CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-744

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	20744	APPLICATION TYPE:	Response to NA letter
SPONSOR:	Dey Lab.	PRODUCT/PROPRIETARY NAME:	Curosurf
		USAN / Established Name:	Poractant
CATEGORY OF DRUG:	Surfactant	ROUTE OF ADMINISTRATION:	Intratracheal
MEDICAL REVIEWER:	L. Miriam Pina, M.D.	REVIEW DATE:	

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
03/03/1998	03/04/1998	Major amendment	Response to NA letter

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
07/03/1996	Original NDA	The sponsor received a "Not approvable" letter on July 3, 1997.

Overview of Application/Review:

The sponsor submitted the protocols and the data obtained from the full auditing of the pivotal trials as requested by this Agency. EURO I and EURO IV provide data to support the efficacy and safety of Curosurf for the treatment of respiratory distress syndrome in premature infants.

Outstanding Issues:

Recommended Regulatory Action:

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDA: Not approved

__X__ Approvable _____ Not Approvable

Signed: Medical Reviewer: _____ Date: _____

Medical Team Leader: _____ Date: _____

CLINICAL AND STATISTICAL NDA REVIEW

NDA :	20-744
NAME OF DRUG:	Curosurf (poractant)
INDICATION:	Respiratory Distress Syndrome of Premature Infants
SPONSOR:	Dey Laboratories
SUBMITTED:	March 3, 1998

REVIEWERS

MEDICAL:	L. Miriam Pina, M.D.
STATISTICAL:	Girish Aras, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

Table of Content

TABLE OF FIGURES

I. Background

Due to critical discrepancies between the source documents and the CRFs found by DSI during the auditing of two of the investigational sites, the Agency requested that the sponsor:

1. Conduct a full auditing of all patients in Euro I, Euro III, Euro IV and the not previously audited by their contractors
2. Submit the protocols that were followed in carrying out the audits, the results of the audits, and an updated analysis of the integrated summaries of efficacy and safety.
3. Submit a list of the patients not previously audited by their contractors.
4. Review hospital records for all patients with missing mortality data and determine whether these patients were alive or dead at Day 28. The determination and the supporting documentation were to be included with the response.

II. Material reviewed and Methods

The sponsor submitted the following data:

1. Protocols for the audits (attachments 3 and 5 of the NDA);
2. Copies of the audit reports for EURO I, III and IV issued by the audit contractor (attachments 2 and 4) and for the issued by (attachment 3);
3. Updated Integrated Summaries of Efficacy and Safety (attachments 7 and 8);
4. Electronic copy of the updated database.

Note: Printed copies of individual source records were not provided. The individual audit reports contained detailed discussion and explanation of the discrepancies found. The site investigators signed these reports, where they agreed with the observations made by the auditors.

Other submissions reviewed: submissions dated March 3 and 19, April 7 and 21, May 18, and July 14 and 29, 1998. The submission of March 3, 1998 constituted a full response to our July 3, 1997 action letter.

To assure a proper review of the new data and to assess the impact of the new observations on the results of the trials, the data were analyzed as follows:

1. The protocols prepared for the audits were reviewed.
2. The audit reports from patients not audited in 1995 were identified and reviewed. The sponsor provided with the original submission a list of the patients that were not fully audited in 1995; that list (referred to as the original list) was compared to the list provided in the present submission ('97 list).
3. The changes were reviewed and each patient's main outcomes were updated as needed;
4. Any patient not listed in the latter list ('97 list), but present in the original list, was individually investigated and discussed with the sponsor. Their main outcomes were reviewed and updated as needed.
5. The new data were analyzed. The data were analyzed in two ways:
    - As submitted by the sponsor (the sponsor analyzed the data in two ways: (1) excluding the patients whose data were not verified and (2) including them as deaths.
    - For the ITT population; the patients whose source records were not located by the auditors in 1997 were evaluated according to the outcome stated in their CRF. When the outcome data were missing, the patient was considered dead.

As we explained in our original review of the application, the open label nature of the trials and the lack of consistent and objective definition of other primary endpoints chosen, rendered these other endpoints invalid to support evidence of efficacy for Curosurf. For the purpose of the evaluation of efficacy in this application, all cause mortality at 28 days in the ITT population is

considered the only valid primary efficacy endpoint across all the studies. This review will mainly discuss the changes and conclusions regarding the primary endpoint, incidence of mortality. The secondary efficacy and safety parameters were fully discussed in the original review. Some discrepancies were seen and there was need for corrections in the safety data. However, no clinically significant changes in the conclusions for safety were derived from the re-audit of the sites. This is true even though the incidence of BPD in survivors at 28 days in EURO I changed from significant to not statistically significant. In this case, the statistical significance seen in the original data was lost when 2 patients in the treated arm had their missing BPD data established as positive.

For consistency with the sponsor's submission, we will refer to the audits conducted in 1997, at the FDA request, as the 1997 series of audits. The audits conducted prior to the submission of the NDA will be referred to as the 1995 series of audits.

III. Statistical methods

In the sponsor's original report Fisher's exact test was used on some occasions. The original protocols were silent on the issue of which test was to be used. We are aware that both test procedures, Fisher's exact and Pearson's chi square, typically generate p-values that are close to each other, with Fisher's p-value being larger than Pearson's. To maintain consistency across studies, we have reported p-values of Pearson's chi square tests for the mortality data. For EURO I we also reported Fisher's p-values, as this was the method used in the original review.

IV. Results

A. AUDIT PROTOCOLS

1. Audits conducted by (for EURO I, EURO III, and EURO IV)

The auditing covered all the patients in Euro I, III and IV who, for various reasons, were not fully audited during the 1995 series of audits. The individual audit reports from each site were signed by the site investigator and submitted. The source data for some of the patients were not available at the time of the audits. The auditors identified these patients. The details are discussed under the individual trials.

In addition, the auditors were to recheck for the existence of any records from the Euro I, III or IV studies which could not be located during the 1995 series of audits that would provide data on mortality at Day 28.

2. Audit conducted by

The original audit plan for , required that 100% of the patients' records from sites entering 20 or more patients be audited. A total of 180 /255 patients were audited (70.5% of patients enrolled), from 6 of the 14 investigational sites. Twenty-five patients from these sites were not fully audited in 1995.

The '97 series of audits were performed by staff from during November and December of 1997. The remaining centers were audited at this time and the individual audit reports were submitted. The 25 patients whose source records were not available for the '95 series were not re-audited in 1997. Two patients' CRFs were also missing.

Note: Both contractors submitted the list of the ID numbers of the patients for whom source records were not available for the '97 series of audits. However, for some of these patients, the contractors found enough evidence to determine the patients' mortality outcome at Day 28. The source of the information was discussed and reported. No photocopies of the documents were submitted.

B. EURO I

The original audit plan for EURO I was to have 100% of the records audited. However, several patients were not fully audited for various reasons. The ID numbers of the patients who were not fully audited during the 1995 series of audits are listed in Table 1. In addition, Table 1 includes the ID of the patient who in the opinion of the sponsor was a duplicate (the sponsor determined that the records of patient COO124 were a duplicate of patient CO3135. The sponsor excluded this patient [COO124] from the analysis). The sponsor hasn't been able to justify this decision. (Table 2 shows some of the patient's demographic characteristics).

In 1997, DSI found the source data for two patients in the Lund site whose mortality outcome at 28 days had been erroneously categorized as "alive". The review of the CRF also revealed the outcome at 28 days of two other patients for whom the outcome data were missing. With these changes to the data, the analysis rendered a non-statistically significant difference in mortality to 28 days between the sham and the surfactant-treated group (Table 4).

According to the '97 series of audits:

- Source data were found for all patients.
- The mortality outcome data at 28 days was established for four patients whose outcome data was missing; two patients (both in the treated group) were alive and two (one patient in each arm) were dead.
- All other mortality outcome data had been correctly categorized in the '95 series of audits.
- One patient in the control group (C03124) was considered a duplicate of C03135. Both CRFs reported the patients as alive at 28 days but had different birth dates, birth weights and gestational ages. Furthermore, one of the patients had a birth date out of the range of the study period (See Table 2 for details). The sponsor explained this inconsistency as an error at the time the data were entered into the CRF from the source document.

The '97 series of audits were able to locate source records for all patients with missing outcome data for mortality (4 patients). No other discrepancies in mortality outcome were found. With these changes in the data, the difference in the incidence of mortality between the treatment arms was statistically significant in favor of the Curosurf-treated group.

The analysis of the mortality data including patient C03124's data as reported did not change the conclusions (see Table 5).

As explained before, the open label nature of the trial and the lack of pre-specified, objective definitions for the endpoints chosen by the sponsor (incidence of BPD and survival without BPD) prevent the results of these endpoints from being reliable. For the purpose of the evaluation of efficacy in this application, all cause mortality at 28 days in the ITT population is considered the primary endpoint of efficacy.

Despite the deficiencies in the definitions of certain complications and the approach taken in this review to consider mortality as the only valid efficacy endpoint, the results on the incidence of complications of prematurity in EURO I are further discussed in this review.

This is relevant information that can be included in the label because EURO I is the only trial that compared adverse events in infants with comparable severity of RDS who were randomized to receive Curosurf or sham (no treatment).

After the '97 series of audits, the difference in the incidence of pneumothorax and pulmonary interstitial emphysema (PIE) remained statistically significant in favor of the surfactant-treated group. The incidence of BPD in survivors at 28 days was statistically significant in the original analysis (22% versus 46% respectively, p= 0.0197) while this difference did not reach statistical significance in the '97 audited database (26% vs. 44%, respectively, p=0.0771). This change occurred when 2 patients (patients with ID # 003016 and 003036) in the treated arm had their missing BPD data established as positive (see Table 6).

In summary, there were 24/78 (31%) deaths verified in the surfactant-treated group and 32/67 (48%) deaths in the control group. The re assessment of the data showed a statistically significant difference in mortality (p=0.036; see Table 5) in favor of the surfactant-treated group when compared to the sham group. The incidence of BPD in survivors at 28 days lost its statistically significant difference. The incidence of pneumothorax and PIE remained statistically significant.

Table 1 EURO I - Patients not fully audited in 1995

ID number	Reason for not being fully audited	Previous outcome	'97 series Corrected outcome
C03123	Source data missing	dead	dead
C03124	CRF missing	alive	considered duplicate of C03135
C03126	Source data missing	alive	alive
C03128	Source data missing	dead	dead
C03080	Not audited	alive	alive
C03133	Source data missing	alive	alive
C03508	CRF missing	alive	alive
C03090	Source data missing	dead	dead
003089	Source data missing	alive	alive
003503	CRF missing	alive	alive
003068	Only hospital summary avail.	dead	dead
003082*	Only hospital summary avail.	alive	dead
003103*	Only hospital summary avail.	alive	dead
003016	Outcome data missing	-	alive
003036	Outcome data missing	-	alive
003504	Outcome data missing	-	dead
C03026	Outcome data missing	-	dead

* Patient's records were found and their outcome was corrected by DSI in 1997.

Table 2 Demographic characteristics of the patients considered duplicate

CASE ID	TREATED	SEX	BIRTH WT	DOB	GEST AGE	DELIVER	OUTCOME
C03124	Sham	Female	1100 g	10/31/88	30 weeks	C-section	alive
C03135	Sham	Female	1050 g	04/10/87	29 weeks	C-section	alive

Table 3 Mortality to 28 days. Original data ('95 audit series). Number/total (percentage) of patients. EURO I

Treatment Group	Excluding patients with missing data	Patients with missing data included as deaths.
Surfactant-treated (n=78)	21/75 (28%)	24/78 (31%)
Controls (n=67)	31/66 (47%)	32/67 (48%)
p-value[1]	0.02 (0.0235)	0.036 (0.0413)

[1]P-value from Pearson's chi square test (Fisher's exact).

Table 4 Mortality to 28 days. Post DSI audit. Number/total (percentage) of patients. EURO I.

Treatment Group	Excluding patients with missing data*	Patients with missing data included as deaths.
Surfactant-treated (n=78)	24/76 (32%)	26/78 (33%)
Controls (n=67)	32/67 (48%)	32/67 (48%)
p-value[1]	0.048 (0.06)	0.077 (0.09)

* Two patients (003504 and CO3026) whose outcome were determined by the medical reviewer after reviewing the case report forms and the two patients whose records were found by DSI (003082 and 003103) are included.
[1]P-value from Pearson's chi square test (Fisher's exact).

Table 5 Mortality to 28 days. Corrected data ('97 audit series). EURO I.

Treatment Group	Mortality at 28 days excluding "duplicate"	Mortality including the "duplicate"
Surfactant-treated (N=78)	24/78 (31%)	24/78 (31%)
Controls (N=67)	32/66 (48%)	32/67 (48%)
p-value[1]	0.0298 (0.039)	0.036 (0.041)

[1] P-value from Pearson's chi square test (Fisher's exact).

Table 6 Complications of prematurity at 28 days. EURO I

Parameter	Original data		Corrected data	
	Rescue N=78	Sham N=67	Rescue N=78	Sham N=67
PIE [n/N*(%)]	16/78 (21)	26/67 (39)[1]	16/78 (21)	25/66 (38)[1]
Pneumothorax [n/N*(%)]	16/78 (21)	24/67 (36)[1]	16/78 (21)	24/66 (36)[1]
ICH total [n/N*(%)]	39/77 (51)	43/67 (64)	40/78 (51)	42/66 (64)
NEC[n/N*(%)]	1/78 (0.01)	1/67 (0.01)	1/78 (0.01)	1/66 (0.01)
Acquired pneumonia [n/N*(%)]	11/76 (15)	14/67 (21)	13/78 (17)	14/66 (21)
Acquired sepsis [n/N*(%)]	11/75 (15)	12/67 (18)	11/77 (14)	12/66 (18)
PDA [n/N*(%)]	47/78 (60)	32/67 (48)	47/78 (60)	32/66 (48)
BPD[n/N*(%)]	12/54 (22)	16/35[1] (46)[1]	14/54 (25)	15/34 (44)

*Denominators represent total number of patients with data.
[1] Pearson's and Fisher's p<0.05

Reviewers' conclusion from EURO I

According to our previous review of the data and the present update, EURO I provides evidence to support the efficacy and safety of Curosurf for the treatment of premature infants with RDS.

C. EURO III

The original audit plan for EURO III was to have ≥ 80% of the records audited. Thirteen of the 28 investigational sites were audited (118/195 patients were audited or 60%). In December of 1996, the sponsor submitted a list of the patients who were not audited in 1995 because they did not have source data available (See Table 7). In addition, in 1997, the sponsor provided the ID number of the patients enrolled at sites not audited in 1995.

According to the '97 series of audits the findings were as follows:

- The mortality outcome was established on 4/5 patients with missing outcome data (see Table 8).
- The source documents were not available for 7 patients: 1 in the early group (who had the outcome data missing) and 6 in the late/control group (one control was dead and 5 were alive at 28 days (see Table 9).
- One patient, P00009, randomized to the early treated group, had wrongly been categorized as alive when indeed was dead (the auditor reported that death occurred at 36 hours of age not 36 days). Note: the sponsor's database was not updated for this death. This death was included in our analysis (see Table 12).
- The mortality outcome was verified for all other patients. However, the audit reports for patients E00005, C00134 and P00003 P00007, P00008, and P000013 were missing. We requested the audit report for patients E00005, C00134, and P000013 (2 from the early treated and 1 from the control group) to confirm that they were alive on Day 28 (shaded in Table 7). The sponsor responded that no individual audit reports were available for those patients, but that there was no inconsistency listed for them.

The early treated group had 14 verified deaths. In addition, one patient remained with missing outcome data (This patient (P00005) was counted as dead) - for a total of 15/95 deaths. The late/control group had 24 verified deaths - plus 1 unverified death - for a total of 25/100 deaths. The difference in mortality between the treatment groups was not statistically significant (p-value = 0.069 from Pearson's chi square).

APPEARS THIS WAY
ON ORIGINAL

Table 7 Patients not fully audited in 1995. EURO III

ID number	Reason for not being fully audited	Previous outcome	'97 series. Corrected outcome
E00005*	did not have source data available	alive	audit report not available
L00050	did not have source data available	dead	dead
C00020	did not have source data available	alive	source data not available
C00021	did not have source data available	alive	source data not available
C00081	did not have source data available	alive	source data not available
L00019	did not have source data available	alive	source data not available
E00022	did not have source data available	dead	dead
C00023	did not have source data available	alive	alive
E00024	did not have source data available	alive	alive
C00026	did not have source data available	alive	alive
E00029	did not have source data available	alive	alive
E00039	did not have source data available	alive	alive
C00134*	did not have source data available	alive	audit report not available
C00159	did not have source data available	dead	dead
P00001	CRF not available	no data	alive
P00002	CRF not available	dead	dead
P00003	CRF not available	dead	audit report not available
P00004	CRF not available	dead	source data not available
P00005	CRF not available	no data	source data not available
P00006	CRF not available	no data	dead
P00007	CRF not available	dead	audit report not available
P00008	CRF not available	dead	audit report not available
P00009	CRF not available	alive	dead
P00010	CRF not available	dead	dead
P00011	CRF not available	dead	dead
P00012	CRF not available	dead	dead
P00013*	CRF not available	alive	audit report not available

* The audit report has been requested to confirm the status at 28 days.

Table 8 Patients with changes in mortality outcome at 28 days. EURO III

ID number	Allocation	Previous Outcome data	'97 series. Corrected outcome
C00058	Control	Missing	Dead
L00119	Late	Missing	Alive
P00001	Early	Missing	Alive
P00005	Early	Missing	No source records available
P00006	Early	Missing	Dead
P00009	Early	Alive	Dead

Table 9 Patients not audited in 1997. EURO III

ID number	Reason for not being fully audited	Allocation	Previous outcome	
			Mortality	BPD
P00004	did not have source data available	Control	Dead	- (was dead)
P00005	did not have source data available	Early	Missing	Missing
L00073	did not have source data available	Late	Alive	Not present
L000019	did not have source data available	Late	Alive	Not present
C00020	did not have source data available	Control	Alive	Not present
C00021	did not have source data available	Control	Alive	Not present
C00081	did not have source data available	Control	Alive	Not present

Table 10 Mortality. Original data ('95 audit series). Number/total (percentage) of patients. EURO III.

Treatment Group	Excluding patients with missing data	Patients with missing data included as deaths.
Early treated	12/92 (13%)	15/95 (16%)
Late/Controls	24/98 (25%)	26/100 (26%)
p-value[1]	0.044	0.08
Late	13/52 (25%)	14/53 (26%)
Controls	11/46 (24%)	12/47 (25%)

[1]P-value from Pearson's chi square

Table 11 Mortality. Corrected data ('97 audit series). Number/total (percentage) of patients. EURO III.

Treatment Group	Excluding patients with unverified data	Patients with unverified data included as deaths.
Early treated	13/94 (14%)	14/95 (15%)
Late/Controls	24/94 (26%)	30/100 (30%)
p-value[1]	0.044	0.011
Late	13/51 (26%)	
Controls	11/43 (26%)	

[1]P-value from Pearson's chi square

Note: The data in Table 11 do not include the death of patient P0009 in the early treated group, which makes 14 deaths from 94 verified records. With this correction, Table 11 "excluding patients with unverified data" should show 14/94 deaths in the early group versus 24/94 deaths in the late/control group (p value = 0.069 from Pearson's chi square test). Thus, the difference in the incidence of mortality at 28 days between the early and the late/control group was not statistically significant in this trial.

Table 12 Reviewer's analysis: Modified Mortality to 28 days. EURO III.

Treatment Group	Patients with unverified data included as reported in the CRF*
Early treated	15/95 (16%)
Late/Controls	25/100 (25%)
p-value[1]	0.111

[1]P-value from Pearson's chi square

* The outcome data for patient P0009, in the early group, has been corrected. A patient with missing data, in the early group, was included as a death.

APPEARS THIS WAY
ON ORIGINAL

Other endpoints

As explained in the original review of EURO III, BPD was poorly defined in EURO III. The protocol defined BPD as the need of oxygen supplements and CXR changes at 28 days; however, it failed to specify the criteria used to provide the O_2 supplement or the algorithm to describe the radiological findings. This flaw is more critical because of the open label nature of the trial. Regardless of the results, this endpoint can not be considered a valid endpoint of efficacy. Thus, all cause mortality at 28 days is the primary endpoint of efficacy evaluated in this trial.

Table 13 Survival at 28 days without BPD. '97 series of audits. EURO III

Treatment Group	Excluding pts. with missing data	p-value*	Pts. with missing data included as deaths or with BPD	p-value*
Early	73/94 (78%)		73/95 (77%)	
Late/Control	58/93 (62%)	0.0224	58/100 (58%)	0.0051
Late	*31/50 (62%)*			
Control	*27/43 (63%)*			

* p value from Pearson's chi square

Table 14 Reviewer's analysis: Modified Survival at 28 days without BPD. EURO III.

Treatment Group	Patients with unverified data included as reported in the CRF*
Early treated	72/95 (75)
Late/Controls	64[2]/100 (64)
p-value[1]	0.0732

[1] p value from Pearson'chi square

[2] DSI determined that one patient (L00063 from Paris) did not meet BPD criteria. He was on FiO2 for 26 days only. These data also excludes patient P00009 who died before 28 days.

Reviewers' conclusion from EURO III

EURO III, with the updated data, doesn't provide enough evidence to support the efficacy of Curosurf for the early versus late treatment of premature infants with RDS when the ITT population was evaluated relative to all cause mortality. No claims can be made regarding survival without BPD, because of the critical flaws found in the collection of the data, and considering the open label nature of the trial (no criteria were given for the diagnosis of BPD concerning X ray findings or oxygen therapy).

D. EURO IV

The original audit plan for EURO IV was to audit 10 to 20% of the patients' records. The source records of 86 patients randomly chosen were audited from nine of the 15 investigational sites or 24% of the patients enrolled into the study.

According to the '97 series of audits the findings were as follows:

- **The 15 investigational sites were audited.**
- **The source data or the outcomes for 22 patients were not verified.**
- **The mortality outcome at 28 days was established for 5 patients with missing outcome data (see Table 15).**
- **Eleven patients randomized to the single dose group received more than one dose.**

We reviewed the data against the database on file and no discrepancies in the reports were found. To ensure that the excluded patients did not change the results, the data were evaluated in the ITT population, where the patients with unverified data were included according to the outcome reported in their CRFs (Table 18).

There were 11 patients randomized to the single dose group who actually received multiple doses of surfactant. Two of these patients died and the rest were alive at Day 28. A secondary analysis of the data, including in the multiple dose group the eleven patients randomized to the single dose group who received multiple doses of surfactant, did not change the conclusions. The analysis again showed that 21% of the patients in the single dose group died by Day 28 versus 13% in the multiple dose group.

Regardless of the analysis used, the multiple-dose treatment arm presented a statistically significant difference in mortality to 28 days in its favor when compared to the single-dose arm (see Table 17 and Table 18).

Table 15 Patients with changes in outcome at 28 days. EURO IV.

ID number	Allocation	Previous Outcome data	'97 series. Corrected outcome
40043B	multiple	Missing	Dead
40204A	single	Missing	Dead
40206 B	multiple	Missing	Dead
40367A	single	Missing	Dead
40456A	single	Missing	Dead

Table 16 Mortality to 28 days. Original data ('95 audit series). Number/total (percentage) of patients. EURO IV.

Treatment Group	Excluding patients with missing data	Patients 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's chi square

Table 17 Mortality to 28 days. Corrected data ('97 audit series). Number/total (percentage) of patients. EURO IV.

Treatment Group	Excluding patients with unverified data	Patients with unverified data included as deaths.
Single-dose (n=184)	38/171 (22%)	51/184 (28%)
Multiple-dose (n=173)	21/164 (13%)	30/173 (17%)
p-value*	0.024	0.019

* Pearson's chi square

Table 18 Reviewer's analysis: Modified Mortality to 28 days. EURO IV.

Treatment Group	Patients with unverified data included as reported in the CRF.
Single-dose (n=184)	39/184 (21%)
Multiple-dose (n=173)	23/173 (13%)
p-value*	0.048

* Pearson's chi square

Reviewers' conclusions from EURO IV

EURO IV provides evidence to support the efficacy and safety of Curosurf for the treatment of premature infants with RDS relative to all cause mortality at 28 days.

E. EURO VI

The agency did not request that the investigational sites for this trial be re-audited. No changes were made to its database.

Reviewer's conclusion from EURO VI

Based on the original review of the data for EURO VI, this trial doesn't provide enough evidence to support the efficacy and safety of Curosurf for the treatment of premature infants with RDS.

F. [redacted]

V. Updated Integrated Summary Of Efficacy

The evaluation of efficacy for this application is now focused only on the pivotal trials for which the Agency requested full auditing, i.e., EURO I, EURO III, EURO IV, and the

Following the same guidelines adopted in the original submission, mortality to 28 days was considered the primary endpoint of efficacy. Table 24 presents the data on mortality to 28 days obtained from the four pivotal trials.

The efficacy of Curosurf in decreasing mortality at 28 days in premature infants with RDS is supported by EURO I and EURO IV. EURO III failed to show statistical significance in the ITT population (See Table 24), however it showed a numerical trend in favor of the early treated group.

Table 24 Mortality to 28 Days for the ITT Populations, '97 SERIES OF AUDITS. All Pivotal Studies

	Patients with unverified data excluded		Patients with unverified data included as deaths		Patients with unverified data included as reported	
Study/ Treatment Group	Mortality n/N (%)	P-value [1]	Mortality n/N (%)	P-value[1]	Mortality n/N (%)	P-value[1]
EURO I						
Curosurf	24/78 (31%)		-		24/78 (31%)	
Sham	32/66* (48%)	0.030	-	-	32/67 (48%)	0.036
EURO III						
Early	14/94 (15%)		15/ 95 (15%)		15/95 (16%)	
Late/Control	24/94 (26%)	0.069	30/ 100 (30%)	0.011	25/100 (25%)	0.111
EURO IV						
Single	38/171 (22%)		51/ 184 (28%)		39/184 (21%)	
Multiple	21/164 (13%)	0.024	30/ 173 (17%)	0.019	23/173 (13%)	0.048

* The sponsor considered one patient as a duplicate and excluded him from the analysis. The analysis of the data including that patient did not change the results.

[1] P values from Pearson's chi square

VI. Updated Integrated Summary of Safety

The following 9 complications of prematurity were assessed at 28 days:

- pneumothorax
- pulmonary interstitial emphysema (PIE)
- intracranial hemorrhage (ICH)
- necrotizing enterocolitis (NEC)
- retinopathy of prematurity (ROP)
- acquired pneumonia
- acquired septicemia
- persistent ductus arteriosus (PDA)
- bronchopulmonary dysplasia

The auditors found some inconsistencies between the source data and the CRFs. Most of the inconsistencies related to a more strict definition of the 28-day period or of the condition in question. The corrections, for the majority of the complications, did not change the ultimate conclusions obtained from the original data. Only one complication showed a change from being statistically significant to not significant. In EURO I the incidence of BPD in survivors at 28 days was statistically significant in the original analysis (22% versus 46% respectively, p= 0.0197) while this difference failed to reach statistical significance in the 1997 audited database (26% vs. 44%, respectively, p=0.0771).

Comparisons among treatment groups by exposure to Curosurf (rescue and not treated) are not reliable because the disease status of the three groups are not comparable. All patients in the rescue group had RDS at different stages, while patients in the The not treated group did not develop RDS (with exception of the patients in the sham arm of EURO I).

EURO I is the only trial that compared the use of Curosurf against sham (no surfactant given) for the treatment of RDS. Thus, this trial is useful to compare the incidence of complications of prematurity between Curosurf-treated and non-treated patients. The new data from the '97 series of audits for EURO I is presented below and can be included in the labeling. The remaining trials (EURO III, IV and the studied different regimens of Curosurf therapy. Thus, the comparison of the incidence of complications of prematurity between treatment arms in the remaining trials may not be as valuable as the information obtained from the analysis of EURO I regarding the effect of the use Curosurf upon complications of prematurity. The data from EURO I is presented in Table 25. The Curosurf-treated group showed lower statistically significant incidence of pneumothorax and PIE when compared to the sham group.

APPEARS THIS WAY
ON ORIGINAL

4. ADVERSE EVENTS during the administration of Curosurf: should include a general statement about the adverse effects generally seen with the administration of surfactants, e.g., bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation.
5. DOSAGE: The NDA only supports an initial dose of 200 mg/Kg of body weight to be given for the rescue treatment of RDS.
6. 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.

/S/ 8/11/98
Liza Miriam Pina, M.D.
Clinical Reviewer

/S/
Girish Aras, Ph.D.
Statistical reviewer

Concurrence by Deputy Director/Supervisor:
Yes ✓ No____
Comments:
see secondary review memo.

Signature/Date /S/ 8/12/98

Concurrence by Team Leader:
Yes ✓ No____
Comments:

Signature/Date /S/ 8/12/98

Concurrence by Division Director:
Yes ✓ No:
Comments:

Signature/Date /S/ 8/13/98

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

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

MEDICAL OFFICER REVIEW

Division Of Pulmonary Drug Products (HFD-570)

APPLICATION #:	20 - 744	**APPLICATION TYPE:**	NDA
SPONSOR:	Dey, L.P.	**PROPRIETARY NAME:**	Curosurf®
CATEGORY:	surfactant	**USAN NAME:**	Poractant alpha
		ROUTE:	intratracheal
MEDICAL OFFICER:	Debra Birenbaum, M.D.	**REVIEW DATE:**	October 14,1999

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
14 May 1999	25 May 1999	package insert draft	Amendment No. 042
2 July 1999	7 July 1999	Safety update	Amendment No. 048

REVIEW SUMMARY: The sponsor has submitted a safety update that indicates no ongoing Curosurf studies conducted by Dey since the FDA CH letter 30 September, 1998. Safety information contained in this update includes information from foreign studies sponsored by One adverse event was reported for this period from Great Britain. Curosurf was administered intratracheally to a 4 old month old male infant with bronchiolitis, as part of a dose finding study for Curosurf in severe bronchiolitis. The baby experienced hypoxemia and bradycardia, followed by full cardiac arrest that responded well to resuscitation. The AE was considered drug related by the investigator. No conclusions about this SAE can be made regarding safety of Curosurf in premature infants with RDS, given that that this SAE occurred after Curosurf was given in a different population and for a different indication. No other safety issues were submitted by the sponsor in its list and descriptions of 11 Curosurf clinical studies of adults with ARDS, premature infants with RDS, and older infants with bronchiolitis, or one *in vitro* study of biologic effects of Curosurf on the cultured type II pneumocyte, or pharmacodynamic study of cerebral and systemic blood flow after surfactant in neonatal pigs.

The package insert draft label was reviewed and edited to reflect only those statements supported by submissions to the NDA. The edited draft package insert is attached to this review.

OUTSTANDING ISSUES: none. CMC issues have been resolved.

RECOMMENDED REGULATORY ACTION

New Clinical Studies: ______ **HOLD** ______ **MAY PROCEED**

NDA/Efficacy/Label Supplements: ______ **APPROVABLE** ______ **NOT APPROVABLE**

SIGNATURES

Reviewer: /S/ **Date:** 10/19/99

Team Leader: of note, nothing comments differ somewhat from those Rec'd to sponsor & should be addressed with next **Date:** version of label

APPEARS THIS WAY ON ORIGINAL

NDA 20-744 Amendment No. 042
NDA 20-744 Amendment No. 048

Medical Officer Review

REVIEWER: Debra L. Birenbaum, M.D.
PRODUCT: Curosurf ® (poractant alpha)
CATEGORY: pulmonary surfactant
ROUTE: intratracheal
INDICATION: established Repiratory Distress Syndrome (RDS) in the premature infant
SPONSOR: DEY Laboratories
2751 Napa Valley Corporate Drive
Napa, California 94558
TEL (707) 224-3200
FAX (707) 224-1364
Peggy J. Berry
Regulatory Affairs Senior Manager
SUBMITTED: 14 May 1999 Amendment No. 042
STAMP DATE: 25 May 1999 Amendment No. 042

SUBMITTED : 02 July 1999 Amendment No. 048
STAMP DATE: 07 July 1999 Amendment No. 048
REVIEWED: 14 October, 1999

PRIOR PERTINENT SUBMISSIONS: Medical Officer review dated 04/17/97 of original Curosurf NDA (Document date 07/03/96) by Miriam Pina M.D., and Medical Officer review dated 08/12/98 of NDA audits and new data (Document date 03/03/98), by Miriam Pina, M.D. are relevant.

SAFETY UPDATE SUMMARY

The sponsor has submitted a safety update that indicates no ongoing Curosurf studies conducted by Dey since the FDA CH letter 30 September, 1998. Safety information contained in this update includes information from foreign studies sponsored by One adverse event was reported for this period from Great Britain. Curosurf was administered intratracheally to a 4 old month old male infant with bronchiolitis, as part of a dose finding study for Curosurf in severe bronchiolitis. The baby experienced hypoxemia and bradycardia, followed by full cardiac arrest that responded well to resuscitation. The AE was considered drug related by the investigator. No conclusions about this SAE can be made regarding safety of Curosurf in premature infants with RDS, given that that this SAE occurred after Curosurf was given in a different population and for a different indication. No other safety issues were submitted by the sponsor in its list and descriptions of 11 Curosurf clinical studies of adults with ARDS, premature infants with RDS, and older infants with bronchiolitis, or one *in vitro* study of biologic effects of Curosurf on the cultured type II pneumocyte, or pharmacodynamic study of cerebral and systemic blood flow after surfactant in neonatal pigs.

PACKAGE INSERT

The package insert draft label was reviewed and edited to reflect only those statements supported by submissions to the NDA. A copy of the revised package insert is attached to this review.

Debra Birenbaum, M.D.

cc.NDA 20-744
HFD 570/Division File
HFD 570/Himmel
HFD 570/Birenbaum
HFD 570/Dunn

APPEARS THIS WAY
ON ORIGINAL

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

30 pages

NDA 20-744

CLINICAL AND STATISTICAL REVIEW

NAME OF DRUG:	Curosurf (poractant)
INDICATION:	Respiratory Distress Syndrome of Premature Infants
SPONSOR:	Dey Laboratories
SUBMITTED:	July 03, 1996
COMPLETED:	April 07, 1997

REVIEWERS

MEDICAL:	L. Miriam Pina, M.D.
STATISTICAL:	Girish Aras, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

TABLE OF CONTENT

I. General Introduction

A. Material Utilized in Review

Six studies were submitted to demonstrate the safety and effectiveness of Curosurf in the treatment of RDS: five studies were considered adequate and well controlled: Four rescue trials: Euro I, Euro III, Euro IV, Euro VI The sixth trial was not considered well-controlled by the sponsor's auditors, but was reviewed as supportive of the NDA. Additional experience with Curosurf in five clinical trials, Studies Protocol 50.01/CT/01/92 Protocol EURO V, CTCV01-87. (Vol. 1.26), and Protocol EURO II. (Vol. 1.25), investigated open-label use in about 620 infants.

Other submissions reviewed in this NDA are as follows:
03-Jul-96, 07-Aug-96, 09-Aug-96, 29-Aug-96, 30-Aug-96, 30-Aug-96, 04-Sept-96, 10-Sept-96, 04-Oct-96, 10-Dec-96, 13-Dec-96, 16-Dec-96, 20-Dec-96.

B. Other Related IND's and NDA's

NDA 20-044 - Exosurf, a synthetic surfactant. It was approved in 1990, under orphan drug status, for the prevention and treatment of RDS in premature infants.

NDA 20-032 - Survanta, a natural, fortified, surfactant from cows extract. It was approved in 1991, under orphan drug status, for the prevention and treatment of RDS in premature infants.

NDA 20-521 - Infasurf, a natural surfactant from calf lung lavage. Currently being reviewed by the Division. Its proposed indication is the prevention and treatment of RDS in premature infants.

C. Background

1. Indication

The Sponsor, Dey Laboratories, is seeking approval of Curosurf® (poractant), a natural surfactant extract of porcine lung for the treatment and prophylaxis of respiratory distress syndrome (RDS) in premature infants.

RDS is a major life-threatening illness in premature infants, characterized by a rapidly progressive respiratory failure, attributed to a lack or insufficiency of endogenous pulmonary surfactant.

2. Proposed Directions for Use

General

Curosurf is white to creamy white. It should be stored in a refrigerator at +2 to +8 °C. Before use the vial should be slowly warmed and gently turned upside-down, without shaking, in order to obtain a uniform suspension.

Dosage and Administration

Initial Dose.

Curosurf is intended for intratracheal administration only. It is instilled through a 5 French end-hole catheter inserted into the infant's endotracheal tube. The proposed initial dose of Curosurf is 100 mg (1.25 ml/Kg) or 200 mg (2.5 ml/Kg) of surfactant/kg body weight (the sponsor provides a Curosurf dosing chart based on the birth weight of the infant to help determine the dose).

Immediately before Curosurf administration, the infant's ventilator setting should be at a rate of 60 breaths/minute/ IT of 0.5 second and enough FiO2 to maintain SaO2 >92%, then should be briefly disconnected . Curosurf should be instilled through the French catheter in a bolus over 2 to 3 seconds. The infant should be reconnected to the ventilator at the same setting as immediately before dosing.

Repeat Doses

Up to 2 repeat doses of 100 mg/Kg of birth weight , 12 hours apart, have been given in controlled pivotal clinical trials if the patient was still intubated with persisting or deteriorating respiratory status.

3. Foreign Marketing

Curosurf was first approved in Italy, France, Spain, and Portugal between June and November of 1992.
Currently, Curosurf has been approved in the following countries:

Table 1 **Countries where Curosurf has been approved.**

Country	Approval Date	Country	Approval date
France	6/92	Spain	6/92
Brazil -	9/92	Italy	10/92
Germany	10/93	Portugal	11/92
Great Britain	11/93	Switzerland	7/93
Denmark	11/93	Sweden	10/93
Holland	1/94	Luxembourg	12/93
Cyprus -	4/94	Ireland	9/94
Finland	4/94	Norway	12/94
Greece	8/94	Iceland	1/95
Belgium -	1/95	S. Korea	3/95
Austria -	6/95	Israel	4/95

The sponsor stated that, to date, Curosurf has not been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness.

4. Chemistry

USAN name:	Chiese has applied for the name poractant
Commercial name:	Curosurf
Manufacturing sites:	The purified paste is manufactured at:

Curosurf is a creamy-white suspension containing a complicated mixture of phospholipids and hydrophobic proteins extracted from porcine lung surfactant. It contains the following components:

Solids:	
Polar lipids:	99% (mainly phospholipids)
Phosphatidylcholine:	of phospholipids
Dipalmitoyl-PC (DPPC):	of phospholipids
Total protein:	(no spec. for SP-B or SP-C)

5. History of the Submission

On March 21, 1995 the agency met with the sponsor to discuss a protocol of a domestic Phase III trial using an active control, that would support the submission of an NDA. Given the difficulties of planning an equivalency trial against a suitable comparator, and the extensive European research program already accomplished by the sponsor, the agency agreed to review an NDA based on the existing European data. The sponsor conducted an internal audit of the main controlled clinical trials (6 trials) to validate the data entered in the case report forms and concluded that the data were reliable. The sponsor, then, submitted the NDA.

Therefore, in this review, it was necessary to rely heavily on a retrospective, post-hoc designation of mortality as the primary endpoint.

Additionally, it is important to realize that many of the p-values reported herein are derived from exploratory analyses and should be considered descriptive.

II. Description of Clinical Trials

The main sources of data to support efficacy and safety of Curosurf reviewed in this NDA are:

1. Four pivotal trials for the rescue treatment of RDS:
   a) Euro I: 145 infants received either Curosurf or "Sham" treatment
   b) Euro III: 195 infants received Curosurf either early or late in the disease process.

c) Euro IV: 357 patients received Curosurf as single or multiple doses.
d) Euro VI: 2168 infants received low or high doses of Curosurf.

2.

3. Other supportive studies:
a) Protocol 50.01/CT/01/92
b)
c)
d) EURO V, CTCV01-87
e) EURO II

The individual trials are discussed in detail in the following sections. The sponsor's results are presented first, the medical and statistical reviewers' comments follow. The reviewers' comments are in a different font to distiguish them from those of the sponsor's.

CONTROLLED RESCUE CLINICAL TRIALS.

III. EURO I (Vol. 1.17)

CUROSURF COLLABORATIVE CONTROLLED EUROPEAN MULTICENTRE STUDY

A. Investigators and investigational centers.

1. Trial Director.

Bengt Robertson
St Göran's Children's Hospital,
Stockholm, Sweden

2. Surfactant Preparation.

Tore Curstedt
Karolinska Hospital,
Stockholm, Sweden.

3. Investigational Centers.

Eight European neonatal intensive care units participated.

B. Objective.

Assess the efficacy of surfactant replacement therapy using a single dose of Curosurf in the management of severe neonatal RDS.

C. Study Design.

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

1. Population.

   a) Inclusion Criteria

      (1) Birth weight 700 to 2000 g,
      (2) Clinical and radiological findings typical of neonatal RDS,
      (3) Age at treatment 2 to 15 hours,
      (4) $FiO2 \geq 0.60$
      (5) Requirement of artificial ventilation
      (6) No complicating disease

   b) Exclusion Criteria

      (1) Prolonged rupture of membranes $\geq$ 3 weeks
      (2) Intracraneal hemorrhage of Grade III or IV
      (3) Birth asphyxia (onset of seizures first 12 hours)
      (4) No major congenital anomalies (CHD, myelomeningocele, etc.)
      (5) Evidence of streptococcal infection (gastric aspirate or GBS antigen test)

   c) Stabilize before randomization to exclude or treat

      (1) Hypoglycemia
      (2) Metabolic acidosis
      (3) Anemia
      (4) Hypotension
      (5) Pneumothorax should be treated before surfactant replacement

2. Randomization procedures

   Patients were stratified for randomization based on birth weight:
   a) 700 - 1200 g
   b) 1201 - 2000 g
   Five minutes before the randomization, every patient was disconnected from the ventilator and suctioned.

3. Administration and dosage

   a) Surfactant treated subjects.

      The patient was disconnected from the ventilator while surfactant was instilled into each main bronchus via a feeding tube. Total dose was 2.5 ml/kg (Phospholipid 80 mg/ml). The patient was manually "bagged" between and after the instillations for a total of 2 minutes, using 100% O2, at a rate of 40 to 60/min.

   b) Control subjects.

      The patient was disconnected from the ventilator for 2 minutes. The patient was then hand bagged using 100% O2 at a rate of 40 to 60/min.

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 a PaO_2 of about 55 mm Hg, $PaCO_2$ 35 to 45 mm Hg and pH>7.30, with the lowest FiO_2. The weaning from the ventilator was initiated when FiO_2 <0.4 and peak pressure <20 cm H_2O. PEEP was kept at 3 - 5 cm H2O during the whole period of artificial ventilation.

Reviewer's Note: Even though the protocol specified that the surfactant would be given into each main bronchus via a feeding tube, the report of the study explained that the surfactant was either instilled into the two main bronchus or as a bolus into the lower trachea. No criteria was given to follow either method. The sponsor explained that only one center administered the surfactant as a single bolus into the lower trachea. The rest of the centers used the protocol specified method.

4. **Endpoints**

The following parameters were compared between treated babies and controls:

a) **F_iO_2**
b) **Blood gases**
c) **Peak inspiratory pressure (PIP)**
d) **Mean airway pressure (MAP)**
e) **Transthoracic impedance (if possible)**
f) **Functional residual capacity (FRC) (nitrogen wash-out)**
g) **CXR changes**
h) **Lung compliance**
i) **Cytological findings**
j) **Incidence of complications: cerebral hemorrhage (diagnosed by ultrasound according to Papile system) , PDA (diagnosed by echocardiography), pulmonary interstitial emphysema (PIE), pneumothorax and bronchopulmonary dysplasia ([BPD] diagnosed by oxygen dependence and/or CXR changes at 28 days).**
k) **Mortality**

Reviewer's note: The protocol did not categorize the above parameters as primary or secondary, or as safety or efficacy endpoints. In the subsequent study report, the following efficacy endpoints were defined:

* Improvement in the quotient PaO2/FiO2 by 100% within 6 hours after surfactant replacement,
* Reduction in the period of artificial ventilation in survivors,
* Reduction in neonatal mortality.

The sponsor expected to demonstrate a 30% relative difference in the incidence of mortality (from 63% in the control to 45% in the treated group). In the trial, mortality was 47% in the control group and 28% in the treated group, a relative difference of 40%. In analyzing this endpoint, the sponsor has tested the null hypothesis of 'no difference in incidence of mortality between two groups' against the alternative hypothesis that ' the incidence of mortality is different in two groups'.

The report considered the following safety parameters: Adverse events, laboratory tests (hematological and blood chemistry), and vital signs.

5. Statistical Analysis

a) Sample size

Assuming a power of 80%, a significance level of 5% (two tailed), and calculating from the standardized differences in a pilot study, it was estimated that 52 babies would have to be randomized for the first endpoint; 34 patients for the second end-point and 236 patients (118 in each group) for the third end-point (the protocol page 215, Vol. 1.17). For the third end-point the mortality rates were assumed to be 15% and 30% in the treatment and control groups, respectively.

Based on the interim analysis that was conducted at sample size 39, it was concluded that the mortality rates were underestimated. The revised rates were 45% and 63% in the treatment and control groups , respectively. The recalculated sample size was 120 per arm.

The second interim analysis was conducted at sample size 129. The mortality was 29% and 52% in the treatment and control groups, respectively. Based on this as well as other characteristics, the sponsor decided to terminate the study. Meanwhile 17 more patients were included in the final analysis. The effective sample size at the conclusion of the study was 146.

Reviewer's note: At the beginning of the study, two interim looks were planned, first one at 0.25 of the sample size and the second at 0.5 of the sample size. (interim analyses were not mentioned in the original protocol, but the sponsor produced documented evidence that they were planned prior to the trial.) The sponsor did not adjust for interim analyses in the calculation of sample size, nor did it mention how it would like to spend the type one error (α) at the interim looks. This should be part of the statistical design and, hence, should be specified prior to the experiment. There are several well known statistical plans which prescribe 'spending function' for α. With two interim looks planned, the

appropriate sample size under the O'Brian and Fleming[1] rule, which comes closest to fixed sample allocation among the known plans, is 259. Also, the first look was too early (0.16 of sample size instead of 0.25 of sample size, which would be 60).

b) **Primary efficacy endpoint analysis**

Differences between the groups were evaluated by the Wilcoxon two tailed test and the Chi-Square test.

In addition, the first two of the primary efficacy variables were analyzed using a multiple regression technique with the following independent variables:

- **maternal steroid treatment (yes/no)**
- **inborn (yes/no)**
- **birth asphyxia defined as Apgar score at five minutes < 6 (yes/no)**
- **male (yes/no) gestational age**
- **birth weight**
- **age when randomized**
- **FiO_2**
- **surfactant (yes/no)**
- **hospital allocation**

The third efficacy endpoint was analyzed using logistic regression technique with covariates same as above.

Reviewer's note: In contrast to recommended practice for confirmatory trials, the regression analysis was conducted in a post-hoc manner. In the final model only the variables that showed significance were used for the best fit. The third endpoint, mortality is considered to be a "hard" endpoint by the reviewer and will be analyzed later using Fisher's exact test.

D. Results.

1. Neonatal Characteristics.

One hundred forty eight subjects were randomized. Two patients (one surfactant-treated and one control) were excluded for protocol violations: the Fi02 at entry was =0.5 in both cases. There were 146 patients included in the efficacy and safety analysis: 69 controls and 77 surfactant-treated subjects. There were no statistically significant differences with regard to gestational age (GA), birth weight (BW), sex, age when randomized, and FiO2 on entry.

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

Table 2 Neonatal characteristics. Euro I

Characteristics	Surfactant-treated (N=77)	Controls (N=69)
Gestational age [mean wk (SD)]	28.8 (2.0)	28.4 (2.2)
Birth weight [mean g (SD)]	1246 (306)	1182 (318)
Male [No (%)]	50 (65)	40 (58)
Age when Rz. [median (range) hours]	9.0 (2-15)	8.0 (2-15)
FiO2 before treatment	0.8 (0.15)	0.8 (0.15)

* All comparisons were not statistically significant.

Reviewer's note: Even though the sponsor reported that there were 148 patients included in the analysis (78 surfactant treated and 70 controls), the post-audited electronic data sent by the sponsor only accounts for 145 patients (78 patients in the surfactant-treated group, and 67 patients in the control group), explaining that 3 patients in the sham group had duplicated CRF's and since the duplicated CRF's were not identical these patients were excluded from the analysis.

To assess the baseline comparability of the groups, in addition to the comparisons made by the sponsor in the report, the APGAR scores at 1 and 5 minutes, and the RDS scores were evaluated. There were no statistically significant differences between both groups for any of these parameters.

Table 3. APGAR scores at 1 and 5 minutes. Euro I.

APGAR at 1 min	Treated	Controls	APGAR at 5	Treated	Controls
Unknown	4	2	Unknown	3	3
0	0	1	1	1	1
1	4	5	2	-	1
2	10	12	3	6	1
3	19	10	4	3	2
4	12	10	5	6	10
5	9	11	6	8	13
6	5	6	7	17	10
7	7	5	8	22	14
8	3	1	9	9	10
9	5	4	10	3	2
Mean	8.22	7.11	Mean	7.8	7.5
p-value*	0.356		p-value	0.867*	

*Pearson's Chi-Square test

Table 4 RDS scores by treatment group. Number of patients. Euro I.

	RDS Score			
	Unknown	2	3	4
Treated	5	13	25	35
Controls	4	10	26	27
Distributional p-value	0.6781 (Savage test)			

It is of note to say 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.

2. Maternal characteristics:

The only pregnancy-related variables recorded were: the delivery type, the number of products delivered and usage of steroids. There were no statistically significant differences between the treated group and the controls on these variables.

Table 5. Maternal characteristics. Number (percent) of patients*. Euro I.

	DELIVERY TYPE		NUMBER OF PRODUCTS		STEROID USE	
	C-Section	Vaginal	Single	Multiple	>48 hours	<48 Hours
Treated (n=78)	40 (51)	34 (44)	62 (79)	16 (20)	9 (12)	67 (86)
Controls (n=67)	28 (42)	38 (57)	54 (80)	13 (19)	5 (7)	57 (85)
P- Value	0.289.		0.868		0.5759	

*Percentages based on total sample; percent missing not displayed.

Reviewer's note: It is not known the causes for which the surgical deliveries were performed (e.g., fetal or maternal distress) and other maternal conditions that could have compromised the outcome of the subjects. However, the mean APGAR scores at 1 and 5 minutes and the other baseline characteristics of the subjects studied, which could be indicators of their baseline status, were not statistically significantly different between the treatment groups. The data submitted were comparable at baseline, suggesting that patients were appropriately assigned at random.

3. Primary Efficacy endpoints.

a) Improvement in the quotient PaO2/FiO2

Improvement in the quotient PaO2/FiO2 by 100% within 6 hours after surfactant replacement.
Even though the treatment with surfactant resulted in a rapid improvement of the PaO2 from an average of 57 mm Hg to 148 mm Hg., the response varied considerably and in some cases the improvement was transient. The PaO2/FiO2 ratio, though, was found to remain statistically significantly better in the treated group up to 48 hours.

Reviewer's note: The significance of this finding is difficult to assess because of the open label nature of the trial. The lack of specific criteria set beforehand for ventilatory management of the subjects in both groups could potentially have introduced bias in the way the individual patients were managed.

b) Reduction in the period of artificial ventilation in survivors by 33%.

At 4 weeks, there was no statistically significant difference in the time required to use mechanical ventilation (treated = 160 hours vs. controls = 252 hours).

Reviewer's note: No parameters were specifically set beforehand to extubate the subjects. In addition, the definition of extubation was not given. It is unknown whether these patients remained extubated throughout the entire study period or they where reintubated at some point within the first 28 days. These facts may have provided extensive variability in the management between centers and between investigators, thus affecting the results obtained. Again, the lack of specific criteria for the assessment of this parameter in an open label trial makes it difficult to assess the validity of these results.

c) **Reduction in neonatal mortality by 30%**

Reduction in Mortality of all causes during the first 4 weeks was statistically significant for the surfactant-treated group (p-value = 0.019). When controlled for other independent variables (maternal steroid treatment, inborn or not, APGAR score at 5 min <6, gender, birth weight, age when randomized, FiO2, hospital allocation and use of surfactant) using Logistic regression, surfactant treatment remained significant. The adjusted p-value is 0.035. In addition, the following independent variables showed statistical significance, with positive regression coefficients: body weight and allocation to Lund, and with negative coefficients: APGAR scores (at 5 minutes ≤ 6), allocation to Stockholm, and male sex.

Table 6 Mortality at 28 days. Original study report. Number/total (percentage) of subjects. Euro I.

	Surfactant-treated	Controls	p-value
Mortality at 28 days	24/77 (31%)	35/69 (51%)	0.0187 *[1](unadjusted)

* Fisher's exact test

[1] P-value adjusted for the above mentioned independent variables is 0.035.

Table 7 Mortality at 28 days using the post audit database. Number/total (percentage) of patients. Euro I.

Treatment Group	Excluding pts. with missing data	Pts. with missing data included as deaths.
Surfactant-treated	21/75 (28%)	24/78 (31%)
Controls	31/66 (47%)	32/67 (48%)
p-value[1]	0.0235	0.0413

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

Reviewer's note: As the sample size originally proposed was cut almost in half, and no statistical method was defined for the interim looks conducted, we shall perform two separate statistical analyses. In the first one, we shall examine whether the significance was observed at the second interim look to warrant the

termination of the trial. We shall use the O'Brian and Fleming boundary [2] to allocate type one error probability at interim looks. In this scheme less of α is spent on the interim looks and most of it is saved for the final sample size. Hence statistical significance is achieved only when there is substantial evidence of difference between the two arms. In the second analysis, we shall assume that the observed results were based on a fixed sample experiment and use the statistical methods accordingly.

We used the software package called EaSt from CyTEL software corporation to generate the nominal critical points for the interim looks.

Table 8 Mortality at the second interim look. Euro I

	Patients Alive	Patients Dead	Total (N=129)	Value of the Statistic
Surfactant	46 (71%)	19 (29%)	65	2.58
Control	31 (48%)	33 (52%)	64	

Table 9 Mortality and BPD at the second interim look. Euro I

	Patients Alive	Patients Dead	Total (N=129)	Value of the Statistic
Surfactant	37 (57%)	28 (43%)	65	3.33
Control	18 (28%)	46 (72%)	64	

Table 10 Nominal critical points using the O'Brian Fleming boundary. Euro I

Look number	Number of patients enrolled	Process time	Nominal critical point
1	39	0.1625	4.8
2	129	0.5375	2.8*
3	240	1	1.98

* value of the statistic for 'mortality' is 2.58 and for 'mortality or BPD' is 3.33

The critical value at sample size 129 of the test statistics is 2.58 for mortality endpoint and was 3.33 for 'mortality or BPD' endpoint. This is based on 29% deaths in the treatment group and 52% deaths in the control group, and 28% 'mortality or BPD' in the treatment group against 57% in the control. As we can see from the above tables, if we strictly apply the O'Brian Fleming boundary, the sponsor should have continued sampling if he looked at Mortality endpoint to make his decision to stop sampling; however with 'mortality or BPD' as an endpoint, the stopping at 129 was appropriate and it resulted in rejection of the null hypothesis of 'no treatment effect'.

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

Now, we shall ignore the fact that the data resulted from a truncated clinical trial due to an interim look. We shall treat it as a fixed sample. The incidence of mortality, as presented in the post auditing database, was analyzed by the sponsor, first excluding the patients that they found had missing information about this endpoint, and then, including these patients as if all were dead. The CRF's of the 4 patients reported as with missing data (003504, 003036, 003016 and C03026) were requested and reviewed. The CRF's of the patients with ID #003504 (in the surfactant group) and C03026 (control) were found to have information about the mortality endpoint, the patients died at 5 and 5.4 days, respectively . Patients 003016 and 003036 (both in the surfactant group) did not have mortality information at 28 days (these patients, in fact, did not have information on any efficacy or safety parameter). Therefore, the first part of the post auditing table (patients with missing data excluded) is incorrect in that it does not include patients 003504 and C03026. (22/76 vs. 32/67 p-value 0.025). This correction does not change the significance of the difference in mortality in favor of Curosurf found between both treatment groups in this trial. The difference continued to be statistically significant when the patients without data were included in the calculations as if they were dead.

Table 11 Modified incidence of mortality to 28 days. Euro I.

Treatment Group	Excluding pts. with missing data	Pts. with missing data included as dea
Surfactant-treated	22/76 (29%)	24/78 (31%)
Controls	32/67 (48%)	32/67 (48%)
p-value1	0.025	0.0413

[NOTE: Please refer to DSI Audits section for further comments and analysis of mortality based on the DSI auditor's finding that two patients that had been reported as alive in the treated group had actually died before 28 days of age].

Since no data were collected regarding the cause of death, no conclusions can be derived relative to the incidence of mortality specifically due to RDS or other causes.

To assess the effect of increased mortality found in Stockholm, by the regression analysis, and the increased survival in Lund, the centers were compared for birth weight, gestational age, FiO_2 at entry and mortality within the treatment groups. It is interesting that Lund, who had a positive coefficient for survival, had the smallest and youngest babies, especially in the control group. This made the distributional p-value statistically significant for birth weight and gestational age among the centers within the controls. If the data from Lund are excluded from the analysis, then, no statistically significant differences for any of the parameters among the centers would be found. There were no statistically significant differences in the incidence of mortality between the treated group and the controls among the centers, but, except for Paris, all centers had a significant difference in mortality in favor of the treated group within each center.

Table 12 Mortality, Birth weight and Gestational age by site. Euro I.

	Mortality		Birth Weight		Gestational Age Birth Weight	
SITE NAME	Treated	Control	Treated	Control	Treated	Control
Amsterdam	7/20 (35)	9/18 (50)	1315	1243	29.5	28.6
Belfast	5/19 (26)	8/18 (44)	1287	1298	28.1	28.7
Gottingen	0/4 (0)	1/2 (50)	1350	1651	29.7	31.5
Groningen	1/7 (14)	1/4 (25)	1276	1186	28.8	27.75
Lund	1/9 (11)	3/9 (33)	1022	906	27.4	25.8
Paris	2/5 (40)	1/3 (33)	1316	1433	29.4	29.6
Parma	2/8 (25)	3/6 (50)	1038	1025	27.8	28.8
Stockholm	3/6 (50)	5/7 (71)	1370	1163	29.1	28.4
Distributional P-value	.57	.866	.1137	.0128*	0.962	.0126**

* If we ignore the observations from Lund , the p-value is .211.
** If observations from Lund are excluded, then the p-value is .506

d) **Secondary efficacy endpoints**

PIP, I/E ratio, MAP, respiratory frequency, PEEP, and blood gases were not statistically significantly different between the surfactant-treated group and the controls.

4. **Safety endpoints**

Incidence of complications.
The following complications of prematurity were compared between groups: pulmonary interstitial emphysema (PIE), pneumothorax, patent ductus arteriosus (PDA), pneumonia, and bronchopulmonary dysplasia.

The surfactant-treated group showed a lower statistically significant incidence of PIE and pneumothorax. There were no statistically significant differences between the treated group and the controls in regard to PDA, ICH (all grades), pneumonia, and BPD regardless of the database used.

APPEARS THIS WAY
ON ORIGINAL

Table 13 Complications of prematurity as reported in the original report and in the post auditing database. Number/total (percent) of patients with data. Euro I.

Complications	Treated		Controls		
	Original	Post-audit	Original	Post-audit	Post-audit P-value
PIE	18/77 (23)	16/78 (20)	27/69 (39)	26/67 (39)	0.0178
Pneumothorax	14/77 (18)	16/78 (20)	24/69 (35)	24/67 (36)	0.0430
ICH					
Total*	36/77 (47)	39/77 (51)	38/69 (55)	43/67 (64)	0.1291
Grade I & II	16/77 (21)	-	22/69 (32)	-	
Grade III & IV	20/77 (26)	-	16/69 (23)	-	
PDA	46/77 (60)	47/78 (60)	32/69 (46)	32/67 (48)	0.1373
Pneumonia	11/77 (14)	11/76 14.5)	14/69 (20)	14/67 (21)	0.3797
BPD					
Total*	-	13/76 (17)	-	16/67 (24)	0.41
Grade III-IV	12/77 (16)	-	18/69 (26)	-	-

*The post auditing database did not provide ICH and BPD grade differentiation.

Reviewer's note: Note that the protocol did not include the criteria used to categorize BPD grades. Furthermore, since the patients' line listings section did not include the data related to grades of BPD or ICH assigned, this reviewer could not recreate the original study report table. The post auditing data, sent by the sponsor, did not characterize different grades of BPD. The data were given as incidence of BPD in general. As analyzed by the sponsor, the difference found in the incidence of BPD between the treatment groups is not statistically significant. However, there are some issues that need to be discussed.

The evaluation of the data revealed that two cases in the treated group (003036 and 003016) did not provide information of their status on day 28. Because these patients were counted as dead in the previous table (incidence of mortality), they are not counted as positive for BPD in the analysis of the incidence of BPD at 28 days (by definition the patients were required to be alive and with BPD reported as present). In addition, one patient (CRF 003130) was reported dead by day 28 but had BPD reported as present. Again, this patient might not need to be counted as positive in the analysis of incidence of BPD. If the incidence of BPD is calculated using the above corrections and using the survivors as the denominator, a statistically significant difference on the incidence of BPD in survivors between the treatment groups in the post auditing database and on the data provided by the original study report, the difference between the treatment groups in the incidence of BPD is significant in favor of the treated group.

Table 14 Incidence of BPD in the survivors at 28 days. Number/total alive (percentage) of subjects. Euro I.

	Original study report			Post auditing report		
Parameter	Treated	Controls	p-value	Treated	Controls	p-value
BPD	12/53 (23)	18/34(53)	.0005	10/54 (18.5)	16/35 (46)	.0176

BPD results in this study, however, should be interpreted with caution for the following reasons:
a) As in any unblinded study, the investigators were aware of the treatment received by the patients;
b) The present protocol did not characterize the different criteria followed to diagnose BPD, hence maximizing the possibilities of bias.
The endpoints should be very well defined and the criteria to assess the endpoints should be laid out meticulously beforehand, to minimize biases, especially in unblinded studies.
In the case of BPD, the criteria to continue or discontinue the oxygen supplement was not specified in the protocol. The person doing the interpretation of CxR's should have been clearly determined in the protocol, and possibly this person should have been kept blinded. The algorithm describing the radiological findings should also have been clearly stated beforehand. These issues make it questionable that this study can support the claim that the incidence of BPD was significantly reduced in the surfactant treated group.

The surfactant treated group showed a statistically significant decrease in the incidence of PIE and pneumothorax when compared to the controls. But again, it is unknown whether the Xray reader was blinded to the treatment received by the patients. The other complications of prematurity studied did not show any statistically significant differences between the treated group and the controls.

It is noteworthy that the present study failed to collect important information regarding the adverse events encountered by the care givers while the surfactant was being administered to the patient. Several adverse events during the administration of surfactants have been reported for other surfactants and that information has been included in those surfactant's package inserts.
The lack of this information for Curosurf should be discussed at the time of the discussions of the package insert if such information is not provided by the rest of the studies submitted with this NDA.

E. One, two and five year follow-up. (Vol. 1.20)

The post natal growth, respiratory status and neurodevelopmental outcome of surviving babies enrolled in this study were assessed at 1 and 2 years of corrected age. Sixteen patients from one center were examined at 5.5 years. Histological lung sections from 44 (18 in the treated and 26 in the control groups) babies who did not survive to 28 days and 2 who died later on, were re-examined in a blinded manner by a single observer.

1. Histological examination of lung sections.

Histological lung sections were examined for degree of expansion, presence of RDS, bronchitis, pneumonia, macrophages, hemorrhage, fluid, and pulmonary interstitial emphysema. The only statistically significant difference found between the treated and the control group was the increased incidence of PIE in the controls ($p<0.02$).

2. Clinical follow-up

There were 5 late deaths in the first year after the 28 days early post natal period. Four in the treated and 1 in the control group. Three babies in the treated group and the control baby died of BPD; the fourth treated baby died of Klebsiella pneumonia and sepsis.

a) Findings at 1 year.

Forty five treated and 31 control babies (93% of the surviving babies enrolled) were seen at 1 year of corrected age. There were no statistically significant differences for birth weight, weight and length, persistent respiratory symptoms, incidence of cerebral palsy, visual impairment or auditory impairment between the groups.

b) Findings at 2 years.

Forty four treated and 29 control babies were followed to 2 years corrected age. Three babies considered developmentally normal at 1 year of age moved from the area and were not available for examination at 2 years.

There were no statistically significant differences in weight and height and respiratory symptoms. Seventy eight percent of all babies examined at 2 years were developmentally normal. There were no statistically significant differences in specific type of disability or overall disability rate.

Table 15 Characteristics of surviving babies at 1 and 2 years follow-up. Euro I.

Characteristic	One year		Two years	
	Treated (N=45)	Control (N=31)	Treated (N=44)	Control (N=29)
Weight (kg)*	8.4 (1.4)	8.4 (1.1)	11.0 (1.6)	10.8 (1.6)
Length (cm)*	72.4 (3.8)	72.2 (3.2)	84.2 (3.8)	82.6 (8.2)
Respiratory symptoms [n (%)]	7 (16)	5 (16)	4 (10)	2 (7)
Cerebral palsy [n (%)]	7 (16)	5 (16)	8 (18)	6 (20)
Visual impairment [n (%)]	0 (0)	0 (0)	0 (0)	0 (0)
Auditory impairment [n (%)]	2 (4)	1 (3)	0 (0)	2 (7)
Developmental quotient*	91.2 (18)	90.8 (9)	–	–
Seizures at >1 month of age [n (%)]	2 (4%)	0 (0)		

*Mean (SD)

c) Findings at 5 years.

Sixteen infants (10/14 treated [70% of the treated survivors] and 6/10 controls [60% of the control survivors] from 24 survivors from Belfast Center were examined at 5.5 years corrected age. Developmental quotient (DQ) was derived using Griffiths Mental Developmental Scales.

There were no statistically significant differences between the groups.

Table 16 Characteristic of surviving infants at 5.5 years follow-up from Belfast Center.

	Treated (n=10)	Controls (n=6)
Originally enrolled in Euro I	19	18
Alive at 28 days	14 (74%)	10 (55%)
Examined at 5.5 years	10 (52%)	6 (33%)
Birth weight, g.[a]	1309 (339)	1,566 (275)
Gestational age, weeks[a]	28.6 (1.3)	29.9 (3.0)
DQ[b]	103 (74-126)	110 (90-125)

[a] Mean (SD)
[b] Developmental quotient, Median (range)

3. **Immunological studies.**

Titers of surfactant-anti surfactant immune complexes and serum antibodies to Curosurf were evaluated in about 30 babies in the treated group and 9 babies in the control group at a median of 14, 21 and 99 days.

Both groups presented immune complexes and serum antibodies irrespective of treatment. The differences were not statistically significant, nor the maximum antibody titer attained in either group. There was no major change in titers of immune complexes or antibodies in either group with advancing postnatal age.

Table 17 Immunological studies. Euro I.

Sample time (days) Median (range)	Immune complexes Treated	Immune complexes Control	Antibodies to Curosurf Treated	Antibodies to Curosurf Control
14 (0-17)	0.12 ± 0.08 (17)	0.13 ± 0.07 (4)	0.18 ± 0.12 (15)	0.11 ± 0.03 (4)
21 (20-40	0.12 ± 0.09 (21)	0.10 ± 0.08 (4)	0.19 ± 0.15 (21)	0.35 ± 0.34 (4)
99 (55-379)	0.09 ± 0.05 (17)	0.06 ± 0.07 (6)	0.23 ± 0.28 (17)	0.18 ± 0.19 (6)
Maximum titer	0.14 ± 0.09 (30)	0.10 ± 0.07 (9)	0.23 ± 0.14 (30)	0.27 ± 0.26 (9)

Reviewer's note: It is not clear how the control infants could develop antibodies to Curosurf, we assume that the antibodies in question were directed against surfactant in general.

F. Discussion and Conclusions

This is a multicenter, randomized, open label, sham controlled study of Curosurf, 200 mg/Kg (2.5 ml/Kg), single dose, administered intratracheally through the ETT to premature infants with RDS.

The sponsor did not mention in the protocol how it planned to spend the type one error α on the interim analyses. The statistical reviewer applied the O'Brian Fleming methodology to the data. As mentioned earlier, the sponsor should have continued sampling at the second interim look, based on a strict interpretation of the O'Brian Fleming method; however, the value of the statistic (2.58) was close to the nominal critical value (2.79), and the stopping was appropriate if mortality was looked at in conjunction with BPD (value of the statistic was 3.33). Hence the reviewer is inclined to agree with the sponsor in declaring statistical significance on this endpoint.

The treated and the control groups were not significantly different with respect to the key baseline demographic variables listed (refer to tables 1, 2, and 3 above).

Curosurf showed a statistically significant beneficial effect in the treated group in the reduction of mortality at 28 days. Regarding safety parameters, the treated group showed a statistically significant reduction in pulmonary air leaks (pneumothorax and PIE). Withstanding the criticism made to the design of the trial, BPD showed a favorable difference in the surfactant treated group. Other complications of prematurity studied (PDA, ICH, and pneumonia) did not show statistically significant differences between the treatment groups. The present study failed to collect important information regarding the adverse events encountered by health care providers while the surfactant was being administered, e.g., bradycardia, cyanosis, ETT obstruction, etc. These adverse events have been reported in trials of other surfactants. This issue should be addressed at the time the package insert is discussed.

Overall, the results of this study support the efficacy and safety of Curosurf for the treatment of RDS of prematurity.

IV. EURO III (Vol. 1.18)

RANDOMIZED MULTICENTER CLINICAL STUDY ON THE TREATMENT WITH NATURAL SURFACTANT OF NEONATAL RESPIRATORY DISTRESS SYNDROME IN PREMATURE INFANTS: COMPARISON BETWEEN EARLY AND LATE TREATMENT

A. Investigators and investigational centers.

1. **Trial Director:**

   Bengt Robertson
   St Göran's Children's Hospital,
   Stockholm, Sweden

2. **Surfactant Preparation:**

   Tore Curstedt
   Karolinska Hospital,
   Stockholm, Sweden.

3. **Investigational Centers**

   Twenty eight European centers.

B. Objective.

Assess the efficacy of Curosurf replacement therapy given early versus late in the treatment of RDS.

C. Study Design.

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

1. Population.

a) Inclusion Criteria

(1) Birth weight 600 to 2000 g,
(2) Clinical and radiological findings typical of neonatal RDS,
(3) Age at randomization 2 to 24 hours, age at treatment 2 to 48 hours,
(4) $0.40 \leq FiO2 < 0.6$
(5) Requirement of artificial ventilation
(6) No complicating disease

b) Exclusion Criteria

(1) Prolonged rupture of membranes $\geq$ 3 weeks
(2) Intracraneal hemorrhage of Grade III or IV
(3) Birth asphyxia (APGAR at 5 min <3)
(4) No major congenital anomalies (CHD, myelomeningocele, etc.)

c) The following conditions were to be stabilized before giving the surfactant:

- Hypoglycemia
- Metabolic acidosis
- Anemia
- Hypotension
- Pneumothorax should be treated before surfactant replacement

2. Randomization procedures

Patients were randomized based on two categories:
a) 600 - 1200 g
b) 1201 - 2000 g

Randomized study arms:
a) Early treated arm.
Patients that met the inclusion criteria (i.e., the FiO2>40% but <60%) and were randomized to receive Curosurf treatment immediately after enrollment;
b) Late/control arm.
Patients in this arm met the inclusion criteria and were enrolled, but did not receive Curosurf treatment immediately after enrollment. This arm consisted of two subsets, depending on the FiO2 requirements of each infant:
i) the late treated group: included infants <48 hours of age, whose FiO2 requirement increased to >0.6, whose CxR changes remained typical of RDS. These patients qualified to receive a dose of Curosurf, and
ii) the control group: included infants whose FiO2 requirement did not increase above 0.6. These patients did not receive Curosurf treatment.

3. Administration and dosage

a) Surfactant treated subjects.

Early treated group. The patient was disconnected from the ventilator while surfactant was instilled into each main bronchus via a feeding tube. Total dose was 2.5 ml/kg (80 mg of surfactant/ml). Patient was manually "bagged" between and after the instillations for a total of 2 minutes, using the same FiO_2 as before the instillation maneuver, at a rate of 40 to 60/min.

b) Control subjects.

Control/late treated group. The patient randomized to this arm was disconnected from the ventilator for 2 minutes and hand-bagged using the same FiO_2 as before the randomization, at a rate of 40 to 60/min. If he/she did not require FiO2>0.6 Curosurf was not given (i.e., the control group). If the baby was not yet 48 hours of age and required $FiO_2 \geq 0.6$ with CxR changes remaining typical of RDS, he/she was allowed to receive a single dose of surfactant (late treatment group). No retreatment was allowed.

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. PEEP was kept at 3 - 5 cm H_2O during the whole period of artificial ventilation.

Reviewer's note: This trial presents the same inconsistency between the protocol and the study report as was pointed out in the previous study. The original protocol described the administration procedure as an instillation into each main bronchus, with hand bagging between instillations. The study report describes the procedure as one single bolus into the lower trachea. The sponsor has been asked to clarify this procedure, how the surfactant was actually administered and, if both methods were used, how many patients used each method.

4. Endpoints

The primary endpoints were:

a) To improve the a/APO_2 ratio by 40% in the "early" vs. the "late" treatment group, during 6 hours after surfactant replacement;

b) To reduce mortality + incidence of BPD from 45% (late treatment) to 25% (early treatment).

Other parameters compared between the treatment groups were:

a) F_iO_2

b) Blood gases

c) Peak inspiratory pressure (PIP)

d) a/APO_2
e) Mean airway pressure (MAP)
f) Lung compliance
g) Functional respiratory capacity (FRC) (nitrogen wash-out)
h) CXR changes
i) Incidence of complications: cerebral hemorrhage (diagnosed by ultrasound) , PDA (diagnosed by echocardiography), interstitial emphysema (PIE), pneumothorax and bronchopulmonary dysplasia ([BPD] diagnosed by oxygen dependence at 28 days and radiological findings).
j) Antibody levels against surfactant proteins by the Groningen group (blood samples taken at randomization, age of 2 months, 1 year and 2.5 years).
k) Follow-up at 1 and 2.5 years of age, including FRC and CxR.
l) A complete neuro-developmental exam at 2.5 years.

Reviewer's note: In March of 1988, the first primary endpoint (40% reduction of the a/APO2 during 6 hours) was changed to be considered as a secondary endpoint. The only explanation given for this change was that "only selected groups were using it."

The protocol projected a 44.4% difference in the combined incidence of mortality and BPD (from 45% in the late/controls to 25% in the early group). In the trial the observed difference was 40% (35% in the late control group to 21% in the early group).

Refer to the statistical analysis section for a detailed discussion of the primary efficacy endpoint.

5. Statistical Analysis

a) **Sample size.**

To obtain a power of 80% with a level of significance <0.05 (two-tailed), a sample size of 50 patients in each group was required for the oxygenation endpoint, and 90 patients per arm for the second primary endpoint (mortality + BPD).

Reviewer's note: The reviewer's calculations show 97 patients per arm were required for the second primary endpoint.

b) **Primary efficacy endpoint analysis.**

No discussion was provided in the protocol regarding the analysis of the primary endpoints.

Reviewer's note: The sponsor expected to demonstrate a 44.4% relative difference in the combined incidence of mortality and BPD (from 45% in the late/controls to 25% in the early group). In the trial, the combined incidence of mortality and BPD was 35% in the late/control group and 21% in the early-

treated group, a relative difference of 40%. In analyzing this endpoint, the sponsor has tested the null hypothesis of 'no difference in the combined incidence of mortality and BPD between two groups' against the alternative hypothesis that ' the combined incidence of mortality and BPD is different in two groups'.

D. Results.

One hundred and ninety six patients were randomized, 96 to early and 100 to controls (late/control treatment). As in the previous study, the data were audited and revised by [redacted] after verification of source documentation. Subsequently, the sponsor elaborated their integrated summary of efficacy and safety based on these post auditing reports. Thus, the data will be referred to, in this review, as in the original report or as in the post-auditing database as appropriate. Where the data between both sources differ statistically, this review will present both data; otherwise, only the post auditing information will be presented.

Of the 196 patients randomized, the original study report accounts for 182 patients only (86 early and 96 controls), because 14 patients were excluded for protocol violations. The post auditing database includes 195 patients because one CRF was not located during the audits.

1. Neonatal Demographics

Both treatment groups (early vs. late/control) were compared for gestational age, birth weight, sex, RDS score on entry, and APGARs at 1 and 5 min.

There were no statistically significant differences between both treatment groups regarding neonatal characteristics.

Table 18 Neonatal Demographics. Euro III.

Parameter	BW*	GA*	Sex (male/female)
Early treatment	1281.9	29.8	51/44
Late /Control	1291.3	29.6	60/40
p-value	.86	.5	.39

*Mean values

APPEARS THIS WAY
ON ORIGINAL

Table 19 Neonatal characteristics (continued). Euro III.

Parameter	Early treatment	Late/Control	p-value
RDS score on entry			
1	1 (1)	5 (6)	0.83
2	18 (20)	24 (28)	
3	47 (52)	35 (41)	
4	25 (28)	21 (25)	
Missing data	4	15	
APGAR at 1 min			
0 - 2	26 (29)	20 (20)	0.89
3 - 5	35 (39)	42 (43)	
6 - 7	19 (21)	27 (28)	
8 - 10	11 (12)	9 (9)	
Missing data	4	2	
APGAR at 5 min			
0 - 2	3 (3)	1 (1)	0.38
3 - 5	23 (26)	20 (23)	
6 - 7	29 (33)	35 (39)	
8 - 10	32 (37)	33 (37)	
Missing data	8	11	

Reviewer's note: When the groups were analyzed by treatment received (i.e., early vs. late vs. controls), the controls had lower statistically significant RDS scores on entry. All other parameters were comparable among the groups.

Table 20 Neonatal Demographics by treatment received. Euro III.

	BW*	GA*	RDS score on entry*	SEX (male/female)	RDS score* (male/female)	APGAR at 1 min*	APGAR at 5 min*
Early treatment	1281.9	29.6	3.0	51/44	2.9/3.1	4.2	6.4
Late treatment	1277.6	29.4	3.2	28/25	3.3/3	4.6	6.7
Control	1306.4	29.4	2.5	32/15	2.5/2.3	4.3	6.7
p-value	0.92	0.8	0.001	0.16	-	0.49	0.67

*Mean value

As explained in the review of Euro I, 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, hence, the validity of the addition of this variable to the clinical comparability of the treatment groups is again questionable.

2. Maternal Demographics

The randomized groups (early vs. late/control) were compared for type of pregnancy (c-section vs. vaginal), number of products (single vs. multiple), and steroid used before delivery (for >48 hours, or for ≤48 hours or none used).

For patients who had information on these variables, there were no statistically significant differences between groups.

Table 21 Maternal characteristics by treatment arm. Euro III.

	DELIVERY TYPE		TYPE OF PREGNANCY		PREMATURE RUPTURE OF MEMBRANES		STEROID USE	
	C-Section	Vaginal	Single	Multiple	No	Yes	≥48 hours	<48 Hours
Early treated (N=95)	58 (62)	35 (38)	76 (81)	18 (19)	64 (83)	13 (17)	2 (3)	76 (97)
Late/Controls (N=100)	52 (53)	46 (47)	78 (78)	22 (22)	70 (84)	13 (16)	3 (4)	80 (96)
p-value	0.23		0.73		1		1	

Reviewer's note: When the groups were analyzed again by treatment received (early vs. late vs. controls) there were no statistically significant differences, although in the control group the type of delivery had a different pattern than that seen in the early and the late treated groups (more vaginal deliveries than c-sections).

Table 22 Maternal characteristics. Number (percent)of patients. Euro III.

	DELIVERY TYPE		# OF BABIES DELIVERED		STEROID USE	
	C-Section	Vaginal	Single	Multiple	>48 hours	<48 Hours
Early Treated (N=95)	58	35	76	18	2	76
Late (N=53)	32	21	42	11	1	44
Control (N=47)	20	25	36	11	2	36
p- Value	0.07		0.59		0.59	

3. Primary Efficacy endpoint.

a) Mortality at 28 days.

The original study report stated that at 28 days, 9.3% of the early group died, vs. 22% of the late/control group. The post auditing database reports that the mortality rate at 28 days was 13% vs. 25% respectively. Both sources of data revealed a statistically significant difference (p-value <0.05) in favor of the early treated group.

If patients with missing data for this endpoint were included as deaths, the early treated group continued to be numerically better, but the two groups were not statistically significantly different.

Table 23 Mortality at 28 days using the post auditing database. Number/total (percentage) of patients. Euro III.

Treatment Group	Excluding pts. with missing data	Pts. with missing data included as deaths.
Early treated	12/92 (13)	15/95 (16)
Late/Controls	24/98 (25)	26/100 (26)
p-value[1]	0.044	0.08
Late	13/52 (25)	14/53 (26)
Controls	11/46 (24)	12/47 (25)

[1]P-value from Pearson's Chi-Square

Stepwise regression analysis was used to determine which baseline and demographic characteristics (gestational age class, birth weight class, RDS severity score, Apgar score at 1 and 5 minutes, gender, age at randomization, type of delivery, type of pregnancy, premature rupture of membranes and maternal corticosteroid use prior to delivery) had a significant effect on mortality rates and rates of survival without BPD. Treatment group was also included as a factor in the stepwise regression model. A logistic regression was then used to calculate the significance of the factors identified by the stepwise regression model for each study.

Reviewer's note: There were 5 patients without information on mortality at 28 days. Of them, 3 were randomized to the early treated group: P00001, P00005, and P00006 (these patients did not have any further information on any complication including BPD at 28 days) and one patient each to the late group, L00119, and the controls, C00058. Patient L00119 has date of birth 4/1/90 and date of death 7/7/90, thus, this patient died after day 28 and had BPD reported as positive at day 28. Patient C00058 had date of birth 4/18/89 and a note stating the age of death as 7 hours. When all patients with missing data were analyzed as deaths, the difference between treatment groups was not statistically significant.

When the rate of mortality was analyzed within the late/control group, the addition of surfactant did not appear to change the mortality rate between the late treated group (25%) and the controls (24%); no statistically significant difference was shown between both groups. An analysis of the incidence of mortality to the end of the study showed that only one patient died after day 28 in the early treated group and none in the late/control group. In this analysis the patients without information were included as deaths.

The regression analyses were conducted in a post-hoc fashion. To fit the logistic model to the mortality data as discussed above, due to missing values for the response or explanatory variables, the sponsor deleted 104 out of 195 observations! The sponsor found only 'gestation age class' as a significant variable, i.e., other variables including treatment were reported non-significant. The statistical reviewer followed the same procedure with fewer response variables, namely, gestational age class, birth weight class, RDS severity score., Apgar score at 5 minutes, gender and type of delivery. This resulted in loss of 44 data points (as compared to 104) due to missing values of explanatory variables.

In the analysis, all the variables mentioned above, except gender and gestational age class, showed significance. The adjusted p-values are reported below.