Table 24 Significant predictors of Mortality for the ITT Population. Euro III.

Factor	P-value
Treatment	0.048
Apgar Score at 5 Minutes	0.003
RDS Severity Score	0.016
Birth Weight Class	0.0001
Type of delivery	0.0007

b) Survival at 28 days without BPD.

This was the primary efficacy endpoint of the study. It included patients that survived to day 28 without bronchopulmonary dysplasia (BPD). BPD was defined as the need for supplemental oxygen and radiological findings at 28 days.

The original study report and the post auditing data, both showed that the survival without BPD was statistically significantly better in the early-treated group than in the late/controls (82.4% vs. 66.3%, p-value <0.05 and 79% vs. 65% p-value = 0.02, respectively).

Table 25 Survival at 28 days without BPD . Original study report. Euro III.

Treatment Group	Alive without BPD
Treated early (n=85)	70 (82.4%)
Late/controls (n=95)	63 (66.3)
p-value	0.02

Table 26 Survival to 28 days without BPD. Post auditing data. Euro III.

Treatment Group	Excluding pts. with missing data	Pts. with missing data included as deaths or with BPD
Early treated (n=95)	73/92 (79%)	73/95 (77%)
Late/Controls (n=100)	62/96 (65%)	62/100 (62%)
p-value	0.0245	0.025
Late (n=53)	32/50 (64%)	32/53 (60%)
Controls (n=47)	30/46 (65%)	30/47 (64%)

Reviewer's note: Besides the 5 patients who did not have information on mortality at 28 days (3 patients in the early group and 1 patient each in the late and in the controls), there were 2 cases in the late group whose CRF's did not have information on the BPD at 28 days endpoint (ID# L00063 and L00104). In this case, even when all patients with missing data were included as deaths or alive with BPD, the early-treated group continued to show a statistically significant difference compared to the late/control group. Although it is difficult

to argue that this endpoint is not clinically relevant or that it does not provide a clinically important benefit to the patient, one can challenge the results when the variable in question is so ill defined there can be multiple interpretations, specially in an open label trial like the present one. The definition of BPD as used in this trial is somewhat empirical, inasmuch as the protocol included in the definition of BPD the need of oxygen supplements and CXR changes, however, it failed to specify the criteria used to provide the O2 supplement or the algorithm describing the radiological findings.

Overall, the result of the primary efficacy endpoint, the survival without BPD at 28 days, is supported by the trend in the same direction found in the incidence of mortality at 28 days, showing a benefit of surfactant administered in the early treated group, as opposed to the late-treated/control group.

4. Secondary efficacy endpoints.

a) Incidence of bronchopulmonary dysplasia (BPD) at 28 days.

All patients who survived to day 28 were assessed for incidence of BPD. BPD was defined, as described in the previous section, as the requirement of supplemental oxygen on day 28 associated with radiological findings in the lungs.

There was no statistically significant difference between the treatment groups.

Table 27 **Incidence of BPD on patients alive at 28 days. Post auditing data. Euro III.**

Treatment Group	Excluding pts. with missing data
Early treated (n=80)	7/80 (9%)
Late/Controls (n=74)	10/72 (14%)
p-value	0.3155
Late (n=39)	5/37 (14%)
Controls (n=35)	5/35 (14%)

Reviewer's note: There were 2 patients in the late-treated group who were alive on day 28 but did not have data on BPD at 28 days.

b) Oxygenation requirements at 28 days.

Supplemental oxygen requirements at 28 days were not statistically significantly different between the treatment groups.

Reviewer's note: Again, the protocol did not specify the criteria used to decide the use of supplemental oxygen. In addition, the raw data to recreate these tables were not provided with the NDA, thus, no further comments can be elaborated on this parameter.

5. **Safety endpoints.**

The following complications were evaluated: Pulmonary interstitial emphysema (PIE), pneumothorax, intracranial hemorrhage (ICH), patent ductus arteriosus (PDA), pneumonia, sepsis, retinopathy of prematurity (ROP), and necrotic enterocolitis (NEC).

The incidence of the most common complications of prematurity were comparable between the treatment groups except for the incidence of air leaks in general. The early treated group had a lower statistically significant incidence of PIE, and, numerically, had less pneumothorax than did the controls.

Table 28 Complications of prematurity. Euro III.

Complication	Early treated (N=95)	Late/Control (N=100)	P-value	Late treated (N=53)	Controls (N=47)
PIE	5 (6)	18 (19)	.007	10	8
Pneumothorax	6 (7)	14 (14)	.10	9	5
Acquired pneumonia	16 (17)	15 (15)	.85	5	10
PDA	32 (34)	23 (23)	.11	13	10
Intracranial hemorrhage (ICH)	37 (39)	49 (49)	.20	26	23
Necrotizing enterocolitis (NEC)	2 (2)	5 (5)	.45	3	2
Acquired septicemia	8 (8)	13 (13)	.36	5	8
Retinopathy of prematurity (ROP)	7 (7)	4 (4)	.36	3	1

Reviewer's note: Again, the protocol did not define the complications to be reported, nor did it specify the person assigned to read the CxR's and the head ultrasounds. It is unknown whether this person was blinded to the treatment received by the patient.

As in Euro I, the present study failed to collect important information regarding the adverse events encountered by the health care provider while the surfactant was being administered. This is important because several adverse events during the administration of other surfactants have been reported in the literature.

E. Discussion and Conclusions

This is a multicenter, randomized, single dose, open label study comparing Curosurf 200 mg/Kg (2.5 ml/Kg), administered intratracheally through the ETT to premature babies with RDS, in early treatment (when the FiO2 requirement is >0.4<0.6) vs. late/control (This group included two subgroups: a late-treated subgroup, those babies who required surfactant because of further deterioration of their condition requiring FiO2 >0.6, and the controls, those infants whose condition did not worsen and were not treated with surfactant).

The primary parameter of efficacy, survival at 28 days without BPD, showed a statistically significant difference in favor of the early treated group, when compared to the late/control group. Because of the open label nature of the trial and the lack of well defined criteria in the characterization of this endpoint, this variable is considered a weak

measure of efficacy. Mortality, on the other hand, is a more objective and appropriate endpoint of efficacy in an open label trial. The early treated group showed a lower, statistically significant, incidence in mortality at 28 days when all the patients with missing data were excluded from the analysis. Mortality at 28 days was numerically (even though not statistically) better in the early treated group, when compared to the late/control group in an intent-to-treat analysis, when all patients with missing data were considered dead at 28 days.

The complications of prematurity were not significantly different between treatment groups, except for the incidence of air leaks. The early treated group had less statistically significant PIE and numerically less pneumothoraces than the late/control group.

Overall, the results of the present trial support the efficacy and safety of Curosurf given to premature infants with RDS under the conditions of the trial. Under those conditions, the group that received the dose early in the course of the disease appear to have done better in the combined incidence of survival without BPD than did the late/control group. However, this and other endpoints could have been biased due to the unblinded nature of the trial. Even though mortality was not specified in the protocol as one of the primary endpoints, it can be considered the most reliable efficacy endpoint of this study. Its result support the efficacy of Curosurf in the early treated group.

V. EURO IV (Vol. 1.19, and 8/29/96 submission).

RANDOMIZED EUROPEAN MULTICENTER TRIAL OF SURFACTANT REPLACEMENT THERAPY FOR SEVERE NEONATAL RESPIRATORY DISTRESS SYNDROME: SINGLE VERSUS MULTIPLE DOSES OF CUROSURF

A. Investigators and investigational centers.

1. Trial Coordinator:
   Christian P. Speer, M.D.
   University of Gottingen,
   Gottingen, Germany.

2. Surfactant Preparation:
   Tore Curstedt
   Karolinska Hospital,
   Stockholm, Sweden.

3. Investigational Centers:
   Fifteen European neonatal intensive care units.

B. Objective.

Assess the efficacy of surfactant replacement therapy using multiple doses of Curosurf.

C. Study Design.

This is a multicenter, randomized, open label, parallel study.

1. Population.

a) Inclusion Criteria

(1) Birth weight 700 to 2000 g,
(2) Clinical and radiological findings typical of RDS,
(3) Age at treatment 2 to 15 hours,
(4) FiO2 >0.60
(5) Requirement of artificial ventilation

Reviewer's note: The protocol did not define the criteria used to diagnose RDS clinically or radiologically.

b) Exclusion Criteria

(1) Prolonged rupture of membranes > 3 weeks
(2) Intracranial hemorrhage of Grade III or IV
(3) Birth asphyxia (5 min. APGAR score <4)
(4) Major congenital anomalies (CHD, myelomeningocele, etc.)

c) Should be treated before surfactant replacement:

- Hypoglycemia
- Acidosis
- Anemia
- Hypotension
- Pneumothorax
- Neonatal infections (GBS)

2. Randomization procedures

Patients were randomized to the single-dose or the multiple-dose treatment group by means of sealed envelopes, stratified for birth weight based on two categories:

a) 700 - 1200 g
b) 1201 - 2000 g

3. Administration and dosage.

a) Treatment A.

Curosurf single-dose treatment. The patient was disconnected from the ventilator while surfactant was instilled into each main bronchus via a feeding tube (Ch5, 39 cm). Total dose was 2.5 ml/kg - 200 mg/Kg (Phospholipid 80 mg/ml). Patient was manually "bagged" between and after the instillations for a total of 2 minutes, using the same FiO_2 as before instillation, at a rate of 40 to 60/min.

b) Treatment B.

Curosurf multiple-dose treatment (up to 3 total doses). The patient received the initial dose the same as in treatment A, 2.5 ml/kg. At 12 and 24 hours the patient received 1 or 2 more doses of 1.25 ml/kg (equivalent to 100 mg of surfactant/kg) if the FiO_2 required was >0.21. If the FiO_2 at 12 hours = 0.21 no further surfactant was provided.

c) For both groups.

After the procedure, the babies were reconnected to the ventilator at the same settings they had before the procedure. The settings were then modified with respect to the clinical response, to maintain $Pa0_2$ 50-70 mmHg, $PaCO_2$ 40-50 mmHg, pH 7.3. PEEP was to be kept at 3 - 5 cm H_2O during the whole period of artificial ventilation.

4. Endpoints.

The primary efficacy endpoint was the combined incidence of mortality and severe BPD. Severe BPD occurred if oxygen supplement (FiO2>0.21) was still required after 28 days from birth and if grade III and IV radiological changes (classification according to Northway scale) were present.

The following parameters were compared between treated babies and controls :

- F_iO_2
- Blood gases
- Peak inspiratory pressure (PIP)
- Mean airway pressure (MAP)
- CXR changes
- Bronchial secretions
- Incidence of complications: cerebral hemorrhage (diagnosed by ultrasound), PDA (diagnosed by echocardiography), parenchymal interstitial emphysema (PIE), pneumothorax and bronchopulmonary dysplasia.
- Antibody formation

5. Statistical Analysis

a) Sample size.

It was estimated that 150 patients in each arm were required to obtain a level of significance of 5% (two tailed), with a 90% power; calculating a reduction of the combined incidence of mortality and BPD from 45% in the single dose group to 25% in the multiple dose group.

Reviewer's note: With above parameters, the statistical reviewer's calculations show the sample size estimate to be 128 with continuity corrected Chi-Square and 118 with the classical Pearson's Chi-Square.

b) Primary efficacy endpoint analysis

A logistic analysis was used to assess any influence of the center on the primary endpoint. The following influencing factors were considered:

- Treatment
- Center
- Birth weight
- Gestational age
- Sex
- Time of treatment initiation

c) Other secondary efficacy and safety analysis

Other endpoints were evaluated with either Wilcoxon Test or Fisher's Test.

d) Interim analysis.

The protocol provided that in order to observe significant differences between treatments, a group-sequential approach was going to be used. Alpha level was 5% and was adopted in accordance with O'Brian and Fleming[3]. Analysis were planned when data on 60, 120, 180 patients were available. If there was any difference between treatments, the trial would be interrupted.

The study report stated that two interim analyses were performed: one after the first year of recruitment (n=101) and another after 2 years (n=245), shortly before the trial was finished. Outcome measures showed no difference between the groups after one year and the trial was not stopped prematurely.

Reviewer's note: The logistic regression was performed in a post-hoc manner. We shall evaluate the primary endpoint with a two-by-two contingency table. Two interim analyses were conducted approximately as scheduled, though the first one was conducted a little too early. The sponsor admits that there was no significant difference at the first look, but does not report the outcome of the second one. Since the trial continued beyond the second analysis, we presume that the results were not significant at that stage either. The data at the interim analysis is not reported in either case.

D. Results.

Three hundred fifty seven patients were randomized (184 in the single-dose and 173 in the multiple-dose groups). As in the previous studies, the results of this study were published by the investigator as the original study report. Subsequently, the original data were audited and revised by (contracted by the sponsor of Curosurf) to verify source documentation. The sponsor elaborated their

[3] O'Brian, P.C., Fleming, T.R.: A Multiple Testing Procedure Trials. Biometrics 35 (1979), 549-556

integrated summaries of efficacy and safety based on these post auditing reports. Where the conclusions from the data from both sources differ statistically significantly, this review will present both data, otherwise only the post auditing information will be presented. The data will thus be referred to, in this review, as "in the original report" or as "in the post-auditing database" as appropriate.

The original report excluded 14 patients from the final statistical analysis because of protocol violations (8 patients in the single-dose, and 6 in the multiple-dose group). The post-auditing database included all patients randomized.

1. Neonatal Demographics

The demographic characteristics of the 357 patients enrolled was assessed for birth weight, gestational age, RDS score on entry, and APGAR scores at 1 and 5 min. No statistically significant differences were shown between groups in the original report or in the post auditing database.

Table 29 Neonatal characteristics. Euro IV.

	BW (grams)*	GA*(weeks)	SEX (male/female)
Single-dose (n=184)	1221.9	29.2	103/81
Multiple-dose (n=173)	1187.1	28.9	96/77
p-value	0.33	0.23	1

*Mean values

Table 30 Neonatal Demographics (continued). Euro IV.

	Single-dose (N=184)	Multiple-dose (N=173	p-value
RDS score on entry			
1	1	2	0.48
2	11	21	
3	99	85	
4	64	52	
Missing data	8	13	
APGAR at 1 min			
0 - 2	23	30	0.61
3 - 5	78	66	
6 - 7	57	51	
8 - 10	23	25	
Missing data	3	1	
APGAR at 5 min			
0 - 2	1	0	0.72
3 - 5	20	26	
6 - 7	65	44	
8 - 10	97	102	
Missing data	1	1	

Reviewer's note: The protocol did not include the criteria used for the scoring of RDS. In the sponsor's integrated summary of efficacy, the RDS scores were defined using the following x-ray criteria:

1. Reticulo-granular pattern,

2. Reticulo-granular pattern plus air bronchogram,
3. Same as 2 above plus hazy or indistinct cardiac contour,
4. Entirely collapsed, i.e., white lungs.

Note that the above RDS scoring system does not account for oxygen requirements or other measurements of the clinical respiratory status of the patients at the time of the assessment.

The RDS and the APGAR scores at 1 and 5 min were analyzed by the sponsor by comparing the number of patients that presented each score. The average values of the RDS and APGAR scores at 1 and 5 min were calculated. There were no statistically significant differences between the treatment groups in the means of RDS and APGAR scores at 1 and 5 minutes.

Table 31 Mean RDS and APGAR scores by treatment group. Euro IV.

	RDS score on entry*	APGAR at 1 min*	APGAR at 5 min*
Single-dose	3.3	5.0	7.4
Multiple-dose	3.2	4.9	7.5
p-value	0.16	0.57	0.78

2. **Maternal Demographics.**

The following characteristics were evaluated: type of delivery (vaginal or C-section), type of pregnancy (single or multiple), premature rupture of membranes >24 hours (yes or no), and prenatal use of steroids (none or <48 hours or ≥48 hours).

There were no statistically significant differences between the treatment groups in the maternal characteristics.

Table 32 Maternal demographics. Euro IV.

	DELIVERY TYPE		TYPE OF PREGNANCY		PREMATURE RUPTURE OF MEMBRANES		STEROID USE	
	C-Section	Vaginal	Single	Multiple	No	Yes	≥48 hours	<48 Hours
Single-treated (n=184)	137	31	146	37	136	30	43	131
Multiple-treated (n=173)	124	34	129	41	118	36	43	120
p- Value	0.49		0.44		0.27		0.80	

Reviewer's note: The protocol was not designed to have a fixed 3-dose multiple dose arm. The second and third dose would be given only if the patient required FiO_2 >0.21 at 12 and 24 hours (additional doses of Curosurf would not be given at 24 hours even when the FiO_2 at 24 hours was >0.21 if the FiO_2 at 12 hours had been 0.21). When the level of exposure to Curosurf was analyzed, it showed that the mean dose received in the multiple-dose group was 2 doses. In addition, almost half of the patients in the multiple-dose group received only one

dose of surfactant. This could probably explain the small difference found in the effect between the treatment groups.

Table 33 Total doses received by treatment group. Euro IV.

Total doses	Single-dose (N=184)	Multiple-dose (N=173)
1	184 (100%)	78 (45%)
2	-	31 (18%)
3	-	64 (37%)

3. **Primary Efficacy endpoint.**

The primary efficacy endpoint was the combined incidence of mortality and severe BPD at 28 days.

Neonatal mortality was defined as death up to 28 days from birth. Severe BPD occurred if oxygen supplement (FiO2>0.21) was still required after 28 days from birth and if grade III and IV radiological changes (classification according to Northway scale) were present.

For the primary end-point of the study, the combined incidence of mortality and BPD, the multiple dose-treatment resulted in a 20% relative reduction of these events, but this impact of surfactant replacement was not statistically significant. The sponsor stated that the main reason for this failure in yielding statistical significance was due to an assumption made in the sample size calculation. On the basis of the first European Multicenter Trial, they estimated that 45% of the patients in the single dose-group would experience a primary event, but in the study the combined incidence of mortality or BPD was only 33%. Therefore, the sponsor believes that the study size was too small to prove statistical significance on the reduction of the primary endpoint events.

Table 34 Survival without severe BPD at 28 days. Euro IV.

Treatment Group	Excluding pts. with missing data	Pts. with missing data included as deaths or alive with BPD
Single-dose (n=184)	117/181 (65%)	117/184 (64%)
Multiple-dose (n=173)	122/170 (72%)	122/173 (71%)
p-value	0.15	0.16

Reviewer's note: Six patients did not have information on this endpoint. Five patients did not have data on mortality at day 28 (3 in the single-dose [40204A, 40456A, 40367A] and 2 in the multiple-dose group [40206B, 40043B]) and 1 patient in the multiple-dose group without data on BPD at 28 days (40175B). It is noteworthy that all the patients who had missing data on mortality at 28 days, died before discharge.

The sponsor claims that due to an error in the calculations, the sample size was too small to detect a significant difference. In the protocol, a reduction of 44.4% (from 45% to 25%) was used for the sample size calculation. In the actual study, the primary event in the single dose group turned out to be 33%. A 44.4% reduction applied to 33% yields 18.3% as the expected incidence of primary events in the multiple dose group. If one calculates sample size with these numbers, instead of the original ones, we still get 176 patients per arm. The sample size in the study is close to 176 per arm. Hence, the sponsor's argument that the sample size was too small to detect the difference is not convincing.

4. Secondary efficacy endpoints

a) Mortality at 28 days.

As stated above, this endpoint included all causes of death that occurred from birth to day 28.

There was a statistically significant difference in the incidence of mortality between treatment groups in favor of the multiple dose group, even if the patients with missing data were considered dead.

Table 35 Mortality to 28 days. Post auditing database. Euro IV.

Treatment Group	Excluding pts. with missing data	Pts. with missing data included as deaths.
Single-dose (n=184)	36/181 (20%)	39/184 (21%)
Multiple-dose (n=173)	21/171 (12%)	23/173 (13%)
p-value*	0.0528	0.049

*Pearson Chi Square Test.

Reviewer's note: There were 5 patients with missing information on mortality at 28 days (3 patients in the single dose arm: 40456A, 40367A, and 40204A and 2 patients in the multiple dose arm: 40206B and 40043B) The CRF of all of the patients showed evidence that the infants died before 28 days of life (ICH and air leaks being mentioned as the cause of death in the first 3 days of life).

In the above table the p-values were calculated with Pearson Chi Square Test instead of the Fisher's test proposed in the protocol. If the p-values are calculated with Fisher's Test, we have about the same results in the ITT analysis.

Table 36 Mortality to 28 days Fisher's test used. Euro IV.

Treatment Group	Excluding pts. with missing data	Pts. with missing data included as deaths.
Single-dose (n=184)	36/181 (20%)	39/184 (21%)
Multiple-dose (n=173)	21/171 (12%)	23/173 (13%)
p-value*	0.06	0.0516

*Fisher's test.

No information was collected on the causes of death, therefore it was not possible to determine if mortality was affected in any particular subset.

5. **Safety endpoints**

The following complications were evaluated at day 28 in the original study report: Pulmonary interstitial emphysema (PIE), pneumothorax, intracranial hemorrhage (ICH), patent ductus arteriosus (PDA), and BPD. The post auditing database added to the above: pneumonia, sepsis, retinopathy of prematurity (ROP), and necrotic enterocolitis (NEC).

The original study report (which excluded 14 randomized patients) showed a lower statistically significant incidence of pneumothorax in the multiple-dose group ($p<0.01$). There were no other significant differences between the treatment groups in the incidence of complications of prematurity.

Table 37 Complications of prematurity . Original study report. Euro IV.

Complication	Single-dose (N=176)	Multiple-dose (N=167)	p-value
PIE	48 (27%)	38 (23%)	0.38
Pneumothorax	32 (18%)	15 (9%)	0.018
ICH			
Total	75 (43%)	71 (43%)	1.0
Grade I-II	41 (23%)	33 (20%)	0.40
Grade III-IV	34 (20%)	38 (23%)	
PDA	91 (52%)	93 (57%)	0.51
BPD	21 (12%)	22 (13%)	0.75

The post auditing database included all randomized patients, however, there were several patients that had some data missing. The analysis was performed including in the denominator only the patients that had data reported for the individual parameter.

Except for pneumothorax, which the multiple-dose group presented less frequently than the single-dose group ($p = 0.03$), there were no statistically significant differences between the treatment groups in the incidence of complications of prematurity studied.

Table 38 Complications of prematurity at 28 days. Number/total subjects with data (percentage).

Complication	Single-dose (N=184)	Multiple-dose (N=173)	p-value
Acquired pneumonia	30/140 (21)	22/130 (17%)	0.36
Acquired septicemia	53/178 (30%)	55/172 (32%)	0.73
BPD	29/184 (16%)	27/172 (16%)	1.0
Intracranial hemorrhage (ICH)	82/181 (45%)	73/173 (42%)	0.59
Necrotizing enterocolitis (NEC)	6/180 (3.3%)	5/172 (3%)	1.0
Patent ductus arteriosus (PDA)	93/181 (51%)	98/169 (58%)	0.24
Pneumothorax	32/184 (17%)	16/173 (9%)	0.03
Pulmonary Interstitial Emphysema (PIE)	50/183 (27)	37/169 (22%)	0.27
Retinopathy of prematurity (ROP)	39/166 (23%)	41/159 (26%)	0.70

E. Discussion and Conclusions

This is a multicenter, randomized, open label study comparing Curosurf initial dose 200 mg/Kg (2.5 ml/Kg), administered intratracheally through the ETT to premature babies with RDS, in a single-dose vs. a multiple-dose approach. The repeat doses consisted of 1.25 ml/Kg- 100 mg/Kg up to a total of 3 doses if the patient still required extra FiO_2 at 12 and 24 hours.
The demographic (neonatal and maternal) characteristics of the treatment groups studied were comparable.

In the evaluation of efficacy, the primary parameter of efficacy, survival at 28 days without BPD, did not show a statistically significant difference between the treated groups (p=0.16). The incidence of mortality, considered a more valid efficacy endpoint for this open label trial, showed a numerical trend in favor of the multiple dose group without reaching statistical significance (20% vs. 12% p=0.06 if patients with missing data are excluded, and 21% vs. 13%, p=0.052 if those patients are included as dead).

In the evaluation of safety, except for the incidence of pneumothorax, the incidence of complications of prematurity was not significantly different between the treatment groups; this included the incidence of BPD, ICH and PDA. The incidence of pneumothorax was statistically significantly lower in the multiple-dose treatment group (p=0.03).

Overall, this trial showed a modest effect of multiple doses of surfactant over single doses (a numerical improvement in mortality without statistical significance and a significant improvement in air leaks). One should keep in mind that, by protocol, the extra doses of surfactant in the multiple dose group were given only if the patient required FiO_2 >0.21. Thus, 45% of the patients in the multiple dose group received a single dose of surfactant. On one hand, the size of the multiple dose arm was decreased by half; decreasing the likelihood of showing a significant effect, should there be

any. On the other hand, the fact that almost half of the patients in the multiple dose group did not require an extra dose of surfactant raises the question of the optimal dose regimen for these patients.

VI. EURO VI (Submission of August 29, 1996)

CUROSURF COLLABORATIVE CONTROLLED EUROPEAN MULTICENTRE STUDY

A. Investigators and investigational centers.

1. Trial Coordinator:

   Henry Halliday, M.D.
   Royal Maternity Hospital
   Belfast, Northern Ireland.

2. Investigational Centers:

   Eighty two European neonatal intensive care units.

B. Objective.

Assess the efficacy of surfactant replacement therapy using two different multiple-dose regimens of Curosurf.

C. Study Design.

This is a Phase III, multicenter, randomized, open label, dose-comparison, parallel study involving two dose regimens.

1. Population.

   a) Inclusion Criteria

      (1) Age at treatment 2 to 72 hours,
      (2) Clinical and radiological findings of neonatal RDS,
      (3) The a/A ratio is <0.22
      (4) Requirement of artificial ventilation
      (5) No complicating disease

   b) Exclusion Criteria

      None.

   c) The following should be stabilized to exclude or treat:

      - Hypoglycemia
      - Acidosis
      - Anemia
      - Hypotension
      - Pneumothorax

2. Randomization procedures

Patients were randomized according to telephoned instructions obtained from Belfast. The randomized groups were studied openly in parallel.

3. Administration and Dose regimens:

a) Low dose subjects.

An initial dose of 100 mg/kg (1.25 ml/kg) of Curosurf was given. Two further doses of 100 mg/kg were given at 12 hour intervals if the baby was still intubated, less than 72 hours of age, and requiring supplementary FiO_2 to maintain $Pa0_2$ >50 mmHg.

b) High dose subjects.

A dose of 200 mg/Kg was given (2.5 ml/Kg). Four extra doses of 100 mg/kg could be given at 12 hour intervals, if the baby was still intubated, less than 72 hours after enrollment, and requiring supplementary FiO_2 to maintain $Pa0_2$ >50 mmHg.

c) For both groups:

The patient was disconnected from the ventilator while surfactant was instilled via a feeding tube. The baby is turned to one side while the first half of the dose is given. Then the patient receives mechanical or manual ventilation for 1 minute using the same FiO_2 as before instillation. The baby then is turned to the other side and the rest of the dose is given. The patient should not have been suctioned for 6 hours .

4. Endpoints

The primary measures of outcome were:

a) Death or BPD at 28 days of age;
b) Death to discharge and to the closure of the trial data collection;
c) For patients entered at <37 weeks of gestational age only: Prolonged oxygen dependence.

Secondary measures of outcome:

a) Days of stay in hospital
b) Days to discontinue O2 supplements
c) Days to final day in 40% O2
d) Total days chronically intubated
e) Incidence of complications of prematurity

5. Statistical Analysis

a) Sample size

The rate of death or survival with BPD was anticipated to be about 20%. If 2000 infants (1000 per group) were recruited,

there would be 80% power of detecting a reduction in death or survival with BPD from 20% to 15%.

b) Primary efficacy endpoint analysis

Analysis of primary measures of outcome will employ appropriate 2-tailed tests of significance. Should it prove necessary, chance imbalances between randomized groups will be adjusted for using multiple regression analysis.

Reviewer's note: This review relies on the analysis of the mortality results. Therefore, the above mentioned post-hoc analysis was not reviewed.

c) Other secondary efficacy and safety analysis

Although the emphasis will be on comparisons based on the three principal measures of outcome, the same analysis will be repeated for the secondary measures of outcome.

D. Results.

There were 2,172 infants originally said to have been randomized into the trial. Four of the infants were later excluded from the analysis for having received the surfactant without being previously randomized (3 cases) or for being a "duplicate" (1 case). A total of 2,168 patients were included in the analysis, 1069 in the low dose group, and 1099 in the high dose group.

Reviewer's note: There were 26 cases where the a/APO_2 entry criteria was not reported, of them, 12 cases were in the low-dose group and 14 cases in the high-dose group. These violations to the protocol appear to be equally distributed to both arms.

1. Neonatal Demographics

The randomized treatment groups were compared for mean gestational age, mean birth weight, RDS severity score (0 to 4), gender, and APGAR scores at 1 and 5 minutes.

There were no statistically significant differences between the treatment groups in any of these parameters.

Table 39 Neonatal Demographics. Euro VI.

Treatment group	BW*	GA*	Sex (male/female)	Initial FiO_2	a/A PO_2 at entry
Low dose (N=1069)	1390.4	29.4	619/450	0.77	0.13
High dose (N=1099)	1358.3	29.3	629/470	0.76	0.12
p-value	.22	.52	.76	.54	.82

Table 40 Neonatal Demographics (cont.). Number (percentage) of subjects. Euro VI.

Parameter	Low Dose	High Dose	Distributional p-value
RDS score on entry			
1	75 (7%)	77(7%)	.89
2	296 (28%)	315 (29%)	
3	459 (44$)	467 (44%)	
4	211 (20%)	211 (20%)	
Missing data	20	25	
APGAR at 1 min			
0 - 2	204 (20%)	185 (18%)	23
3 - 5	374 (36%)	407 (39%)	
6 - 7	258 (25%)	240 (23%)	
8 - 10	199 (19%)	224 (21%)	
Missing data	34	43	
APGAR at 5 min			
0 - 2	25 (2%)	20 (2%)	.41
3 - 5	133 (13%)	133 (13%)	
6 - 7	297 (29%)	298 (28%)	
8 - 10	579 (56%)	611 (58%)	
Missing data	35	37	

Reviewer's note: Note that the protocol did not include the criteria used for the scoring of RDS. In the sponsor's integrated summary of efficacy, the RDS scores were defined using characteristics of the x-ray as follows:

1. Reticulo-granular pattern,
2. Reticulo-granular pattern plus air bronchogram,
3. Same as 2 above plus hazy or indistinct cardiac contour,
4. Entirely collapsed, i.e., white lungs.

The above RDS scoring system does not account for oxygen requirements or other measurements of the clinical respiratory status of the patients at the time of the assessment.

The RDS and the APGAR scores at 1 and 5 min were analyzed by the sponsor by comparing the number of patients that presented each score. As in the previous study, we calculated the average value of the RDS and APGAR scores at 1 and 5 min. There were no statistically significant differences between the treatment groups in the means of RDS and APGAR scores at 1 and 5 minutes.

Table 41 Mean RDS and APGAR scores by treatment group. Euro VI.

Treatment group	RDS score on entry	APGAR at 1 min	APGAR at 5 min
Low Dose	2.7	5.0	7.4
High Dose	2.7	5.0	7.5
p-value	.83	.57	.50

2. Maternal Demographics.

The following characteristics were evaluated: type of delivery (vaginal or C-section), type of pregnancy (single or multiple products), premature rupture of membranes >24 hours (yes or no), and prenatal use of steroids (none or <48 hours or ≥48 hours).

There were no statistically significant differences in the maternal characteristics between the treatment groups.

Table 42 Maternal demographics. Euro VI.

Treatment Group	DELIVERY TYPE		TYPE OF PREGNANCY		PREMATURE RUPTURE OF MEMBRANES		STEROID USE	
	C-Section	Vaginal	Single	Multiple	No	Yes	≥48 hours	<48 Hours
Low Dose (N=1069)	636 (60%)	424 (40%)	816 (76%)	253 (24%)	883 (83%)	185 (17%)	173 (16%)	888 (84%)
High Dose (N=1099)	643 (59%)	440 (41%)	808 (74%)	291 (27%)	901 (82%)	193 (18%)	189 (18%)	880 (82%)
p-Value	.79		.74		.87		.42	

3. Total drug exposure.

Patients in the low dose group were to receive up to a maximum cumulative dose of 300 mg/Kg (up to a total of 3 doses of 100 mg/Kg each), and patients in the high dose group were to receive one initial dose of 200 mg/Kg plus up to four additional doses of Curosurf 100 mg/Kg to a maximum cumulative dose of 600 mg/Kg.

The mean cumulative dose was 238.6 and 373.9 mg/Kg ($p<0.01$) and the mean number of doses was 2.3 and 2.7 ($p<0.01$) for the low- and the high-dose groups, respectively.

Overall, 80% of the subjects in the low dose group received more than one dose of surfactant vs. 72% of the subjects in the high dose group.

Table 43 Total drug exposure by treatment group. Euro VI.

	Low Dose	High Dose	High Dose P-values
Mean Number of Doses	2.3	2.7	<0.01
Mean Cumulative Dose (mg/kg)	238.6	373.9	<0.01

Table 44 Total number of doses by treatment group. Euro VI.

Total # of doses received	Low Dose (N= 1,069)	High Dose (N=1,099)
0 Dose	19 (2%)	29 (3%)
1 Dose	193 (18%)	275 (25%)
2 Doses	228 (21%)	214 (19%)
3 Doses	616 (57%)	224 (20%)
4 Doses	11 (1%)	121 (11%)
5 Doses	2 (0.2%)	236 (21%)
p-value	<0.01*	

*Determination of p-value not appropriate. See reviewer's note below.

Reviewer's note: No explanation was provided for the 48 patients that did not receive Curosurf at all in either group (whether they had met eligibility criteria or not), or the 13 patients that received non-protocol doses in the low dose group (i.e., patients that received one or two extra doses over the allowed maximum of three). There were more patients in the high dose group than in the low dose group who required one dose of surfactant only (25% vs. 18%, p-value = 0.002) for the treatment of RDS. With all other factors remaining the same, the latter could be interpreted that an initial dose of 200 mg/Kg of Curosurf is more effective than 100 mg/Kg.

Regarding the repeat doses, the protocol should have been designed to allow the low dose group to receive the same total number of doses of surfactant, to be able to assess how many subjects required the 4 extra doses. It is not appropriate to determine a p-value for design dependent distributional differences.

The results of the present study are not conclusive concerning the optimal number of repeat doses of surfactant, considering that, by protocol, subjects in the low dose group were not to receive a 4th and a 5th dose regardless of their condition, and in the high-dose group, even though less subjects received extra doses of surfactant, 32 % of the subjects received 4 or 5 doses.

4. **Efficacy endpoints**

The primary measures of outcome were:

a) **Death or BPD at 28 days of age; BPD was defined as the use of supplementary oxygen at 28 days.**

b) **Death to discharge and to the closure of the trial data collection.**

c) **For patients entered at <37 weeks of gestational age only: Prolonged oxygen dependence, defined as still receiving daily O_2 supplement on the expected date of delivery.**

There were no statistically significant differences between the treatment groups on any of the primary endpoints. Logistic regression with gestational age, birth weight, and gender as independent variables did not yield statistical significance for any of the primary endpoints.

Table 45 Primary Efficacy Parameters. Number (percentage) of subjects. Euro VI.

Parameter	Low Dose (N = 1069)	High Dose (N = 1093)	P-value
Status at 28 days			.92
Alive or discharged home	517 (48%)	533 (48.5%)	
Alive but oxygen dependent	317 (30%)	332 (30%)	
Dead	224 (21%)	218 (20%)	
Not known	11 (1%)	16 (1.5%)	
Status at discharge			.52
Alive	797 (74%)	834 (76%)	
Not yet discharged	7 (0.7%)	7 (0.6%)	
Dead	265 (25%)	256 (23%)	
Not known	0	2 (0.2%)	
Status at expected date of delivery			.77
Alive or discharged home	710 (66%)	736 (67%)	
Alive, oxygen dependent	89 (8%)	87 (8%)	
Dead	248 (23%)	243 (22%)	
>37 weeks	9 (0.8%)	9 (0.8%)	
Not known	13 (1.2%)	24 (2%)	

Reviewer's note: Note that the definition of BPD in this trial, i.e., use of supplementary oxygen at 28 days, is very loose; in contrast to the other studies discussed in this NDA, no CXR criteria were included in its definition. In addition, the use of oxygen was not standardized. These deficiencies in the definition and the evaluation of an efficacy endpoint make the results difficult to interpret, specially in an unblinded trial with unknown treatment bias. The lack of a standard definition of the endpoint make the results of this study difficult to compare with other studies.

The reviewer's calculations yielded sample size of 945 per group given the parameters stated above (see 6. a).The sample size of this study was sufficiently large to detect any clinically relevant difference between the two dose regimens. This study did not show evidence that either dose regimen was more effective than the other.

5. **Secondary efficacy endpoints**

The following parameters were considered secondary measures of outcome:

a) **Days of stay in hospital;**
b) **Days to discontinue O_2 supplements;**
c) **Days in 40% O_2;**
d) **Total days chronically intubated; and**
e) **Incidence of complications of prematurity.**

The data showed no statistically significant differences between the treatment groups for these parameters, except perhaps for a small improvement in days in >40% O_2, which is shown in more detail in the table below.

Table 46 Secondary endpoint parameters. Median (quartiles). Euro VI.

Variable	Low Dose	High Dose	P-value
Days of stay in hospital	44 (19,75)	45 (13, 76)	0.81
Days to O_2 weaning	10 (4, 34)	8 (4,31)	0.20
Days in 40% O_2	3 (1, 11)	3 (1, 12)	0.04
Days intubated	6 (3, 14)	5 (3,15)	0.38

Table 47 Total days spent in >40% O2 . Euro VI.

Days in 40% O2	Low Dose	High Dose
None	122 (11%)	166 (15%)
1 - 3 days	423 (40%)	450 (41%)
4 - 6 days	166 (16%)	113 (10%)
1 -2 weeks	111 (10%)	93 (8.5%)
2 weeks - 1 month	117 (11%)	117 (11%)
> 1 month	118 (11%)	135 (12%)
Not known	12 (1%)	25 (2%)
Median (quartiles)	3 (1, 11)	3 (1,12)

Reviewer's note: The secondary variable ' days in 40% O_2 ' is statistically significant using the Mann-Whitney test, however the reviewer could not verify the p-value due to lack of data on this variable. Even when the difference in the days where oxygen supplement >40% appears to be statistically significant in favor of the high dose group, the clinical relevance of this finding is questioned in an unblinded trial where there were no prespecified criteria of oxygen management. Furthermore, the electronic data, provided with the NDA, did not include FiO2 data beyond the 36 hours post treatment time point, therefore revision of the data beyond this time point could not be established. Complications of prematurity are discussed below.

6. Safety endpoints

a) Complications of prematurity.

Information on the following complications of prematurity were collected: air leaks (pneumothorax or air leak), pneumonia, patent ductus arteriosus (PDA), intracraneal hemorrhage (ICH), Necrotizing enterocolitis (NEC), septicemia, and retinopathy of prematurity.

There were no statistically significant differences in the incidence of complications of prematurity between the treatment groups.

Table 48 Complications of prematurity. Number (percentage) of subjects. Euro VI.

Complication	Low Dose (N=1069)	High Dose (N=1099)	P-value
Any air leak	201 (19)	178 (16)	0.11
Pulmonary hemorrhage	59 (6)	74 (8)	0.25
Acquired pneumonia	167 (16)	175 (16)	0.86
Patent ductus arteriosus (PDA)	380 (36)	384 (35)	0.79
Necrotizing enterocolitis (NEC)	56 (5)	72 (7)	0.20
Sepsis	329 (16)	335 30)	0.89
Retinopathy of prematurity (ROP)	125 (12)	124 (11)	0.79

Table 49 Intracerebral hemorrhages at 1 and 6 weeks. Euro VI.

Variable	Low Dose (N=1069)	High Dose (N=1099)	P-value
At 1 week			
Hemorrhages			
Any hemorrhage	258 (24)	283 (26)	0.40
Parenchymal lesion	76 (7)	81 (7)	0.87
Not known	171 (16)	167 (15)	0.64
Cysts			
Porencephalic cysts	8 (0.7)	12 (1)	0.50
Cystic leukomalacia	3 (0.3)	2 (0.2)	0.68
Ventricles			
Dilatation	102 (10)	103 (9)	0.94
Hydrocephalus	19 (2)	23 (2)	0.64
At 6 weeks			
Hemorrhages			
Any hemorrhage	110 (8)	111 (10)	0.89
Parenchymal lesion	25 (2)	24 (2)	0.89
Not known	428 (40)	449 (41)	0.73
Cysts			
Porencephalic cysts	40 (4)	37 (3)	0.64
Cystic leukomalacia	19 (2)	20 (2)	1
Ventricles			
Dilatation	79 (7)	81 (7)	1
Hydrocephalus	49 (5)	37 (3)	0.15

b) **Adverse events during administration of the surfactant.**

The following complications were reported as possibly or probably related to the administration of surfactant: bradycardia, hypotension, intraventricular hemorrhage, patent ductus arteriosus, pneumothorax or air leak, pulmonary hemorrhage, tube blockage, and ventilator setting deterioration.

Favoring the low dose group, there were statistically significant differences between the low and the high dose group in the incidence of tube blockage and bradycardia.

Table 50 Adverse events during Curosurf administration. Euro VI.

	Surfactant Dose Schedule		P-value
	Low	High	
Total	1050 (100)	1071 (100)	
First complication			
None	946 (90)	926 (86.5)	0.01
Pulmonary hemorrhage	18 (1.7)	29 (3)	0.14
Pneumothorax or air leak	16 (1.5)	10 (1)	0.24
Tube blockage	5 (0.5)	23 (2)	0.001
Hypotension	13 (1)	9 (1)	0.40
Bradycardia	8 (0.8)	22 (2)	0.016
Intraventricular hemorrhage	9 (0.9)	11 (1)	0.82
Patent ductus arteriosus	15 (1)	12 (1)	0.57
Ventilator setting deterioration	4 (0.4)	5 (0.5)	1
Other	16 (1.5)	24 (2)	0.26
Second Complication			
None	1029 (98)	1047 (98)	0.76
Pulmonary hemorrhage	3 (0.3)	2 (0.2)	0.68
Pneumothorax or air leak	1 (0.1)	2 (0.2)	1
tube blockage	1 (0.1)	3 (0.3)	0.62
Hypotension	1 (0.1)	2 (0.2)	1
Bradycardia	2 (0.2)	4 (0.4)	0.69
Intraventricular hemorrhage	4 (0.4)	2 (0.2)	0.45
Patent ductus arteriosus	1 (0.1)	1 (0.1)	1
Other	8 (0.8)	8 (0.7)	1

Reviewer's note: The incidence of adverse events during the administration of Curosurf is ambiguous in that the protocol did not define the adverse events, e.g., what was going to be considered a bradycardia event, or a tube blockage; or the time frame when an adverse event was going to be considered related to the administration of Curosurf. Potentially indicative of severe underreporting, the incidence of certain adverse events reported in this trial are far lower than reported in the literature for other natural surfactants.

E. Discussion and Conclusions

This is a large, multicenter, randomized, open label study comparing two multiple-dose regimens of Curosurf (Low-dose vs. High-dose arm), administered intratracheally through the ETT to premature babies with RDS. The low-dose regimen consisted of an initial dose of 100 mg/Kg (1.25 ml/Kg), with repeat doses every 12 hours to a maximum total of 3 doses (maximum cumulative dose of 300 mg/Kg). The high-dose regimen consisted of an initial dose of 200 mg/Kg (2.5 ml/kg) plus repeat doses of 100 mg/Kg for a total of 5 doses (maximum cumulative dose of 600 mg/Kg). The repeat doses in either arm were given only if the subject met some oxygenation criteria.

The primary parameters of efficacy, mortality combined with BPD at 28 days and at discharge did not demonstrate statistically significant differences between the treatment groups. For patients <37 weeks of gestation a third primary efficacy endpoint was the oxygen supplement to expected day of delivery. There was no statistically significant difference between the treatment groups for this endpoint either.

The complications of prematurity were not significantly different between the treatment groups, they included the incidence of BPD, ICH and PDA. This is the only trial where adverse events during the administration of the surfactant were reported. However, adverse events during the administration of Curosurf were not properly collected or reported; thus, impairing a full assessment of the surfactant's impact on morbidity during its administration.

Overall, the results of the present study do not support a given dose regimen of Curosurf over the other, as studied in this trial. As discussed under the primary efficacy endpoint section, the study was large enough to demonstrate any clinically relevant difference between the treatment groups (if there had been any). Under the conditions of this trial the optimal number of repeat doses was not established.

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

12 Pages

VIII. SUPPORTIVE STUDIES

A. Protocol 50.01/CT/01/92 (Vol. 1.20)

"Randomized Clinical Trial Of Surfactant Therapy For Neonatal Respiratory Distress Syndrome: Comparison Of Two Treatment Regimens With Natural Surfactant Preparations."

1. Study Characteristics and Definitions

This was a pilot, multicenter (5 German NICUs), randomized, open label study of Curosurf vs. Survanta. Seventy five patients (birth weight 700-1500 g) with RDS requiring mechanical ventilation with $FiO_2 \geq 40\%$ were enrolled before 24 hours of age to receive either Curosurf 200 mg/kg or Survanta 100 mg/kg.(Survanta was instilled as recommended by the manufacturer). Patients who remained intubated with $FiO_2 \geq 30\%$ received up to 2 additional doses of Curosurf (each 100 mg/kg) at 12 hour interval or up to 3 additional doses of Survanta (each 100 mg/kg) 6 hours apart up to 48 hours after the initial dose.

2. Objectives

To determine possible differences between the two surfactant treatment regimens, in preparation of a larger, definitive trial.

3. **Results**

Seventy five patients were enrolled: 35 to Curosurf and 40 to Survanta. There were no statistically significant differences in their demographic characteristics, except for a higher number of females in the Curosurf group.
Gas exchange. No short term endpoints related to oxygenation or ventilator settings were defined in the protocol. Both groups presented improved oxygenation within 5 minutes of the administration of the surfactants. During the first 24 hours after dosing, the Curosurf group had lower PIP and MAP than the Survanta group. These differences did not persist beyond 24 hours after initiation of therapy. Other parameters: the ventilatory efficiency index, inspiration-expiration ratio, PEEP, $Pa0_2$, $PaCO_2$ and pH did not show relevant differences between the groups.
Clinical outcomes. None of the complications of prematurity including mortality had a statistically significant difference between the groups. Differences between groups in the duration of artificial ventilation and total time of exposure to supplemental oxygen in surviving patients were not statistically significant.

Reviewer's note: This is a small, open label, pilot trial comparing the effect of Survanta vs. Curosurf for which no CRF's are available. Even though the study was specifically designed to compare the short term effects of both surfactants, the protocol did not define the parameters by which the results were going to be evaluated; several evaluations with different variables could have been made to find the variables where Curosurf won. In addition, the criteria for the oxygenation and the ventilatory management of the patients were not defined in the protocol. These deficiencies, in an open label trial, question the validity of the results. Regarding the clinical outcomes, the small number of patients could have been a factor in the results obtained. The sponsor claims that all the treatment administration problems were observed in Survanta-treated infants only; however, no data were provided to identify the adverse events occurred during the administration of the surfactants.

The open label nature of the trial, the poorly defined criteria for the management of the patients and the lack of pre-established endpoints with their definitions in the protocol, make the results of this study difficult to evaluate.

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

4 pages

D. Protocol EURO V, CTCV01-87. (Vol. 1.26).

"Surfactant Replacement Therapy in Severe Neonatal Respiratory Distress Syndrome (RDS)

1. Study Characteristics and Definitions

This was a nonrandomized, non controlled, open label collection of data of babies that did not meet inclusion criteria for a parallel-running "early vs. late" study of Curosurf (their oxygen requirement was already >0.6 at birth and/or at the age of admission to the NICU). These babies had very severe RDS and were allowed to receive Curosurf without any randomization. A single dose of 200 mg/kg in one bolus was given. However, babies with major congenital malformations, grade III-IV IVH and prolonged rupture of membranes >3 weeks were not included.

The sample size was not calculated and the primary endpoints were not specified. The study was carried out between December 87 and May 1990.

Severe RDS was considered when an infant demonstrated clinical and radiological evidence of RDS, required mechanical ventilation and FiO2 >0.6 before the first two hours of life or at the moment of admission to the NICU.

Efficacy criteria: were based on outcomes at 28 days: mortality, PIE, pneumothorax, IVH, PDA and BPD (grade III and IV).

Safety parameters: adverse events.

2. Objectives

The objective of this open study was to obtain efficacy and safety data on the use of Curosurf in the management of severe RDS in the newborn, taking account of ethical considerations.

3. Results

There were 86 infants with severe RDS treated with a single dose of 200 mg/kg of Curosurf. Nineteen European centers participated in this trial. No major protocol violations were reported. The characteristics of the babies treated are presented in the table below.

presented: mortality 31%, PIE 23%, pneumothorax 18%, IVH grades III and IV 26%, PDA 60%, and BPD 16%).

E. Protocol EURO II. (Vol. 1.25).

"Curosurf Collaborative Non-randomized European Multicentre Study."

1. Study Characteristics and Definitions

Eight European NICU's participated in this non-randomized trial. Entry criteria included birth weight 700 - 2000 g , age when treated between 2 and 15 hours and requiring mechanical ventilation with FiO2 >0.6. The babies were treated with a single (or split) dose of surfactant (200 mg/kg.).

Since the inclusion and exclusion criteria were identical with those of the EURO I, the data obtained from this study were to be analyzed in conjunction with the data from that randomized study.

Variables like IVH, PDA, and BPD were well defined in the protocol, and oxygenation parameters (a/APO2 at 24 hours) were established as the primary efficacy variables. Other efficacy parameters included complications of prematurity, and BPD + death.

2. Objectives

To extend the available data on the efficacy of surfactants using a single dose of porcine pulmonary surfactant preparation (Curosurf), in an open study in the management of severe neonatal RDS; and to combine these data with those from the earlier randomized controlled study for analysis by suitable means.

3. Results

There were 87 infants enrolled in this study from 8 neonatal centers (same centers that participated in the EURO I trial) from 1987-88. There were no major protocol violations reported.

The characteristics of the infants in this trial are presented in the following table including the EURO I data, for comparison.

Table 73 Characteristics of infants at entry. Euro II.

Parameter	This trial (1987- 88) Treated (n=87)	EURO I (1985-87) Treated (n= 77)	EURO I (1985-87) Controls (n= 69)
Gestational age [Mean (S.D.)]	28.5 (2.4)	28.8 (2.0)	28.4 (2.2)
Birth weight [Mean (S.D.)]	1175g (344)	1246g (306)	1182g (318)
FiO2 before treatment [Mean (S.D.)]	0.84 (0.15)	0.80 (0.15)	0.80 (0.15)
a/APO2 before treatment	0.10 (0.04)	0.11 (0.05)	0.10 (0.05)

Efficacy results

Improvement in oxygenation. The a/APO2 at 24 hours in this group (0.29 ±0.14) improved similarly to the treated group in EURO I 0.30±0.16 (p<0.001 vs. controls).

The mortality rate in this series was 15%, which was significantly lower than among the surfactant-treated babies in the randomized study (31%, p<0.05).

Safety results
PIE was significantly decreased in this series when compared to the surfactant-treated arm of the randomized trial (11% vs. 23%, p<0.05). On the other hand, the incidence of BPD in this trial almost double that of the treated arm of EURO I (30% vs. 16%, p<0.05). There were no other statistically significant differences in the incidence of complications of prematurity.

Table 74 Complications of prematurity. Euro II.

Parameter	This trial (1987- 88) Treated (n=87)	EURO I (1985-87) Treated (n= 77)	EURO I (1985-87) Controls (n= 69)
a/APO2 at 24 hours [Mean (S.D.)]	0.29 (0.14)	0.30 (0.16)	0.15 (0.09)
Mortality (no [%])	13 (15%)*	24 (31%)	35 (51%)
Pneumothorax (no [%])	8 (9%)	14 (18%)	24 (35%)
PIE (no [%])	10 (11%)*	18 (23%)	27 (39%)
IVH grade III and IV (no [%])	19 (22%)	20 (26%)	16 (23%)
PDA (no [%])	26 (35)	41 (53%)	32 (47%)
Pneumonia (no [%])	15 (17%)	11 (14%)	14 (20%)
BPD (no [%])	26 (30%)*	12 (16%)	18 (26%)

*p <0.05 against treated randomized

Reviewer's note: EURO II is a "non-randomized" version of EURO I, with identical inclusion and exclusion criteria, and conducted by the same 8 European NICU centers that participated in EURO I. The only major difference between the trials was the identification of the primary efficacy endpoint. For EURO I, the following three variables were considered as primary efficacy endpoints by the sponsor: 1)Improvement in the quotient PaO2/FiO2 by 100% within 6 hours after surfactant replacement, 2)Reduction in the period of artificial ventilation in survivors by 33%, 3)Reduction in neonatal mortality by 30%.
For EURO II the primary efficacy endpoint was a/APO2 at 24 hours.

The objective of this trial, a non-randomized version of EURO I, is not clear to this reviewer.

Overall, it is difficult to evaluate efficacy and safety results from a non-randomized open label trial, where many of the endpoints were subjected to personal bias with the potential reflection on the results. Further more, it is surprising to note that the mortality rate in this group was so much lower than in the treated arm of the randomized trial (15% vs. 31%, p value <0.05), taking

into account that the study inclusion criteria were identical, that the centers conducting the study were the same, and the two studies were conducted in approximately the same period of time (1987-88).

IX. Integrated Summary of Safety.

The safety database for Curosurf was generated based primarily on the data obtained from 5 adequate and well controlled studies submitted to this NDA: four rescue studies a described below.

- **EURO I: Rescue (1985 -1987). Curosurf 200 mg/kg single dose (Curosurf group) versus "sham" procedure ("sham" group). In the "sham" procedure, patients were disconnected from the respirator for two minutes and manually ventilated using the same protocol as for patients treated with Curosurf except that no material was instilled into the airways. There were 145 patients randomized: 78 patients to Curosurf and 67 to sham procedure.**
- **EURO III: Rescue (1987-1991). Single dose of Curosurf 200 mg/kg (early group) versus single dose of Curosurf 200 mg/kg administered if $FiO_2 \geq 0.60$ (late/control group). There were 195 patients randomized: 95 to the early group, and 100 to the late/control (53 ended in the late treated group and 47 in the controls).**
- **EURO IV: Rescue (1988 - 1990). Single dose of Curosurf 200 mg/kg (single dose group) versus Curosurf 200 mg/kg plus up to two Curosurf 100 mg/kg doses at 12 hour intervals if $FiO_2 > 0.21$ (multiple dose group). A total of 357 patients were randomized: 184 to the single dose group and 173 to the multiple dose group.**
- **EURO VI: Rescue (1990 - 1991). Curosurf 100 mg/kg plus up to two doses of Curosurf 100 mg/kg as needed, maximum cumulative dose of 300 mg/kg (low dose group) versus Curosurf 200 mg/kg plus up to four doses of Curosurf 100 mg/kg as needed, maximum cumulative dose of 600 mg/kg (high dose group). Patients in either group received more than one dose of Curosurf provided they continued to need mechanical ventilation with supplemental oxygen. There were 2,168 patients randomized, 1069 were randomized to the low dose group and 1,099 to the high dose group.**

A total of 3,120 patients participated in these studies, 2,899 patients were exposed to Curosurf (rescue treatment) and 221 patients were not, because they were either randomized to the sham group in EURO I (n=67), to the late/control group in EURO III and did not require treatment (n=47), to the rescue group in and did not need surfactant treatment (n=55), or were protocol violators: randomized to receive treatment with Curosurf but did not receive it (n=1 in EURO I, n=48 in EURO VI, and n=3 in the

Total 52 violators). These 5 studies were conducted in Europe from 1985 to 1991.

Because of the special nature of the disease treated, i.e., respiratory distress syndrome (RDS), which still has a high morbi-mortality rate, it is difficult to evaluate some elements of safety and efficacy separately. In this integrated summary of safety we will evaluate mortality as it applies to the safety assessment of this application. It will also be evaluated as a measure of efficacy as appropriate in the next section. Other variables evaluated in this section are the incidence of complications of prematurity. The incidence of adverse events encountered during the administration of the surfactant from EURO VI will also be discussed.

In addition to evaluating the safety profile of Curosurf study, it was necessary to also group the patients by the treatment modality they received, because by protocol, it involved not only a different population of patients (different gestational age and/or birth weight or lung maturity stage), but also populations with different degrees of illness. Thus, all participants to the five study trials will be presented in 4 different groups:

1. SHAM GROUP. The patients that were randomized to the sham procedure in EURO I constitute a very distinctive subset of patients, and will be analyzed separately. This is the only randomized group of patients that did meet the same RDS entry criteria as the treated group, but did not receive any surfactant treatment. This group constitutes a true control group.
2. NOT-TREATED. The second group will be the not-treated group, patients in the late/control of EURO III or the rescue arm of the whose condition did not deteriorate enough to require surfactant treatment by protocol. This group of patients, by design, presented either a less severe course of disease as in the case of the patients not treated from the late/control group of EURO III, or did not suffer the disease at all, as in the case of the not treated patients randomized to the rescue arm of the This group will also include a small number of patients that for unknown reasons did not receive any Curosurf treatment in violation to the protocol (because the purpose of this section is to try to characterize the possible effects of Curosurf in the target population, we considered appropriate to include these patients in the not-treated group).
3.

4. RESCUE TREATED. The fourth and last group constitutes the surfactant-treated patients that were randomized to the rescue arms of EURO I, EURO III, EURO IV, EURO VI, and ! These patients represent cases with more advanced degrees of RDS at entry and consequently may be due to present different rates of complications.

Table 75 Total number of patients by study and randomization.

Study	Number of patients by study arm		Total
EURO I	Sham = 67	Treated = 78	145
EURO III	Early treated = 95	Late/control = 100	195
EURO IV	Single dose = 184	Multiple dose = 173	357
EURO VI	Low dose = 1069	High dose = 1099	2168
Total			3120

Table 76 Total number of patients by exposure to Curosurf.

Study	Sham	Not treated		Rescue Tx.	Total
EURO I	67	1*		77	145
EURO III		47[a]		148	195
EURO IV				357	357
EURO VI		48[b]		2120	2168
Total	67	154		2768	3120

*1 patient in the rescue arm did not receive Curosurf treatment (protocol violator).
[a] Patients in the late/control arm that did not meet criteria for surfactant treatment
[b] Patients randomized to receive surfactant but did not receive it (violating the protocol).

The above table shows that, according to the investigator's study report, a total of 58 patients were not treated in the . 55 patients in the rescue arm did not develop RDS and did not receive any surfactant, and 3 patients in the did not receive any surfactant in violation of the protocol. The sponsor's post auditing database reported that in the trial, 94 patients in the rescue arm did not require any surfactant, and that there were no violators in the . In a submission dated February 18, 1997, the sponsor agreed that there was an error in the number of doses by patient reported. Thus, according to the sponsor's corrected post auditing database, the above table would look as follows.

Table 77 Number of patients by modality of treatment received. Post auditing database.

Study	Sham	Not treated		Rescue Tx.	Total
EURO I	67	1*		77	145
EURO III		47[a]		148	195
EURO IV				357	357
EURO VI		48[b]		2120	2168
Total	67	190	134	2729	3120

*1 patient in the rescue arm did not receive Curosurf treatment (protocol violator).
[a] Patients in the late/control arm that did not meet criteria for surfactant treatment
[b] Patients randomized to receive surfactant but did not receive it (violating the protocol).

Reviewer's note: The difference in reported treatment received by the patients was confirmed by the agency's DSI auditor, who also found that several patients received more than two doses of surfactant, contrasting with the sponsor's statement that no subject in either arm in the

trial received more than 2 doses of surfactant. The sponsor was made aware of this discrepancy in their data and sent their response on February 18, 1997.

Where appropriate, the analysis was also made excluding the from the results.

A. Demographic Characteristics

A total of 3,120 patients participated in 5 pivotal studies (4 rescue and trials). From them, 2,899 patients were exposed to Curosurf (as or rescue treatment) and 221 patients were not exposed (reasons stated above). The following table shows some of the main baseline neonatal characteristics of the patients by randomized treatment group.

Except for gestational age, there were no statistically significant differences in neonatal characteristics between the arms of any study. The small difference in the mean gestational age between the infants in the trial was statistically significant in favor of the The increase in gestational age was not reflected in increased APGAR score at 1 or 5 minutes.

Across studies, EURO VI had infants with the highest mean birth weight.

By design, the infants in the study they did not have RDS score evaluated at birth.

Table 78 Neonatal characteristics by study and treatment.

Parameter	EURO I		EURO III		EURO IV		EURO VI	
	Rescue N=78	Sham N=67	Early N=95	Late/Control N=100	Single N=184	Multiple N=173	Low N=1069	High N=1099
Birth weight								
N	78	67	95	99	184	173	1069	1099
Mean (SD)	1249(309)	1202 (324)	1282 (359)	1291 (389)	1222 (345)	1287 (324)	1390 (604)	1358 (605)
Gestational age (wk)								
N	78	67	95	100	184	173	1069	1099
Mean (SD)	29 (2)	28 (2.2)	29 (2.4)	30 (2.4)	29 (2.5)	29 (2.2)	29 (3.1)	29 (3.2)
Gender								
Male	50 (64%)	39 (58%)	51 (54%)	60 (60%)	103 (56%)	96 (56%)	619 (58%)	629 (57%)
RDS severity score								
N	78	67	95	100	184	173	1069	1099
Mean	3.3	3.3	3.0	2.8	3.2	3.1	2.7	2.7
APGAR score at 1 min								
N	78	67	95	100	184	173	1069	1099
Mean	4.3	4.1	4.2	4.5	5.0	4.9	5.0	5.0
APGAR score at 5 min								
N	78	67	95	100	184	173	1069	1099
Mean	6.9	6.8	6.5	6.7	7.4	7.5	7.4	7.5

The following table shows the baseline characteristics of the patients within the context of their mode of exposure to Curosurf. Patients who received Curosurf in the rescue group had higher birth weight, probably driven by the increase in birth weight seen in EURO VI, which was a rescue study.

Table 79 Neonatal characteristics by exposure to Curosurf.

Parameter	Sham	Not treated		Rescue Tx.
Birth weight				
N	67	190		2726
Mean (SD)	1202 (324)	1212 (431)		1344 (559)
Gestational age				
N	67	190		2729
Mean (SD)	28.4 (2.3)	28.8 (2.34)		29.34 (3)
Gender				
N	67	190		2729
Male (%)	39 (58.2)	107 (56.3)		1564 (57.3)
RDS severity score				
N	63	65		2643
Mean	3.27 (0.72)	2.4 (0.97)		2.85 (0.86)
APGAR score at 1 min				
N	65	172		2680
Mean	4.14 (2.2)	4.8 (2.65)		4.98 (2.46)
APGAR score at 5 min				
N	64	157		2659
Mean	6.78 (1.86)	7.55 (2.0)		7.4 (1.9)

The following table shows the baseline characteristics of the patients within the context of their mode of exposure to Curosurf without the . Again, the rescue group showed heavier infants, probably driven by the increased mean birth weight seen in EURO VI.

Table 80 Neonatal characteristics by exposure to Curosurf. Rescue trials only.

Parameter	Sham (N=67)	Not treated (N=96)	Rescue Tx. (N=2702)
Birth weight			
N	67	96	2699
Mean (SD)	1202 (324)	1252 (544)	1346 (561)
Gestational age			
N	67	96	2702
Mean (SD)	28.4 (2.3)	29 (3)	29.34 (3)
Gender			
N	67	96	2702
Male	39 (58.2)	60 (62.5)	1548 (57.3)
RDS severity score			
N	63	65	2643
Mean	3.27 (0.72)	2.4 (0.96)	2.8 (1.86)
APGAR score at 1 min			
N	65	78	2653
Mean	4.14 (2.2)	4.37 (2.05)	5 (2.45)
APGAR score at 5 min			
N	64	70	2634
Mean	6.78 (1.86)	6.8 (1.7)	7.39 (1.91)

Reviewer's note: In general, the populations studied were comparable within each study. Across studies, though, infants enrolled in EURO VI were heavier than their peers in other studies.

B. Mortality

Incidence of mortality from all causes was evaluated at 28 days from birth in the ITT population.

Table 81 Neonatal mortality at 28 days by study.

Parameter	EURO I		EURO III		EURO IV		EURO VI	
	Rescue N=78	Sham N=67	Early N=95	Late/Control N=100	Single N=184	Multiple N=173	Low N=1069	High N=1099
Mortality to 28 days excluding patients with missing data (%)	22/76 (29)	32/67 (48)	12/92 (13)	24/98 (25)	36/181 (20)	21/171 (12)	224/1069 (21)	219/1097 (20)
P-value	0.025		0.0442		0.06		0.5677	
Mortality to 28 days patients with missing data included as deaths (%)	24/78 (31)	32/67 (48)	15/95 (16)	26/100 (26)	39/184 (21)	23/173 (13)	224/1069 (21)	221/1099 (20)
P-value	0.036		0.080		0.052		0.626	

Table 82 Neonatal mortality at 28 days by exposure to Curosurf.

Parameter	Sham	Not treated		Rescue Tx.
Mortality to 28 days excluding patients with missing data(%)	31/66 (47)	39/186 (21)		541/2717 (19.9)
Mortality to 28 days with missing data included as deaths(%)	31/67 (46)	39/190(21)		541/2729 (19.8)
Mortality to 28 days excluding patients with missing data (%) (rescue trials only)	31/66 (47)	26/93 (28)		531/2690 (19.7)
Mortality to 28 days with missing data included as deaths (%) (rescue trials only)	31/67 (46)	26/96 (28)	–	531/2702 (19.6)

Reviewer's note: Neonatal mortality was statistically significantly lower in the surfactant-treated arm of EURO I, regardless of the inclusion or exclusion of patients with missing information on mortality in the analysis. In EURO IV and the the difference in mortality was statistically significant in favor of the multiple dose and the group, respectively. In EURO III, patients in the early treated arm had a lower statistically significant mortality when patients with missing data were not included. When the patients with missing data were considered to have died, the difference was not statistically significant. The difference in the incidence of neonatal mortality to 28 days in EURO VI was not statistically significantly different between the low and the high dose arms.

Mortality was compared across studies. and rescue treatments, showed lower mortality when compared to sham. The comparison was made against sham because all infants in this group had by study design RDS. Most

patients in the not-treated group did not receive surfactant because they did not develop RDS or their condition did not deteriorate enough to meet the criteria required by the protocol to be treated with surfactant. It is unknown why some patients in the not treated group (48 infants enrolled in Euro VI) did not receive surfactant treatment.

C. Complications of Prematurity

The following complications were evaluated across all studies: Pneumothorax, pulmonary interstitial emphysema (PIE), intracranial hemorrhage (ICH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), acquired pneumonia, and persistent ductus arteriosus (PDA).

The incidence of air leaks (pneumothorax or PIE) was statistically significantly lower in the treated arm of EURO I, and in the treated groups when the surfactant was given early in the disease process (EURO III) or in multiple doses (EURO IV). Patients treated early in the disease process presented a significant decrease in the incidence of PIE when compared to the late/control group. Note: Some patients in the late/control group did not continue to deteriorate and by design did not require surfactant treatment (these patients constituted the control group).

For all other complications evaluated, the between treatment group comparisons show no statistical significance in the difference of incidence.

The post auditing database for ICH did not include severity of disease. Because the use of surfactants has been associated with an increase in severe intracranial bleedings, it was interesting to note that the original investigator's study report for EURO I did present data on the different grades of severity of ICH, and that the difference in ICH grades III and IV between the treated and the sham procedure group was not statistically significant (26% vs. 23% respectively). ICH was not identified in the CRFs of EURO VI as an individual entry. The data was obtained, for the analysis in this section, from the assessment of head ultrasounds at 1 and 6 weeks provided by the sponsor at a later submission (the sponsor had reported the incidence of ICH for EURO VI from the ultrasounds performed at 6 weeks only, excluding infants who had ICH noted in the ultrasound performed at 1 week and died before the week 6 evaluation). Thus, the incidence of ICH for EURO VI is different in this section than that presented by the sponsor in Appendix C.5, volume 1.30, of the NDA.

Table 83 Complications of prematurity at 28 days or at discharge[5] by study.

Parameter	EURO I		EURO III		EURO IV		EURO VI	
	Rescue N=78	Sham N=67	Early N=95	Late/Control N=100	Single N=184	Multiple N=173	Low N=1069	High N=1099
PIE [n/N*(%)]	16/78 (21)	26/67 (39)[1]	5/87 (6)	12/95 (13)[1]	50/183 (27)	37/169 (22)	**	
Pneumothorax [n/N*(%)]	16/78 (21)	24/67 (36)[1]	5/91 (5)	10/98 (10)	32/184 (17)	16/173 (9)[1]	143//1061 (14)	131/1085 (12)
ICH total [n/N*(%)]	39/77 (51)	43/67 (64)	33/91 (36)	35/98 (35)	82/181 (45)	73/173 (42)	347/925 (38)	382/956 (40)
NEC[n/N*(%)]	1/78 (1)	1/67 (2)	2/92 (2)	4/98 (4)	6/180 (3)	5/172 (3)	56/1055 (5)	72/1076 (7)
ROP [n/N*(%)]	**		7/85 (8)	4/91 (4)	39/166 (24)	41/159 (26)	125/937 (13)	124/935 (13)
Acquired pneumonia [n/N*(%)]	11/76 (15)	14/67 (21)	16/91 (18)	14/97 (14)	30/140 (21)	22/130 (17)	167/1057 (16)	175/1077 (16)
PDA [n/N*(%)]	47/78 (60)	32/67 (48)	29/90 (32)	21/97 (22)	93/181 (51)	98/169 (58)	380/1059 (36)	384/1081 (35)

*Denominators represent total number of patients with data.
**Data not collected in this trial.
[1]$p<0.05$

When the complications of prematurity were compared by exposure to Curosurf, the infants that were exposed to surfactant either as or as rescue, presented lower incidence of air leaks when compared to the sham group ($p<0.01$).

Table 84 Complications of prematurity by exposure to Curosurf.

Parameter	Sham	Not treated	Rescue Tx.
PIE	26/67 (39)	21/131 (16)	135/621 (21)
Pneumothorax	24/67 (36)	15/171 (9)	349/2720 (13)
ICH total	43/67 (64)	55/104 (53)	1028/1809 (57)
NEC	1/67 (2)	8/160 (5)	144/2703 (5)
ROP	*	11/147 (8)	335/2292 (15)
Acquired pneumonia	14/67 (21)	44/164 (27)	432/2616 (16)
PDA	32/67 (48)	41/162 (25)	1041/2688 (39)

*Data not collected in this trial.

Table 85 Complications of prematurity by exposure to Curosurf. Rescue trials only.

Parameter	Sham	Not treated	Rescue Tx.
PIE	26/67 (39)	7/38 (18)	127/594 (21)
Pneumothorax	24/67 (36)	11/80 (14)	342/2693 (13)
ICH total	43/67 (64)	20/46 (43)	971/1703 (57)
NEC	1/67 (2)	4/68 (6)	144/2676 (5)
ROP	*	5/64 (8)	335/2292 (15)
Acquired pneumonia	14/67 (21)	16/71 (23)	419/2589 (16)
PDA	32/67 (48)	19/69 (28)	1033/2661 (39)

*Data not collected in this trial.

[5] No data is available on Euro VI for 28 days, instead, complications of prematurity were recorded at discharge and that could be less or more than 28 days.

Reviewer's note: Overall, the group of patients exposed to Curosurf did not show an increase in the incidence of complications of prematurity when compared to patients that were not exposed to Curosurf. The incidence of air leaks decreased in patients exposed to Curosurf. Within the individual studies, a significant difference was seen in EURO I in favor of the patients treated with Curosurf, in EURO III, in favor of the patients treated early in the disease process, and in EURO IV favoring patients treated with multiple doses.

The results from the supportive studies submitted to this NDA do not contradict the findings summarized in this section.

D. Adverse events

The rescue study Euro VI was the only trial where the investigators reported adverse events "probably or possibly" related to the administration of Curosurf. The relationship of the adverse events to the administration of Curosurf was not defined in the protocol.

Among others, the following adverse events were reported: bradycardia, hypotension, pulmonary hemorrhage, ventilator setting deterioration, tube blockage, intraventricular hemorrhage and patent ductus arteriosus.

Table 86 Adverse events reported in EURO VI during the administration of surfactant.

	Surfactant Dose Schedule		P-value
	Low	High	
Total	1069	1097	
None	999 (93.5)	1002 (91.4)	0.07
Pulmonary hemorrhage	17 (1.6)	24 (2.2)	0.35
Tube blockage	5 (<1)	22 (2)	0.002
Hypotension	12 (1.1)	9 (<1)	0.52
Bradycardia	4 (<1)	11 (1)	0.12
Ventilator setting deterioration	3 (<1)	3 (<1)	1
Intraventricular hemorrhage	9 (0.9)	11 (1)	0.82
Patent ductus arteriosus	15 (1)	12 (1)	0.57

Reviewer's note: The protocol did not provide definitions for the above adverse events and the time frame within which the event would be considered possibly or probably related to the surfactant. It did not define the criteria on which the relationship between the event and the drug was to be established. Thus, it is unclear the type of relationship between the administration of the surfactant and the occurrence of the events reported. This deficiency could have greatly influenced the number of events reported, e.g., the incidence of bradycardia in this trial is <10% of that reported in trials of other surfactants. This is a significant deficiency found in this application.

E. Reviewer's Comments On The Integrated Summary Of Safety.

In the trials reported to this NDA, patients who were exposed to Curosurf for treatment of RDS showed a statistically significant decrease in the incidence of neonatal mortality at 28 days when compared to patients in the sham group. The complications of prematurity evaluated and reported in this series did not show significant increase in incidence in the population exposed to Curosurf above those seen in the sham group of EURO I; in contrast, the Curosurf-exposed population showed a reduction in the incidence of air leaks when compared to those not exposed to surfactant.

However, these trials were markedly deficient regarding collection and reporting of adverse events occurring during the administration of Curosurf. This is an important deficiency that should be addressed in the package insert and should be described in a deficiency letter to the sponsor. Future studies, not necessarily before approval, need to be conducted to provide the appropriate information regarding adverse events during the administration of the drug.

X. Integrated Summary of Efficacy

The evaluation of efficacy for this NDA was based primarily on the 5 pivotal studies submitted by the sponsor (4 rescue: EURO I, EURO III, EURO IV, and EURO VI; and . In addition, there were 6 other supporting studies. All of the studies have been fully discussed in a previous section. We will highlight, in this section, the main endpoints in the evaluation of efficacy. The following tables summarize the 5 pivotal studies.

Table 87 Overview of Studies

Controlled Studies: Rescue

Trial (Study Number) (No. of Centers) Date	Study Design	Diagnosis and Criteria for Inclusion	Treatment (Dose)	No. of Patients	GA (wks) Mean (Range)
EURO I (CH-CUR-0001) Multicenter (8) 1985-1987	Randomized, controlled, multicenter trial of Curosurf vs. "sham" treatment	RDS[a]; BWt: 700-2000 g; Age: 2-15 hours; FiO_2: ≥0.60; IPPV; No complicating disease.	Curosurf 200 mg/kg single dose Control: "sham" procedure (disconnection from respirator and manually ventilated for 2 minutes)	Curosurf - 78 Sham - 67 Total - 145	Curosurf - 28.7 (24-34) Sham - 28.4 (24-34) Total - 28.5 (24-34)
EURO III (CH-CUR-0003) Multicenter (26) 1987-1991	Randomized, controlled, multicenter trial of Curosurf early vs. late treatment/ conventional therapy	RDS[a]; BWt: 600-2000 g; Age: 2-48 hours; FiO_2: ≥0.40 to <0.60; IPPV; No complicating disease.	Early: Curosurf 200 mg/kg single dose at randomization Late/Control: oxygen + ventilation during first 48 hours after birth, with Curosurf 200 mg/kg single dose administered if FiO_2 ≥0.60	Early - 95 Late/ Control - 100 Total - 195	Early - 29.8 (25-35) Late/ Control - 29.6 (24-34) Total - 29.7 (24-35)
EURO IV Multicenter (15) 1988-1990	Randomized, controlled, multicenter trial of Curosurf single vs. multiple doses	RDS[a]; BWt: 700-2000 g; Age: 2-15 hours; FiO_2: ≥0.60; IPPV; No complicating disease.	Single: Curosurf 200 mg/kg Multiple: Curosurf 200 mg/kg + up to two additional doses Curosurf 100 mg/kg at 12 hour intervals if FiO_2 >0.21	Single - 184 Multiple - 173 Total - 357	Single - 29.2 (24-36) Multiple - 28.9 (24-34) Total - 29.0 (24-36)
EURO VI (Curosurf 4) Multicenter (82) 1990-1991	Randomized, controlled, multicenter trial of Curosurf high vs. low dose	RDS[a]; Age: <72 hours; Endotracheal intubation; a/APO_2: <0.22; No complicating disease.	Low: Curosurf 100 mg/kg + up to two additional doses Curosurf 100 mg/kg at 12 hour intervals as needed (max. 300 mg/kg) High: Curosurf 200 mg/kg + up to four additional doses Curosurf 100 mg/kg at 12 hour intervals as needed (max. 600 mg/kg)	Low - 1069 High - 1099 Total - 2168	Low - 29.4 (23-42) High - 29.3 (22-42) Total - 29.4 (22-42)

GA = Gestational age (in weeks); RDS = Respiratory distress syndrome; BWt = Birth weight; Age = Age at treatment; FiO_2 = Fraction of inspired oxygen; IPPV = Intermittent positive pressure ventilation.

[a] As determined by clinical and radiological findings.

Demographic characteristics. The neonatal characteristics of the patients randomized did not differ statistically between arms within each of the rescue trials. [1]

. Clinically, such difference in the gestational age was considered to be small (0.6 of a week). For the demographic characteristics please see table ...in the safety section of this NDA.

A. Rescue Trials

1. Primary Efficacy Endpoints.

The primary efficacy endpoints for each of the trials were:

1. EURO I. Even though the protocol did not specify the primary endpoint, the study report considered as primary endpoints the following:
   - Improvement in the quotient PaO2/FiO2 by 100% within 6 hours after surfactant replacement;
   - Reduction in the period of artificial ventilation in survivors by 33%;
   - Reduction in neonatal mortality by 30%.

2. EURO III.
   - Reduction in mortality plus incidence of BPD from 45% (late treatment) to 25% (early treatment)

3. EURO IV.
   - The combined incidence of mortality and BPD.

4. EURO VI.
   - **Death or BPD at 28 days of age;**
   - **Death to discharge and to the closure of the trial data collection;**
   - **For patients entered at <37 weeks of gestational age only: Prolonged oxygen dependence.**

Reviewer's note: The protocols did not specify the criteria used for the ventilatory and oxygen management of the patients during the trials, and did not provide a definition of the radiological findings to be considered for the diagnosis of BPD in the trials that included CXR changes in the definition of BPD. It is vital that the primary efficacy endpoints used in open label trials, like those being discussed in this application, be objective and clearly defined, to minimize important personal or center-derived biases. Thus, ventilatory/oxygenation parameters or endpoints that included ill-defined variables like BPD are not considered appropriate primary endpoints for the evaluation of efficacy of this application. A more detailed discussion of this issue is included in the review of the individual studies.

Because of the open label nature of the trials, and the lack of consistent and objective definition of the management of the patients and the endpoints chosen, for the purpose of the evaluation of efficacy in this application, all cause mortality at 28 days in the ITT population was considered the primary endpoint of efficacy across all the studies. Other endpoints were considered as secondary endpoints.

a) Mortality to 28 days

All cause mortality to 28 days was reported by treatment received in the intent-to-treat population. For patients with missing information on mortality, an alternative analysis included them as dead. The results of both analyses are summarized in the following table.

Table 89 Mortality at 28 Days for the ITT Populations in Controlled Rescue Studies

	Patients with missing data excluded			Patients with missing data included.		
Study Treatment Group	Total Number of Patients	Mortality N (%)	P-value	Total Number of Patients	Mortality N (%)	P-value
EURO I						
Curosurf	76	22 (29%)		78	24 (31%)	
Sham	67	32 (48%)	0.025	67	32 (48%)	0.036
EURO III						
Early	92	12 (13%)		95	15 (16%)	
Late/Control	98	24 (25%)	0.044	100	26 (26%)	0.080
EURO IV						
Single	181	36 (20%)		184	39 (21%)	
Multiple	171	21 (12%)	0.06	173	23 (13%)	0.052
EURO VI						
Low	1069	224 (21%)		1069	224 (21%)	
High	1097	219 (20%)	0.5677	1099	221 (20%)	0.626

Reviewer's note: The difference in the incidence of mortality was statistically significant in favor of the treated arm of EURO 1 regardless of the analyses done, i.e., including or excluding patients with missing data. The early treated group in Euro III showed less statistically significant mortality when the patients

without data were excluded from the analysis, but not quite when the patients with missing data were included. EURO IV showed numerical trend in favor of the multiple dose without statistical significance (p=0.06) when patients with missing data were excluded, but the difference reached statistical significance (p=0.05) when patients with missing data were included. EURO VI failed to show any significant effect in mortality between the arms.

Overall, in an ITT analysis, the incidence of mortality was statistically significantly decreased in the treated arm of EURO I, and in the multiple dose arm of EURO IV. There was a numerical trend in favor of the early treated group in EURO III.

2. Secondary Endpoints

a) Bronchopulmonary dysplasia at 28 days.

Bronchopulmonary dysplasia was defined differently in each trial.

- **In EURO I - BPD was defined as oxygen dependence and/or CXR changes at 28 days. CXR changes were not defined.**
- **In EURO III - BPD was diagnosed by oxygen dependence at 28 days and radiological findings. CXR changes were not defined.**
- **In EURO IV - It was diagnosed if oxygen supplement (FiO2>0.21) was still required after 28 days from birth and radiological changes (classification according to Northway scale) were present. These was the most stringent definition of BPD.**
- **In Euro VI - BPD was diagnosed if supplemental oxygen was required at 28 days. This was the less stringent definition of BPD.**

Table 90 Incidence of BPD at 28 Days for the ITT Populations. Rescue Studies

Study Treatment Group	Total Number of Patients[a]	Incidence of BPD[a]	P-value
EURO I			
Curosurf (N=78)	54	12 (22%)	
Sham (N=67)	35	16 (46%)	0.0197
EURO III			
Early (N=95)	80	7 (9%)	
Late/Control (N=100)	72	10 (14%)	0.3155
Late	37	5 (14%)	
Control	35	5 (14%)	
EURO IV			
Single (N=184)	145	28 (19%)	
Multiple (N=173)	149	27 (18%)	0.7937
EURO VI			
Low (N= 1069)	839	324 (39%)	
High (N= 1099)	867	338 (39%)	0.8762

[a] Total number of patients alive at 28 days with BPD data

Reviewer's note: EURO I showed statistically significant difference between arms, in favor of the treated group. The incidence of BPD in EURO VI was very high, only second to that in the sham group of EURO I; this was probably

due to the less stringent criteria in the definition of BPD used in this trial. The results on BPD in this series confirm findings in other series, with other surfactants, where the use of surfactants has not consistently improved the incidence of BPD in survivors.

b) Survival without BPD at 28 days.

This endpoint combined the incidence of mortality and BPD by including all patients who were alive at 28 days and did not have BPD as the numerator and all randomized patients in the denominator. Again, two analyses were performed, patients with missing data were excluded from the first analyses, and were included as dead or alive with BPD in the second, as a worst case scenaric analysis.

Table 91 Survival without BPD at 28 Days for the ITT Populations. Rescue studies.

	Patients with missing data excluded			Patients with missing data included.		
Study Treatment Group	Total Number of Patients[a]	Survival without BPD N (%)	P-value[b]	Total Number of Patients	Survival without BPD N (%)	P-value[b]
EURO I						
Curosurf	75	42 (56%)		78	42 (54%)	
Sham	66	19 (29%)	0.0011	67	19 (28%)	0.002
EURO III						
Early	92	73 (79%)		95	73 (77%)	
Late/Control	96	62 (65%)	0.0245	100	62 (62%)	0.025
EURO IV						
Single	181	117 (65%)		184	117 (64%)	
Multiple	170	122 (72%)	0.1524	173	122 (71%)	0.164
EURO VI						
Low	1063	515 (48%)		1069	515 (48%)	
High	1086	529 (49%)	0.9029	1099	529 (48%)	0.985

[b]Pearson Chi square test

Reviewer's note: This analysis investigated whether, in the case of BPD, increased survival was associated with increased morbidity. As discussed above, the evaluation of BPD, in these unblinded trials, raises concerns about the validity of conclusions based on these analyses, since this diagnosis can be subject to investigator bias. The definition of BPD was not consistent in the studies. Therefore, cross-study comparisons should be interpreted with caution.

In general, the results on survival to 28 days without BPD support the findings on mortality discussed earlier on EURO I and EURO III.

C. Reviewer's Comments On The Integrated Summary Of Efficacy.

In this series of 4 pivotal trials of Curosurf for the treatment of RDS of prematurity, patients treated with Curosurf had a lower incidence of mortality to 28 days when compared to patients in the sham procedure (control) group. Mortality to 28 days was also lower when patients received multiple doses (up to 3 doses) of Curosurf vs. a single dose in an ITT analysis (p=0.05). In EURO III, patients receiving Curosurf early vs. late in the disease process, showed a numerical trend toward decreased mortality at 28 days when the patients were treated early (16% vs. 26%, p= 0.08). The results of other endpoints, e.g., survival without BPD at 28 days, provided support to the mortality findings in Curosurf-treated patients. These

4. Several patients were not reported with complications accurately, specially for ICH in Euro VI. In Euro VI, there were 16 patients with intracraneal hemorrhages reported in their CRF's by the clinical investigator who were not reported by the sponsor to the FDA. Please see sponsor's response, below.
5. Some patients did not receive drug dosage in accordance with protocol requirements, or the quantity of drug administered could not be verified.
6. A review of the correspondence file revealed that:
   - Dr. Svenningsen administered Curosurf to seven subjects who were not included in the Euro I study database. The auditors requested the medical records of these patients, and were provided with 5 of the 7. The medical records of the remaining two were not available for review.
   - Other concentrations of Curosurf may have been available and possibly used on site, e.g., one letter dated 6/83 suggested that Dr. Svenningsen received Curosurf from the ___ that had a concentration of 67 mg/ml - Dr. Svenningsen believed this product was used as an initial pilot study done on approximately 5 patients in 1983/84 at Lund; another letter dated 5/4/84 declared that Curosurf had a concentration of 100 mg/ml. DSI auditors were unable to determine if Curosurf with this concentration was ever used on site.

Site: Paris, France.
Study audited: Euro III "Randomized Multicenter Clinical Study On The Treatment With Natural Surfactant Of Neonatal Respiratory Distress Syndrome In Premature Infants: Comparison Between Early And Late Treatment."

1. There were no drug accountability records to show the quantity of drug received and dispensed;
2. There was no written consent for all patients;
3. Quantity of drug administered could not be verified for 7 patients in the early-treated group and for one patient in the late-treated group.
4. Protocol in site was not exactly the same as the protocol submitted to FDA by the sponsor.

Site:
Studies audited: 'Natural Surfactant Replacement Therapy (Curosurf) In
A Randomized Multicentre Trial Of

1. There were no drug accountability records to show the quantity of drug received and dispensed.
2. There was no written consent for 3 patients.
3. The quantity of study drug administered to each subject could not be verified.
4. Verification of actual randomization could not be located.

5. **Protocol in site was not exactly the same as the protocol submitted to FDA by the sponsor.**

B. Sponsor's response to Selected DSI comments.

Comments from Euro I Study.

1. **DSI finding: Two patients reported alive when they were dead before 28 days.**

   Sponsor's response: The investigator, Dr. Svenningsen, attributed this discrepancy to a recording error. The sponsor explained that only hospital summaries were available for the audit. These summary documents did not accurately identify these deaths. The sponsor further explained that "the proportion of cases for which source data was not available at the time of audits was very small; many hundreds of cases were reviewed, and all other cases are reported correctly in the database."

Reviewer's note: On September 4, 1996, the sponsor submitted to this agency the audit reports from where they specified that for the Lund site there were 17 patients, out of 18, for whom source data were audited, and that there were 3 patients for whom only hospital summaries were available. The report for Euro I does not identify the ID number of these patients with missing source data. This information is needed in order to determine if any of these patients correspond to the two cases of mortality found by DSI. Finally, the sponsor did not explain when and how the source data for these two patients were found. This issue raises a serious question regarding the sponsor's auditing procedures, the validity of the data submitted to this NDA, and the conclusions derived form them.

Lund was the only center with a positive coefficient for mortality in the regression analysis made by the sponsor, and that this site was visited, for unknown reasons, for a second time by the auditors from on 12/15/95. These factors prompted its selection as one of the two sites to be audited by DSI.

To assess the impact of this DSI finding, we reanalyzed the mortality data from Euro I, by adding the two deaths to the surfactant-treated group.

The difference in the incidence of mortality to 28 days was not statistically significant between the study arms, including or excluding patients with missing data.

Table 94 Mortality in Euro I after DSI auditing.

Treatment Group	Excluding pts. with missing data	Pts. with missing data included as deaths.
Surfactant-treated	24/76 (32%)	26/78 (33%)
Controls	32/67 (48%)	32/67 (48%)
p-value[1]	0.06	0.12

[1]P-value from Fisher's exact test.

Table 95 Mortality, excluding patients at Lund. Euro I.

Treatment Group	Excluding pts. with missing data	Pts. with missing data included as deaths.
Surfactant-treated	21/67 (31%)	23/69 (33%)
Controls	29/58 (50%)	29/58 (50%)
p-value[1]	0.01	0.07

[1]P-value from Fisher's exact test.

The two patients who were wrongly categorized as alive but were actually dead, were part of the 129 patients on which the second interim analysis was based. Hence 21 patients out of 65 from the surfactant group were dead, instead of the 19 reported earlier. With the modification of the data, the value of the statistic to be checked against the O'Brian & Fleming boundary of 2.8, changed from 2.67 to 2.21. This value does not justify early stopping of the trial based on mortality.

Table 96 Modified mortality at the second interim look. Euro I.

Treatment Group	Patients Alive	Patients Dead	Total (N=129)	Value of the statistic (N=129)
Surfactant	44 (68%)	21 (32%)	65	2.21
Control	33 (52%)	31 (48%)	64	

Similar calculation based on 'Mortality and BPD' results in the value of the statistic equals 3.00 which is greater than 2.8 (O'Brian Fleming boundary). Hence stopping was justified under this endpoint. However this is not one of the primary endpoints stated by the sponsor.

Table 97 Modified mortality and BPD at the second interim look. Euro I.

Treatment Group	Patients Alive without BPD	Patients Dead or with BPD	Total (N= 129)	Value of the statistic (N=129)
Surfactant	35 (54%)	30 (46%)	65	3.0
Control	18 (28%)	46 (72%)	64	

2. **DSI finding:** **Seven Euro I surfactant-treated patients that were not in the Euro I database.**

Sponsor's response: These seven patients were treated with residual Curosurf several months after the Euro I study closed.

These 7 patients were included in the NDA in the Euro II report, which was an open follow up study to Euro I.

Reviewer's note: The sponsor provided the ID numbers for these 7 patients correlating to the Lund case report form numbers. The explanation was found acceptable.

Comments from Euro VI Study.

3. **DSI finding:** <u>Under reported intracraneal hemorrhages</u>.

   The sponsor's response: Because the study's CRF did not identify intracraneal bleedings as an individual entry, this complication's diagnosis was extracted, for Euro VI, from information obtained on the head ultrasounds which were performed at one and 6 weeks of age. By an administrative decision, only the ICH seen at the 6 weeks assessments were reported to the NDA (those infants who had an ICH shown in the ultrasound at 1 week of age were not reported if the baby died before week 6 or if the second ultrasound did not reveal it).

Reviewer's note: We requested the reports of all the head ultrasounds, and identified all babies who had ICH reported at any of these two evaluations. The integrated summary of safety has these new data already incorporated into the discussion of complications of prematurity. The corrected data did not make a significant difference in the observed incidence of ICH between the treatment arms.

4. **DSI finding:** <u>Concentration of Curosurf used in Euro I and Euro VI.</u>

   The sponsor's response: It submitted a table describing the concentration of surfactant per vial present in the Curosurf batches provided for the clinical trials. These batches' concentrations had to be calculated from data contained in the release batch documentation, because these pre-industrial batches did not have a direct determination of surfactant strength, as performed now.

Reviewer's note: We consulted with our chemistry reviewer who agreed that most of the batches appear to be consistent with current specifications (70 - 90 mg/ml), except for one batch which had 93.1 mg/ml. Of note is that neither of the concentrations of Curosurf mentioned in the letters found by DSI in the correspondence file of Dr. Svenningsen appear in the table of concentrations prepared by the sponsors.

Comments from Trial

5. <u>Lack of documentation of the randomization scheme.</u>

   The sponsor was asked about the basis for the auditors from to state that the randomization of this study was robust, on the

XIV. Curosurf Labeling. Issues for Discussion.

1. Method of administration. The NDA supports the administration of Curosurf into each main bronchus via a feeding tube. It does not support its administration as a bolus into the lower trachea as is proposed in the package insert. Only few patients were treated using the latter technique.

2. Initial dose. The NDA only supports an initial dose of 200 mg/Kg of body weight to be given for the rescue treatment of RDS. It does not support an initial dose of 100 mg/Kg as is proposed in the package insert.

3. Reporting of adverse events during the administration of Curosurf. The NDA did not provide accurate information regarding this issue.

/S/
Liza Miriam Pina, M.D.
Clinical Reviewer
04/07/97

/S/
Girish Aras, Ph.D.
Statistical reviewer
04/07/97

Concurrence by Deputy Director/Supervisor:
Yes ✓ No____
Comments:
see secondary medical Review NDA memo
Signature/Date /S/ 5/21/97

Concurrence by Team Leader:
Yes ✓ No____
Comments:
Signature/Date /S/ 4/16/97

Concurrence by Division Director:
Yes ✓ No:____
Comments:
See D.V. Date memo for NDA.
Signature/Date /S/ 6/2/97

Concurrence by Division Director:
Yes ✓ No:____
Comments:
Signature/Date /S/ 4/16/97

cc:
IND
HFD-570 /division file
/Pina
/Himmel
/Aras
/Wilson