours)	Endotracheal poractant alfa		Sham Intervention group		Estimated difference in means (SE)	95% CI	p-value
	Estimated mean result (SE)	95% CI	Estimated mean result (SE)	95% CI			
6	2.87 (0.05)	(2.77 , 2.97)	2.9 (0.05)	(2.80 , 3.00)	-0.03 (0.07)	(-0.16 , 0.11)	0.7150
12	2.88 (0.05)	(2.78 , 2.98)	2.9 (0.05)	(2.80 , 3.00)	-0.03 (0.07)	(-0.16 , 0.11)	0.7150
24	2.89 (0.05)	(2.79 , 2.99)	2.92 (0.05)	(2.82 , 3.02)	-0.03 (0.07)	(-0.16 , 0.11)	0.7150
36	2.9 (0.05)	(2.80 , 3.00)	2.93 (0.05)	(2.83 , 3.03)	-0.03 (0.07)	(-0.16 , 0.11)	0.7150
48	2.91 (0.05)	(2.82 , 3.01)	2.94 (0.05)	(2.84 , 3.04)	-0.03 (0.07)	(-0.16 , 0.11)	0.7150

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 03 Blood Gases v2.0.sas

6.7.4.3 Longitudinal model for SF ratio with time interaction

Table 6-35 Solutions for Fixed Effects for SF ratio with time interaction

Effect	Variable Level	Estimate (95% CI)	Standard Error	DF	t Value	Pr > |t|
Intercept	-	1.84 (1.55, 2.13)	0.15	186	12.48	<.0001
Baseline SF ratio*	-	0.40 (0.31, 0.49)	0.05	1882	8.70	<.0001
Time (hours)*	-	0.00 (0.00, 0.00)	0	1882	3.69	0.0002
Time on MV (prior to randomisation)	1 (≥24 hours)	-0.08 (-0.22, 0.07)	0.07	1882	-1.06	0.2907
	0 (<24 hours)	0.00 (., .)	.	.	.	.
Allocation	Endotracheal poractant alfa	-0.04 (-0.18, 0.10)	0.07	1882	-0.56	0.5770
	Sham Intervention group	0.00 (., .)	.	.	.	.
Allocation * time	Endotracheal poractant alfa	0.00 (0.00, 0.00)	0	1882	0.90	0.3662
	Sham Intervention group	0.00 (., .)	.	.	.	.

**Time calculated from randomisation, baseline SF ratio taken as those prior to first intervention rather than 0 (+/-2 hr window).*

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 03 Blood Gases v2.0.sas

Table 6-36 Mean estimated differences in result with time interaction

Time (hours)	Endotracheal poractant alfa		Sham Intervention group		Estimated difference in means (SE)	95% CI	p-value
	Estimated mean result (SE)	95% CI	Estimated mean result (SE)	95% CI			
6	2.86 (0.05)	(2.76 , 2.97)	2.9 (0.05)	(2.80 , 3.00)	-0.04 (0.07)	(-0.18 , 0.10)	0.5952
12	2.87 (0.05)	(2.77 , 2.97)	2.91 (0.05)	(2.81 , 3.01)	-0.04 (0.07)	(-0.18 , 0.10)	0.6142
24	2.89 (0.05)	(2.79 , 2.99)	2.92 (0.05)	(2.82 , 3.02)	-0.03 (0.07)	(-0.17 , 0.11)	0.6549
36	2.9 (0.05)	(2.80 , 3.00)	2.93 (0.05)	(2.83 , 3.03)	-0.03 (0.07)	(-0.16 , 0.11)	0.6987
48	2.92 (0.05)	(2.82 , 3.02)	2.94 (0.05)	(2.84 , 3.04)	-0.02 (0.07)	(-0.16 , 0.11)	0.7450

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 03 Blood Gases v2.0.sas

6.7.5 Secondary outcome 4 – Duration of oxygen supplementation

Table 6-37 Summary of time on oxygen supplementation

	Endotracheal poractant alfa	Sham Intervention group	Overall
Time on oxygen supplementation (of any kind)			
n	115	117	232
Mean (S.D.)	280.9 (2455.2)	58.4 (74.2)	168.7 (1729.2)
Median (IQR)	40.9 (17.0 to 90.0)	34.0 (16.0 to 81.4)	38.5 (17.0 to 82.0)
Range	0.0 to 26376.3	0.0 to 536.5	0.0 to 26376.3

**Exact stop time of oxygen supplementation not know for 53 patients with at least one time on oxygen supplementation therefore, the last post-mechanical ventilation follow up CRF date and time has been used as the last known timepoint patients received oxygen supplementation. **SAP states "If no oxygen supplementation is recorded then time on post-extubation respiratory support will be assumed to be zero." Due to the data being logged, this will be set to 0.001 (n=73).*

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 04 Duration of oxygen supplementation v1.0.sas

Table 6-38 Results of two-sample t-test for duration of oxygen supplementation

Allocation	Mean	95% CL Mean	Exponential		T Value	Pr > |t|
			Mean	95% CL Mean		
Endotracheal poractant alfa	3.07	(2.58, 3.56)	21.46	(13.14, 35.04)	.	-
Sham Intervention group	2.18	(1.48, 2.89)	8.88	(4.39, 17.94)	.	-
Difference (Endotracheal poractant alfa- Sham Intervention group)	0.88	(0.03, 1.74)	2.42	(1.03, 5.68)	2.04	0.0428

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 04 Duration of oxygen supplementation v1.0.sas

6.7.6 Secondary outcome 5 – Use of steroids to assist extubation

Table 6-39 Frequency of steroid use

Steroids used	Endotracheal poractant alfa	Sham Intervention group	Overall	Chi Square/Fishers exact*		
				Test statistic	Relative Risk	P-value
Yes; n (%)	51 (44.3%)	49 (41.9%)	100 (43.1%)	0.1440	1.06 (0.79, 1.42)	0.7044
No; n (%)	64 (55.7%)	68 (58.1%)	132 (56.9%)			
Total; n (%)	115	117	232			

**Pearsons Chi-square to be used if at least 5 in each category. SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 05 Use of steroids to assist extubation v1.0.sas*

6.7.7 Secondary outcome 6 – Duration of post-extubation respiratory support

Table 6-40 Summary of time on post-extubation respiratory support non-invasive

	Endotracheal poractant alfa	Sham Intervention group	Overall
Time on post-extubation respiratory support (non-invasive)			
n	115	117	232
Mean (S.D.)	17.1 (34.1)	19.5 (48.6)	18.3 (42.0)
Median (IQR)	0.0 (0.0 to 15.7)	0.0 (0.0 to 0.0)	0.0 (0.0 to 11.4)
Range	0.0 to 146.0	0.0 to 285.5	0.0 to 285.5

**Exact stop time not know for 53 patients therefore, the next post-mechanical ventilation follow up CRF date and time has been used as the change from NIV support. **SAP states "If no oxygen supplementation is recorded then time on post-extubation respiratory support will be assumed to be zero." Due to the data being logged, this will be set to 0.001 (n=168). SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 06 Duration of post-extubation respiratory support v1.0.sas*

Table 6-41 Results of two-sample t-test for duration of post-extubation respiratory support

Allocation	Mean	95% CL Mean	Exponential		T Value	Pr > |t|
			Mean	95% CL Mean		
Endotracheal poractant alfa	-3.73	(-4.63, -2.82)	0.02	(0.01, 0.06)	.	-
Sham Intervention group	-4.24	(-5.11, -3.38)	0.01	(0.01, 0.03)	.	-
Difference (Endotracheal poractant alfa- Sham Intervention group)	0.52	(-0.72, 1.76)	1.68	(0.48, 5.80)	0.82	0.4125

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 06 Duration of post-extubation respiratory support v1.0.sas

6.7.8 Secondary outcome 7 – Duration of stay at PICU and in hospital in hours

Table 6-42 Summary of time in hospital in hours

	Endotracheal poractant alfa	Sham Intervention group	Overall
Time in PICU			
n	114	116	230
Mean (S.D.)	121.6 (80.9)	134.8 (198.0)	128.3 (151.5)
Median (IQR)	104.4 (67.9 to 153.1)	93.4 (66.6 to 144.8)	96.7 (67.1 to 149.6)
Range	17.9 to 571.7	24.4 to 2095.9	17.9 to 2095.9
Data unobtainable	1	1	2
Time in hospital (including both time in PICU and time in hospital)			
n	113	114	227
Mean (S.D.)	200.8 (174.3)	171.2 (100.5)	185.9 (142.5)
Median (IQR)	165.3 (111.3 to 231.2)	142.2 (96.6 to 221.9)	154.2 (100.4 to 231.2)
Range	17.9 to 1616.2	34.3 to 430.8	17.9 to 1616.2
Data unobtainable	2	3	5

**2 patients withdrew on the day of randomisation therefore time in PICU/Hospital is unobtainable, 3 patients were not discharged from hospital by day 90.. SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 07 Duration of stay at PICU and in hospital v1.0.sas*

Table 6-43 Results of two-sample t-test for duration of stay in PICU in hours

Allocation	Mean	95% CL Mean	Exponential		T Value	Pr > |t|
			Mean	95% CL Mean		
Endotracheal poractant alfa	4.62	(4.51, 4.73)	101.98	(91.37, 113.83)	.	-
Sham Intervention group	4.62	(4.50, 4.74)	101.41	(89.93, 114.36)	.	-
Difference (Endotracheal poractant alfa- Sham Intervention group)	0.01	(-0.16, 0.17)	1.01	(0.86, 1.18)	0.07	0.9453

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 07 Duration of stay at PICU and in hospital v1.0.sas

Table 6-44 Results of two-sample t-test for duration of stay in hospital (post PICU stay)

Allocation	Mean	95% CL Mean	Exponential		T Value	Pr > |t|
			Mean	95% CL Mean		
Endotracheal poractant alfa	5.09	(4.98, 5.21)	163.18	(145.14, 183.46)	.	-
Sham Intervention group	4.97	(4.86, 5.08)	144.27	(129.03, 161.32)	.	-
Difference (Endotracheal poractant alfa- Sham Intervention group)	0.12	(-0.04, 0.28)	1.13	(0.96, 1.33)	1.51	0.1331

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 07 Duration of stay at PICU and in hospital v1.0.sas

6.7.9 Secondary outcome 8 – Liverpool Respiratory Symptom Questionnaire

Of the 232 patients randomised the LRSQ completion at each timepoint is:

- 27 (11.6%) at 6 months – 13 (11.3%) Endotracheal poractant alfa and 14 (12.0%) Sham Intervention group.
- 1 (0.4%) at 12 months – 1 (0.9%) Sham Intervention group

Of the 27 patients to return at least one LRSQ 1 (3.7%) completed both.

Table 6-45 Summaries of LRSQ data

Timepoint (months)	Endotracheal poractant alfa	Sham Intervention group	Overall
6 months			
n	13	14	27
Mean (Std Dev)	22.1 (25.9)	26.4 (27.8)	24.3 (26.5)
Median (IQR)	12.0 (11.0 to 18.0)	14.5 (4.0 to 60.0)	12.0 (5.0 to 27.0)
Range	0.0 to 80.0	0.0 to 74.0	0.0 to 80.0
12 months			
n	0	1	1
Mean (Std Dev)	-	87.0 (.)	87.0 (.)
Median (IQR)	-	87.0 (87.0 to 87.0)	87.0 (87.0 to 87.0)
Range	-	87.0 to 87.0	87.0 to 87.0
Difference (12 months-6 months)			
n	0	1	1
Mean (Std Dev)	-	23.0 (.)	23.0 (.)
Median (IQR)	-	23.0 (23.0 to 23.0)	23.0 (23.0 to 23.0)
Range	-	23.0 to 23.0	23.0 to 23.0

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\11 - Secondary outcome - 08 Liverpool Respiratory Symptom Questionnaire v1.0.sas

Due to outcome completion the fixed effects model at 12 months has not been fitted.

6.8 Safety outcome data

6.8.1 Safety outcome 1 – Failure to administer intervention due to AE

Table 6-46 Frequency of trial interventions not delivered due to AE

Total trial interventions not delivered	Endotracheal poractant alfa	Sham Intervention group	Overall	Chi Square/Fishers exact*	
				Test statistic	P-value
0; n (%)	112 (97.4%)	117 (100.0%)	229 (98.7%)	3.0922	0.1202
1; n (%)	3 (2.6%)	0 (0.0%)	3 (1.3%)		
Total	115	117	232		

**Pearsons Chi-square to be used if at least 5 in each category, Fisher exact test p-value given but Chi-Square test statistic provided*

. SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\10 - Safety outcomes - 01 Failure to administer intervention due to AE v1.0.sas

6.8.2 Safety outcome 2 – Incidence of air leak

Table 6-47 Frequency of the total incidences or air leak per participant

Total incidences of air leaks	Endotracheal poractant alfa	Sham Intervention group	Overall	Chi Square/Fishers exact*	
				Test statistic	P-value
0; n (%)	114 (99.1%)	116 (99.1%)	230 (99.1%)	0.0001	1.0000
1; n (%)	1 (0.9%)	1 (0.9%)	2 (0.9%)		
Total	115	117	232		

**Pearsons Chi-square to be used if at least 5 in each category, Fisher exact test p-value given but Chi-Square test statistic provided.*

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\10 - Safety outcomes - 02 Incidence of air leak v1.0.sas

6.8.3 Safety outcome 3 – Parent reported readmission to hospital

Of the 232 patients randomised 54 (23.3%) completed the patient reported readmission to hospital, 26 (22.6%) Endotracheal poractant alfa and 28 (23.9%) Sham Intervention group.

Table 6-48 Frequency of the total reported readmissions to hospital

Total readmissions	Endotracheal poractant alfa	Sham Intervention group	Overall	Chi Square/Fishers exact*	
				Test statistic*	P-value
0; n (%)	15 (57.7%)	23 (82.1%)	38 (70.4%)	6.7103	0.0561
1; n (%)	6 (23.1%)	5 (17.9%)	11 (20.4%)		
2; n (%)	1 (3.8%)	0 (0.0%)	1 (1.9%)		
3; n (%)	4 (15.4%)	0 (0.0%)	4 (7.4%)		
4; n (%)	0	0	0		
5; n (%)	0	0	0		
≥ 6; n (%)	0	0	0		
Total	26	28	54		

**Pearsons Chi-square to be used if at least 5 in each category, Fisher exact test p-value given but Chi-Square test statistic provided*
SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs

6.8.4 Safety outcome 4 – Any need to replace the endotracheal tube

Table 6-49 Frequency of endotracheal tubes replacements

Endotracheal tube replaced	Endotracheal poractant alfa	Sham Intervention group	Overall	Chi Square/Fishers exact*		
				Test statistic	Relative Risk	P-value
Yes; n (%)	18 (15.7%)	21 (17.9%)	39 (16.8%)	0.2187	0.87 (0.49, 1.55)	0.6400
No; n (%)	97 (84.3%)	96 (82.1%)	193 (83.2%)			
Total	115	117	232			

**Pearsons Chi-square to be used if at least 5 in each category. SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\10 - Safety outcomes - 04 Any need to replace the endotracheal tube v1.0.sas*

6.8.5 Safety outcome 5 – Death during PICU admission

No deaths have occurred therefore, no formal statistical test has been performed.
SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\10 - Safety outcomes - 05 and 06 v1.0.sas

6.8.6 Safety outcome 6 – All-cause mortality

No deaths have occurred therefore, no formal statistical test has been performed.
SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\10 - Safety outcomes - 05 and 06 v1.0.sas

7. Appendix

7.1 Safety outcome data by safety set – Post hoc

7.1.1 Safety outcome 1 – Failure to administer intervention due to AE

Table 7-1 Frequency of trial interventions not delivered due to AE

Total trial interventions not delivered	Endotracheal poractant alfa	Sham Intervention group	Overall	Chi Square/Fishers exact*	
				Test statistic	P-value
0; n (%)	107 (98.2%)	114 (100.0%)	221 (99.1%)	2.1107	0.2378
1; n (%)	2 (1.8%)	0 (0.0%)	2 (0.9%)		
Total	109	114	223		

**Pearsons Chi-square to be used if at least 5 in each category, Fisher exact test p-value given but Chi-Square test statistic provided*

. SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\15 - Safety outcomes by safety set - 01 Failure to administer intervention due to AE v1.0.sas

7.1.2 Safety outcome 2 – Incidence of air leak

Table 7-2 Frequency of the total incidences or air leak per participant

Total incidences of air leaks	Endotracheal poractant alfa	Sham Intervention group	Overall	Chi Square/Fishers exact*	
				Test statistic	P-value
0; n (%)	108 (99.1%)	113 (99.1%)	221 (99.1%)	0.0010	1.0000
1; n (%)	1 (0.9%)	1 (0.9%)	2 (0.9%)		
Total	109	114	223		

**Pearsons Chi-square to be used if at least 5 in each category, Fisher exact test p-value given but Chi-Square test statistic provided.*

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\15 - Safety outcomes by safety set - 02 Incidence of air leak v1.0.sas

7.1.3 Safety outcome 3 – Parent reported readmission to hospital

Of the 223 patients in the safety set 54 (24.2%) completed the patient reported readmission to hospital, 26 (23.9%) Endotracheal poractant alfa and 28 (24.6%) Sham Intervention group.

Table 7-3 Frequency of the total reported readmissions to hospital

Total readmissions	Endotracheal poractant alfa	Sham Intervention group	Overall	Chi Square/Fishers exact*	
				Test statistic*	P-value
0; n (%)	15 (57.7%)	23 (82.1%)	38 (70.4%)	6.7103	0.0561
1; n (%)	6 (23.1%)	5 (17.9%)	11 (20.4%)		
2; n (%)	1 (3.8%)	0 (0.0%)	1 (1.9%)		
3; n (%)	4 (15.4%)	0 (0.0%)	4 (7.4%)		
4; n (%)	0	0	0		
5; n (%)	0	0	0		
≥ 6; n (%)	0	0	0		
Total	26	28	54		

**Pearsons Chi-square to be used if at least 5 in each category, Fisher exact test p-value given but Chi-Square test statistic provided*
SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\15 - Safety outcomes by safety set - 03 Parent reported readmission to hospital v1.0.sas

7.1.4 Safety outcome 4 – Any need to replace the endotracheal tube

Table 7-4 Frequency of endotracheal tubes replacements

Endotracheal tube replaced	Endotracheal poractant alfa	Sham Intervention group	Overall	Chi Square/Fishers exact*		
				Test statistic	Relative Risk	P-value
Yes; n (%)	18 (16.5%)	20 (17.5%)	38 (17.0%)	0.0418	0.94 (0.53, 1.68)	0.8380
No; n (%)	91 (83.5%)	94 (82.5%)	185 (83.0%)			
Total	109	114	223			

**Pearsons Chi-square to be used if at least 5 in each category. SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\15 - Safety outcomes by safety set - 04 Any need to replace the endotracheal tube v1.0.sas*

7.1.5 Safety outcome 5 – Death during PICU admission and Safety outcome 6 – All-cause mortality

No deaths have occurred therefore, no formal statistical test has been performed as per Section 6.8.5 and 6.8.6.

7.2 Virology – post-hoc request

Table 7-5 Virology reported on the discharge CRF

	Endotracheal poractant alfa	Sham Intervention group	Overall
Number randomised	**115**	**117**	**232**
Adenovirus	3 (2.61%)	6 (5.13%)	9 (3.88%)
Coronavirus OC43	0	1 (0.85%)	1 (0.43%)
Enterovirus	5 (4.35%)	8 (6.84%)	13 (5.60%)
Influenza A	0	2 (1.71%)	2 (0.86%)
Influenza A/H1	0	1 (0.85%)	1 (0.43%)
Influenza B	0	1 (0.85%)	1 (0.43%)
Metapneumovirus	2 (1.74%)	5 (4.27%)	7 (3.02%)
No Infection Identified	8 (6.96%)	5 (4.27%)	13 (5.60%)
No Sample	4 (3.48%)	0	4 (1.72%)
No form returned	2 (1.74%)	1 (0.85%)	3 (1.29%)
Parainfluenza 1	1 (0.87%)	0	1 (0.43%)
Parainfluenza 3	1 (0.87%)	1 (0.85%)	2 (0.86%)
Parainfluenza 4	1 (0.87%)	0	1 (0.43%)
Respiratory Syncytial virus	87 (75.65%)	88 (75.21%)	175 (75.43%)
Rhinovirus	21 (18.26%)	29 (24.79%)	50 (21.55%)
SARS-CoV-2 (COVID-19)	1 (0.87%)	1 (0.85%)	2 (0.86%)

Note: Columns total to more than the number randomised as some patients experienced more than one.
SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\16 - Additional - Virology v1.0.sas

7.3 Bacteriology – post-hoc request

Table 7-6 Bacteriology reported on the discharge CRF

	Endotracheal poractant alfa	Sham Intervention group	Overall
Number randomised	**115**	**117**	**232**
Haemophilus influenzae	18 (15.65%)	17 (14.53%)	35 (15.09%)
No Infection Identified	79 (68.70%)	82 (70.09%)	161 (69.40%)
No Sample	4 (3.48%)	2 (1.71%)	6 (2.59%)
No form returned	4 (3.48%)	4 (3.42%)	8 (3.45%)
Normal flora	3 (2.61%)	0	3 (1.29%)
Staphylococcus aureus	5 (4.35%)	12 (10.26%)	17 (7.33%)
Strep. Pneumonia (group B strep.)	4 (3.48%)	3 (2.56%)	7 (3.02%)

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v1.0\Programs\ 18 - Additional - Bacteriology v1.0.sas

7.4 Ethnicity

Table 7-7 Ethnicity

Ethnicity	Overall
White - British	119 (51.3%)
White - Irish	8 (3.4%)
White - Any other White background	24 (10.3%)
Mixed - White and Black Caribbean	0
Mixed - White and Black African	0
Mixed - White and Asian	1 (0.4%)
Mixed - Any other mixed background	1 (0.4%)
Asian or Asian British - Indian	2 (0.9%)
Asian or Asian British - Pakistani	6 (2.6%)
Asian or Asian British - Bangladeshi	3 (1.3%)
Asian or Asian British - Any other Asian background	4 (1.7%)
Black or Black British - Caribbean	1 (0.4%)
Black or Black British - African	2 (0.9%)
Black or Black British - Any other Black background	0
Other Ethnic Groups - Chinese	0
Other Ethnic Groups - Any other ethnic group	2 (0.9%)
Not stated	44 (19.0%)
Not known	15 (6.5%)
Total number of patients	232

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v3.0\Programs\01 - Ethnicity v1.0.sas

7.5 Gestational age – Post-hoc request

Summaries and sensitivity analysis performed at the request of reviewers.

Table 7-8 Gestational Age summary

	Endotracheal poractant alfa	Sham Intervention group	Overall
Number randomised	115	117	232
Categorised Gestational age			
1 - Extremely preterm (<28 weeks)	5 (4.3%)	5 (4.3%)	10 (4.3%)
2 - Very preterm (28-31 weeks)	7 (6.1%)	13 (11.1%)	20 (8.6%)
3 - Moderate preterm (32-33 weeks)	11 (9.6%)	12 (10.3%)	23 (9.9%)
4 - Late preterm (34-39 weeks)	39 (33.9%)	27 (23.1%)	66 (28.4%)
5 - Term (≥40 weeks)	49 (42.6%)	56 (47.9%)	105 (45.3%)
Not known*	4 (3.5%)	4 (3.4%)	8 (3.4%)
Continuous summary Gestational age			
n (missing)	111 (4)	113 (4)	224 (8)
Mean (S.D.)	36.7 (3.9)	36.5 (4.4)	36.6 (4.1)
Median (IQR)	38.0 (34.0 to 40.0)	39.0 (33.0 to 40.0)	38.5 (34.0 to 40.0)
Range	26.0 to 40.0	24.0 to 40.0	24.0 to 40.0

Note: Gestational age calculated using chronological and corrected age, if a baby was not premature they did not have a corrected age and therefore have been assumed to be 40 weeks gestational age.*Implausible values are set to not known.

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v5.0\Programs\01 - Prematurity v3.0.sas

Table 7-9 Solutions for Fixed Effects for log time on MV (hours) mixed model

Effect	Variable Level		Estimate (95%CI)	Standard Error	Exp Estimate (95%CI)	DF	t Value	Pr > |t|	Alpha
Intercept	-		4.19 (3.86, 4.52)	0.15	65.86 (47.36, 91.60)	14	27.23	<.0001	0.05
Adjusted Age	-		-0.02 (-0.03, 0.00)	0.01	0.98 (0.97, 1.00)	200	-1.71	0.0880	0.05
Time on MV (prior to randomisation)	1 (≥24 hours)		-0.12 (-0.34, 0.10)	0.11	0.89 (0.71, 1.11)	200	-1.06	0.2921	0.05
	0 (<24 hours)		0.00	.	1.00	.	.	.	.
Sex	Female		0.15 (-0.04, 0.35)	0.10	1.17 (0.96, 1.42)	200	1.54	0.1256	0.05
	Male		0.00	.	1.00	.	.	.	.
Gestational Age	Extremely preterm (<28 weeks)		0.44 (-0.24, 1.13)	0.35	1.56 (0.79, 3.08)	200	1.28	0.2033	0.05
	Very preterm (28-32 weeks)		0.14 (-0.32, 0.60)	0.23	1.15 (0.73, 1.81)	200	0.59	0.5534	0.05
	Moderate preterm (32-34 weeks)		0.09 (-0.38, 0.55)	0.24	1.09 (0.68, 1.74)	200	0.36	0.7202	0.05
	Late preterm (34-40 weeks)		-0.06 (-0.41, 0.29)	0.18	0.94 (0.67, 1.33)	200	-0.34	0.7320	0.05
	Term (40+ weeks)		0.00	.	1.00	.	.	.	
	Unknown		0.04 (-0.72, 0.79)	0.38	1.04 (0.49, 2.21)	200	0.09	0.9266	0.05
Gestational age*Allocation	Endotracheal poractant alfa	Extremely preterm (<28 weeks)	-0.18 (-1.14, 0.77)	0.48	0.83 (0.32, 2.17)	200	-0.37	0.7082	0.05
		Very preterm (28-31 weeks)	0.14 (-0.62, 0.90)	0.39	1.15 (0.54, 2.45)	200	0.36	0.7204	0.05
		Moderate preterm (32-33 weeks)	0.16 (-0.50, 0.82)	0.33	1.17 (0.61, 2.26)	200	0.47	0.6382	0.05
		Late preterm (34-39 weeks)	0.16 (-0.30, 0.63)	0.24	1.18 (0.74, 1.87)	200	0.69	0.4911	0.05
		Term (≥40 weeks)	0.00	.	1.00	.	.	.	
		Unknown	0.99 (-0.07, 2.05)	0.54	2.68 (0.93, 7.73)	200	1.84	0.0674	0.05
	Sham Intervention group	Extremely preterm (<28 weeks)	0.00	.	1.00	.	.	.	
		Very preterm (28-31 weeks)	0.00	.	1.00	.	.	.	
		Moderate preterm (32-33 weeks)	0.00	.	1.00	.	.	.	
		Late preterm (34-39 weeks)	0.00	.	1.00	.	.	.	
		Term (≥40 weeks)	0.00	.	1.00	.	.	.	
		Unknown	0.00	.	1.00				
Allocation	Endotracheal poractant alfa		-0.07 (-0.35, 0.20)	0.14	0.93 (0.70, 1.23)	200	-0.53	0.5978	0.05
	Sham Intervention group		0.00	.	1.00	.	.	.	.

SAS file: J:\Statistical Analysis\BESS\Statistical Analysis\Final Analysis\Analysis\v5.0\Programs\03 Primary outcome - additional sensitivity v2.0.sas

The estimated treatment effect for Endotracheal poractant alfa is -0.07 (with an exponential of 0.93) with a p-value of 0.597.

Appendix 1: Mapping report contents to SAP

This report has been created following the BESS Statistical Analysis Plan V2.0 (dated 16/04/2024)

The following table lists each item (tables, figures and section when applicable) in this report and maps each to the relevant SAP section that describes the methods used to compute it.

Section/subsection of SAP	Item within report	Additional details (if required)
Section 14.1 Screening, eligibility, and recruitment	Figure 1 CONSORT diagram Table 5-1 Summary of randomisation Table 5-2 Summary of screening logs Table 5-3 Summary of ineligible patients Table 5-4 Summary of eligible patients not approached for consent Table 5-5 Summary of declined consent Table 5-6 Summary of patients not randomised Figure 2 Final recruitment graph Table 4-1 Randomisation checks Table 4-2 Check of balance across strata	
Section 14.2 Post randomisation discontinuations	Table 6-7 Post randomisation discontinuations	
Section 15 Protocol deviations and serious breaches of GCP	Table 6-4 Data sets analysed Table 6-5 Protocol deviations	
Section 16 Unblinding	Table 6-8 Unblinding details	
Section 17.2 Demographics and other baseline characteristics	Table 6-1 Demographic details Table 6-3 Baseline disease characteristics	
Section 17.3 Compliance with treatment	Table 6-6 Completion of treatment course (three doses)	
Section 17.4.1 Primary outcome	Table 6-19 Summary of time on mechanical ventilator Table 6-20 Results of two-sample t-test for log time on MV Table 6-21 Solutions for Fixed Effects for log time on MV (hours) mixed model Table 6-22 Solutions for Fixed Effects for log time on MV (hours) mixed model sensitivity analysis	
Section 17.4.2 Secondary outcome 1	Table 6-25 Summary of time to readiness for SBT Table 6-26 Frequency of the SBT criteria being met per participant Table 6-27 Result for two-sample t-test for time to SBT Table 6-28 Result for two-sample t-test for time to SBT: sensitivity analysis	
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Section 17.4.4 Secondary outcome 3	Table 6-30 Blood/ gas summaries	

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