TABLE 1. Patients who received Infasurf. (percentage) of evaluated patients.

	Prophylaxis Population* [N=627]	Rescue Population* [N=621]
Gestational Age (weeks)		
29	99/99 (100)	64/101 (63)
30	123/123 (100)	70/134 (52)
31	158/158 (100)	58/161 (36)
32	247/247 (100)	72/225 (32)
All	627/627 (100)	264/621 (43)
Birth Weight (grams)		
≤ 1250	99/99 (100)	44/83 (53)
1251-1500	154/154 (100)	82/157 (52)
1501-1750	165/165 (100)	78/185 (42)
> 1750	209/209 (100)	60/196 (31)
All	627/627 (100)	264/621 (43)

* of patients treated with Infasurf / total of patients in subgroup (percentage).
Cross Reference: Data Listing 1 of Case Report Tabulations (NDA Section XI)

TABLE 2. Efficacy variables per treatment group. (percentage) of patients.

PARAMETER	Prophylaxis Population [N=627]	Rescue Population [N=621]	p-Value
Moderate RDS	39 (6)	79 (13)	< 0.0001
Severe RDS	5 (1)	15 (2)	0.023
PIE	3 (<1)	3 (<1)	0.991
Pneumothorax	8 (1)	11 (2)	0.475
Any air leak	10 (2)	12 (2)	0.651
Total deaths	3 (<1)	11 (2)	0.030
Survival with no O2 at 28 days	599/627 (96)	568/621 (92)	0.003
BPD	29/624 (5)	44/612(7)	0.07
Total Deaths	3 (<1)	11 (2)	0.030
Death due to RDS	0 (0)	1 (<1)	0.315
Death at 7 days	2 (<1)	8 (1)	0.055
Death at 28 days	3 (<1)	9 (2)	0.079
Survival to discharge	624 (99.5)	610 (98)	0.033

Cross Reference: Data Listing 3 and 4 of Case Report Tabulations (NDA Section XI)

TABLE 3. Mortality by Gestational Age and Birth Weight – (Percentage) of Evaluated Patients

	Prophylaxis Population [N=627]	Rescue Population [N=621]	p-Value
Gestational Age (weeks)			
≤ 29	0/99 (0)	5/101 (5)	0.059
30	2/123 (2)	3/134 (2)	NS
31	1/158 (1)	1/161 (1)	NS
≥ 32	0/247 (0)	2/225 (1)	NS
All	3/627 (1)	11/621 (2)	0.033
Birth Weight (grams)			
≤ 1250	0/99 (0)	4/83 (5)	0.042
1251-1500	1/154 (1)	4/157 (3)	NS
1501-1750	2/165 (1)	3/185 (2)	NS
> 1750	0/209 (0)	0/196 (0)	NS
All	3/627 (<1)	11/621 (2)	0.033

Cross Reference: Data Listing 4 of Case Report Tabulations (NDA Section XI)

Safety

The most frequently reported complication documented among neonates in the prophylaxis population were PDA (21%), IVH (13%) and sepsis (6%). In the rescue population, the most frequently documented events were the same: PDA (26%), IVH (14%) and sepsis (6%).

With the exception of PDA, there were no statistically significant differences in most of the complications commonly found in this set of the population between the prophylaxis and treatment groups. TABLE 4 presents the incidence of the most common complications of prematurity in the prophylaxis and the rescue population.

TABLE 4. Incidence of Complications of Prematurity.

Parameter	Prophylaxis Population [N=627]	Rescue Population [N=621]	p-Value
IVH	79/627 (13)	84/621 (14)	0.627
PVL	15/627 (2)	7/621 (1)	0.159
Pulmonary hemorrhage	0/627 (0)	2/621 (<1)	0.155
Patent ductus arteriosus	130/627 (21)	159/621 (26)	0.041
Necrotizing enterocolitis	30/627 (5)	28/621 (5)	0.817
ROP	23/500 (5)	12/489 (3)	0.188
Retrolental fibroplasia	2/510 (< 1)	1/501 (< 1)	0.574
Shock	12/626 (2)	17/620 (3)	0.334
Seizure	11/627 (2)	5/620 (1)	0.137
Sepsis	38/627 (6)	37/621 (6)	0.939
Home on oxygen	19/627 (3)	28/621 (5)	0.170

Cross Reference: Data Listings 6A and 6B of Case Report Tabulations (NDA Section XI)

D. Comments

Even though this protocol has some flaws mentioned below, it does provide interesting comparisons of outcomes between the prophylaxis and the treatment arms in the different age and birth weight subsets.

The study report does not provide follow up information on patients excluded after randomization: one hundred and fifty patients (79 patients in the prophylaxis and 71 patients in the rescue groups) were withdrawn after randomization because either they did meet exclusion criteria (148 patients), their data was lost (1 patient), or the patient was born outside of the site (1 patient). TABLE 5 presents the causes of withdrawal.

TABLE 5. Causes of withdrawal of patients.

Number of Infants	Prophylaxis Population	Rescue Population
Total number dropped from study	79	71
Reason dropped from study		
Congenital anomalies	32	30
Congenital sepsis/pneumonia	22	23
Judged too mature	22	17
Severe perinatal asphyxia	2	0
Lost data	1	0
Not born at a clinical site	0	1

In addition, the definitions of RDS (mild, moderate or severe) do not include PaO2 or any other oxygenation parameter reflective of the patient's gas exchange status, leaving the diagnosis per se and the assignment of severity of RDS up to the individual investigator's style of patient management. The assignment of BPD included patients with oxygen supplementation at 28 days, and "those that the investigator answered yes, (as with BPD) in the CRF" -It is unknown what was the criteria followed by the investigators for determination of BPD, and what was the proportion of patients who received this assignment. There is no validation of the cause of death assignments - total death was mostly due to causes other than respiratory (there were only 3 patients classified as with a respiratory cause of death, all in the rescue group). Only one case had assigned RDS as a cause of death. These facts, in an open label trial make the results difficult to interpret.

Nevertheless, the value of this trial rests on the comparison of outcomes by birth weight and gestational age between groups where the surfactant was given as prophylaxis and when it was given when the patient already had mild RDS. Its results point out that the risk of developing RDS is greater than 50% at < 30 weeks of gestational age, and at a birth weight of < 1500 g. Prophylactic treatment was statistically significantly lower in mortality of any cause in those patients of <29 weeks gestational age and < 1250 g of birth weight, even though we have to have in mind that the mortality rate in any case was low and that the causes of death were categorized mostly as not related to respiratory causes.

3. Study 9303/ Interim Open-label Trial of Infasurf . Ref. Vol 1.33.

A. Study Characteristics and Definitions.
This was a phase III, multicenter (8 centers), open label, uncontrolled, not randomized trial. One hundred ninety-seven infants were enrolled; 72 infants were treated in the prophylaxis population, 118 were treated in the rescue treatment population and seven infants were treated after failing therapy with another surfactant. Prophylaxis treatment with Infasurf was offered to infants whose calculated gestational age was less than 29 weeks. Infants with documented lung maturity before birth were excluded. Rescue treatment was offered if the infant had RDS, was intubated, had not been treated with another surfactant, and required more than 40% oxygen to maintain PaO_2 > 80 torr or had an arterial:alveolar PO_2 (a/A PO_2) < 0.22. Infants who were initially treated with another surfactant were eligible to enter into the study if they had severe and progressive RDS which was defined as mean airway pressure (MAP) of > 10 cm H_2O and FiO_2 > 60%. All infants received the same dose of Infasurf (3 mL/kg of 35 mg of

phospholipid /mL) regardless of treatment population. Prophylaxis infants received a total of three doses of study drug. The first dose was administered at birth and repeat doses were given 12 and 24 hours later if endotracheal intubation was still in place. Rescue treatment and surfactant failure patients received a total of two doses; the second dose was administered 12 hours after the initial dose if endotracheal intubation was still in place.

The primary efficacy endpoint was the incidence of RDS for the prophylaxis group, and the incidence of RDS-related air leaks for the rescue treatment and surfactant failure groups. Secondary outcomes were severity of RDS and incidence of RDS-related air leaks (for the prophylaxis group only), RDS deaths, total deaths and BPD (for all groups).

B. Objectives.

The primary objective was the collection of additional efficacy and safety data on patients treated with Infasurf for prophylaxis of respiratory distress syndrome (RDS) or treatment of RDS. A secondary objective was to provide a mechanism to allow clinical sites who had participated in the Surfactant Comparison Trial (Protocol 9101) to administer Infasurf to their patients, if they wished, on an interim basis.

C. Results.

(1) Demographic Characteristics

TABLE 1. Demographic Characteristics

PARAMETER	PROPHYLAXIS (N=72)	RESCUE TREATMENT (N=118)	SURFACTANT FAILURE (N=7)
Birth weight (grams)*	916	1658	1517
Gestational age (wks)*	27	31	30
Sex (male)	41 (57)	68 (58)	4 (57)
Race (Caucasian)	50 (69)	96 (81)	6 (86)
Apgar score 1 min.* 5 min.*	 4 7	 6 7	 5 8

* Mean

Cross Reference: Data listing 1 of Case Report tabulations (NDA section XI)

(2) Efficacy

For the prophylaxis group, 22% of the patients developed RDS (defined as a CXR positive for RDS at 16 to 32 hours and a requirement of FIO2 ≥ 30% at the time of the CXR, to maintain PaO2> 50 torr). In the Prophylaxis arm of the Study 9101- SCT, the incidence of RDS (its definition was similar to this one) was 16% (Mean birth weight was 896 g) in the Infasurf group and 47% in the Exosurf group (Mean birth weight = 900 grams).

RDS-related air leaks included pneumothoraces and parenchymal interstitial emphysema (PIE). In the rescue treatment and surfactant failure group, there were 22% and 29% incidence of any RDS-related air leak respectively. In Study 9101- SCT, the treated arm of the Infasurf group (mean birth weight =1648 g) had an incidence of RDS-related air leaks of 10.5 to 14% , and the Exosurf group (mean birth weight = 1564 g), had an incidence of 22 to 25%.

TABLE 2. Incidence of Air Leaks in Study Populations - (Percentage) of Patients

Parameter	Prophylaxis Population [N=72]	Rescue Treatment Population [N=118]	Surfactant Failure Population [N=7]
Any Air Leak	17 (24)	26 (22)	2 (29)
PIE	12 (17)	11 (9)	–
Pneumothorax	4 (6)	20 (17)	–

–Not Assessed
Cross Reference: Data Listing 4 of Case Report Tabulations (NDA Section XI)

The secondary outcomes are presented in TABLE 3. Even though the study populations were similar to that of study 9101-SCT, the incidence of RDS death and total mortality in this trial were markedly higher than those registered in the Infasurf group of Study 9101-SCT (For the prophylaxis group RDS death was 2.1% and total death to 28 days was 12%; for the rescue group RDS death was 3.5% and total mortality to day 28 was 8%). The reasons for this increase are not clear.

TABLE 3. Secondary Efficacy Outcomes - (Percentage) of Patients

Parameter	Prophylaxis Population [N=72]	Rescue Treatment Population [N=118]	Surfactant Failure Population [N=7]
Severity of RDS None Mild Moderate Severe	 56 (78) 10 (14) 0 (0) 6 (8)	N/A	N/A
RDS Deaths	10 (14)	9 (8)	2 (29)
Total Deaths	16 (22)	11 (9)	2 (29)
Survival to Discharge	56 (78)	107 (91)	5 (71)

N/A = Not applicable (as an efficacy outcome)
Cross Reference: Data Listing 5 of Case Report Tabulations (NDA Section XI)

(3) Safety

The complications most frequently reported in the prophylaxis population were PDA (57%), followed by IVH (43%), sepsis (28%), pulmonary hemorrhage (13%) and PVL (11%). In the rescue treatment population, the most frequently reported complication of prematurity was PDA (45%) followed by IVH (23%) and sepsis (18%).

The safety outcomes are difficult to compare with those reported in other clinical studies of Infasurf because of the method used to collect the data. (In the case report form they were entered as "other complications" where some investigators reported some events based on different criteria).

No adverse events were collected or reported as drug-related during its administration.

D. Comments.

This small, open-label, non-randomized, non-controlled trial offered little valid data in efficacy and safety outcomes to be compared with other clinical studies.

4. **Protocol 8701/ National Trial of INFASURF Administration at Birth in Premature Infants. Ref Vol. 1.31**

A. **Study Characteristics and Definitions.**

This is an open label, uncontrolled, multicenter (19 centers) trial originally designed to evaluate the safety of Infasurf when used as prophylaxis or for the treatment of RDS. A total of 13,278 infants were enrolled and treated within the study; all were evaluable for efficacy and safety analysis. A total of 9,536 infants were administered Infasurf as a prophylactic treatment and 3,742 infants were given Infasurf in the treatment population.

The primary efficacy endpoints assessed for the prophylaxis population were the incidence of RDS, the incidence of chronic lung disease and the incidence of mortality secondary to RDS. The secondary efficacy endpoints for the prophylaxis population were the incidence of RDS-related air leak syndromes, oxygenation and ventilatory requirements, total mortality, total neonatal mortality, and survival to discharge from the hospital.

In the treatment population, the primary efficacy endpoints were the incidence of RDS-related air leak syndromes, the incidence of chronic lung disease, and mortality secondary to RDS. The secondary efficacy endpoints assessed were oxygenation and ventilatory requirements, total mortality, total neonatal mortality, and total survival to discharge from the hospital.

The dose of Infasurf was: 3 mL /Kg (35 mg of phospholipids/mL suspension). In the prophylaxis arm it was given as a single dose. It could be repeated every 4 hours up to 3 doses, if the patient developed severe RDS. In the treatment arm, Infasurf was given up to three doses if the patient met criteria. Originally, repeat doses were administered at least 12 hours apart. As of 1/11/90 the interval between doses was decreased to 8 hours.

Changes in the definition of Severe RDS:

On 1/26/89 : 70% FiO_2 and MAP ≥12 cm H_20 for PaO_2≤50-70 torr, and PCO_2 40-55 torr

On 7/13/89: 60% FiO_2, and MAP ≥10 cm H_20 for PaO_2≤50-70 torr, and PCO_2 40-55 torr

On 9/3/92: $FiO_2 \geq 40\%$, MAP ≥ 8 cm H_2O, and $PaO_2 \leq 80$ torr or arterial/alveolar $PO_2 \leq 0.33$.

The following changes were made to Case Report Forms: four case report forms were utilized during the conduct of the study. After the study was initiated, no CRF changes were submitted to FDA. The four CRF's and the extent of use of each are presented below.

1987 CRF
The Infasurf Patient Report Form 1987 was the most detailed and was completed for 2120 infants who were treated prophylactically with Infasurf. It was to be used for all patients enrolled through April 30, 1988, and is referred to as the "long form" throughout the report.

1988 CRF
Infasurf Report Form 1988 contained the same categories of information as the 1987 CRF, however, demographic information, and respiratory support information were less detailed. CRF's were completed for 1871 prophylaxis patients and 99 treatment patients. This CRF was to be used in the period from May 1, 1988 to February 28, 1989 and is also referred to as the "long form" throughout the report.

1989 CRF
Infasurf Report Form 1989 collected data similar to the 1988 CRF, however, respiratory status following treatment was requested. "Cause of death" was added to the form. CRF's were completed for 2270 prophylaxis patients and 995 treatment patients. This CRF was to be used in the period from March 1, 1989 to January 31, 1990 and is also referred to as the "long form" throughout the report.

1990 CRF
A substantially condensed, two-part CRF was issued in 1990. It was comprised of a Patient Enrollment Log and an Adverse Event / Death Report. This CRF is referred to as the "short form" throughout the report. CRF's were completed for 3275 prophylaxis patients and 2648 treatment patients. The 1990 CRF was to be used in the period from February 1, 1990 through December 31, 1993.

B. Objectives.

Retrospectively, the objective of the study was expanded to assess the effectiveness of Infasurf administration as well as the safety of Infasurf.

C. Results

(1) Efficacy

Prophylaxis Population

A total of 9,536 infants were administered Infasurf for prophylaxis; for 6,261 patients, study data were recorded on the long CRF forms (patients enrolled from 1987 to 1990), and for 3,275 patients, study data were documented on the short CRF form (patients enrolled from 1990 to 1993). The mean birth weight was 1255.5 grams and the mean gestational age was 28.8 weeks.

In the prophylaxis population, 26% of the infants had RDS, defined as the need for ≥ 30% oxygen at 24 hours of age. PIE was reported in 4.3% of the patients, 6.8% had a pneumothorax and 9.1% were noted to have any air leak. RDS and air leaks were recorded only on the long form CRF's.

The incidence of RDS and air leaks was assessed by birth weight and gestational age, (GA) and were noted to be inversely proportional to the birth weight and GA. (TABLES 1 AND 2).

TABLE 1. Incidence of RDS and Air Leaks* by Birth Weight Groups - Prophylaxis Population.

Parameter	< 700 g [N=938]	700 - 1100 g [N=3016]	> 1100 g [N=5553]
RDS Number	234 (44.2) 529	628 (35.0) 1793	755 (19.3) 3920
PIE Number	65 (12.5) 519	118 (6.6) 1786	82 (2.1) 3914
Pneumothorax Number	88 (16.9) 520	163 (9.1) 1786	168 (4.3) 3917
Any Air Leak Number	122 (23.3) 524	237 (13.3) 1786	206 (5.3) 3919

Number = of patients with available data.
( ) Percentage of patients.
* RDS and air leaks were recorded on long form CRF's only.
Cross Reference: Data Listing 4 of Case Report Tabulations (NDA Section XI)

TABLE 2. Incidence of RDS and Air Leaks* by Gestational Age Groups -Prophylaxis Population-

Parameter	< 29 Weeks (N=4319)	≥ 29 Weeks (N=5201)
RDS	932 (38.2)	688 (18.1)
Number	2439	3811
PIE	206 (8.5)	60 (1.6)
Number	2423	3804
Pneumothorax	278 (11.5)	146 (3.8)
Number	2425	3806
Any Air Leak	390 (16.1)	180 (4.7)
Number	2429	3806

Number = of patients with available data.
( ) Percentage of patients.
* RDS and air leaks were recorded on long form CRF's only.
Cross Reference: Data Listing 4 of Case Report Tabulations (NDA Section XI)

Chronic lung disease [bronchopulmonary dysplasia (BPD)] was diagnosed by the attending neonatologist in 1375 (24.2%) of the 5678 prophylaxis patients with data recorded.

Mean airway pressure (MAP) and fraction of inspired oxygen (FiO_2) decreased within 24 hours after Infasurf treatment in the prophylaxis population. A decrease in MAP of almost 5 cm H_2O was noted after 72 hours, and the FiO_2 decreased from over 50% immediately after treatment to less than 30% at 24 hours. Statistically significant changes ($p<0.05$) in both the MAP and FiO_2 from baseline were noted at 24, 48, and 72 hours.

Of the 9536 evaluable patients in the prophylaxis population, 3.0% (290 patients) died of RDS, 7.2% (690 patients) died by Day 7 and 10.2% (974 patients) died by Day 28. Among the evaluable patients in the prophylaxis population, 88% (8395 of 9536) survived to discharge from the hospital. Mortality was inversely proportional to birth weight and GA. TABLE 3 shows the proportion of patients who died during the study at 7 and 28 days, and to discharge.

TABLE 3. Patients Who Died During the Study - Prophylaxis Population

Survival / Death	Prophylaxis Population [N=9536]
RDS Death	290/9536 (3.0)
Death by 7 Days (any cause)	690/9536 (7.2)
Death by 28 Days (any cause)	974/9536 (10.2)
Survival to Discharge	8395/9536 (88.0)

( ) Percentage of patients.
Cross Reference: Data Listing 5 of Case Report Tabulations (NDA Section XI)

Treatment Population

A total of 3,742 infants were administered Infasurf in the treatment population.

The average birth weight in the treatment population was 2,016.1 grams and the average gestational age was 32.4 weeks.

In the treatment population, 15.2% were noted to have PIE, 20.7% had a pneumothorax, and 27.0% were noted to have any air leak syndrome. TABLE 4 shows the incidence of air leaks in the treatment population.

TABLE 4 Incidence of Air Leaks* - Treatment Population

Measured Parameter	Treatment Population [N=3742]
PIE	166/1093 (15.2)
Pneumothorax	226/1093 (20.7)
Any Air Leak	295/1094 (27.0)
BPD	256/1094 (23.4)

Denominator = number of patients with available data
* Air leaks were recorded on long form CRF's only.
Cross Reference: Data Listing 4 and 6 of Case Report Tabulations (NDA Section XI)

BPD was diagnosed by the attending neonatologist in 256 (23.4%) of the babies with data.

In the treatment population, 4.4% (164 of 3742 patients) of the patients died of RDS. Of the 3,742 evaluable patients in the treatment population, 7.1%

(267 patients) died by Day 7 and 10.5% (392 patients) of patients died by Day 28. Among the evaluable patients, 87.8% (3285 of 3742) in the treatment population survived to discharge. The incidence of death due to RDS and death by 7 and 28 days were inversely proportional to the birth weight groups.

(2) Safety:

The most frequently documented complications of prematurity among neonates in the prophylaxis population were: patent ductus arteriosus (PDA) (27.7%), intraventricular hemorrhage (IVH) (19.7%), retinopathy of prematurity (ROP) (17.5%), and sepsis (13.3%). In general, the incidence of complications of prematurity in the birth weight groups and the gestational age groups were inversely proportional to the birth weights and the gestational ages of the neonates. TABLE 6 presents the incidence of complications of prematurity in the prophylaxis population.

TABLE 5. Incidence of Complications of Prematurity - Prophylaxis Population

Parameter	Prophylaxis Population [N=9536]
IVH	1222/6189 (19.7)
IVH Grade I	562/6189 (9.1)
IVH Grade II	188/6189 (3.0)
IVH Grade III	205/6189 (3.3)
IVH Grade IV	254/6189 (4.1)
Pneumonia	462/5020 (9.2)
PDA	1730/6240 (27.7)
Sepsis	830/6224 (13.3)
NEC	431/6223 (6.9)
PVL	106/4001 (2.6)
RLF	84/6069 (1.4)
ROP	1063/6079 (17.5)

Denominator = of patients with available data.
( ) Percentage of Patients
Cross Reference: Data Listing 3 of Case Report Tabulations (NDA Section XI)

Of the 9,536 patients evaluable, 1,141 infants (12.0%) had died prior to discharge from the hospital. The most frequently reported cause of death was RDS (3.0%) followed by bacterial infection and septicemia (1.5%), lung hypoplasia syndromes (1.2%), NEC (1.0%), renal failure (0.9%), and chronic lung disease (0.9%).

The most frequently documented complications of prematurity in the treatment population were: PDA (38.5%), IVH (21.7%), pneumonia (17.2%), and sepsis (15.6%). In general, the incidence of adverse events in the birth weight groups and the gestational age groups were inversely proportional to the birth weights of the infants and the gestational ages.

TABLE 6. Incidence of Complications of Prematurity - Treatment Population

Parameter	Treatment Population [N=3742]
IVH	232/1070 (21.7)
IVH Grade I	68/1070 (6.4)
IVH Grade II	45/1070 (4.2)
IVH Grade III	54/1070 (5.0)
IVH Grade IV	53/1070 (5.0)
Pulmonary Hemorrhage	45/1093 (4.1)
Pneumonia	69/402 (17.2)
PDA	420/1091 (38.5)
Sepsis	170/1091 (15.6)
NEC	29/1092 (2.7)
PVL	29/1060 (2.7)
RLF	18/1058 (1.7)
ROP	101/1059 (9.5)

Number = Number of patients with available data.
( ) Percentage of Patients
Cross Reference: Data Listing 3 of Case Report Tabulations (NDA Section XI)

Of the 3742 patients in the treatment population evaluable for safety at the time of discharge, 12.2% (457 patients) had died prior to discharge. The most frequently reported cause of death was RDS (4.4%) followed by bacterial infection and sepsis (1.7%), chronic lung disease (1.4%), and lung hypoplasia syndromes (1.0%).

Patients Who Died:

Prophylaxis Population
Of the 9,536 patients in the prophylaxis population evaluable for safety, 1,141 patients (12.0%) died prior to discharge and 290 patients (3.0%) died due to RDS.

The most frequently reported cause of death was RDS (3.0%) followed by bacterial infection and septicemia (1.5%), lung hypoplasia syndromes (1.2%), NEC (1.0%), renal failure (0.9%), and chronic lung disease (0.9%).

Treatment Population
In the treatment population, 457 patients (12.2%) died prior to discharge and 164 (4.4%) of the patients died due to RDS.

The most frequently reported cause of death was RDS (4.4%) followed by bacterial infection and septicemia (1.7%), chronic lung disease (1.4%), and lung hypoplasia syndromes (1.0%).

C. Comment

The meaning of the results of this large, open label, non randomized, non-controlled study are further complicated by a series of changes made in the definition of some of the primary endpoints and entry criteria, and on the CRF's for the collection of data through the years that the study was conducted. Several of the variables measured were not objectively defined. Some of the necessary diagnostic procedures and tests to better define the variables studied, e.g., CXR's, sonograms, were later on left up to the individual investigator, following the standard of care of each center. The latter makes variables like incidence and severity of RDS, incidence of IVH, incidence of air leaks and even RDS death impossible to define across the centers and along the years that the study lasted. The incidence of adverse events during administration of the surfactant was not addressed uniformly,

since it was not entered in the CRF's as such. This study report could be looked at as the report of a complicated combination of at least three different studies, with changes in their entry and retreatment criteria with 4 different CRF's intertwined.

This report, as submitted, can not support any conclusion on safety or efficacy of Infasurf, except on that of the incidence of total mortality in both arms, which are consistent with those obtained in well controlled studies.

V. Integrated Summary of Safety

The safety database for Infasurf was generated by pooling 3 controlled studies submitted by the sponsor to the NDA: the two pivotal studies, 9101 SCT-P and 9101 SCT-T, comparing Infasurf to Exosurf, and the only other controlled study ISCT-92, where Infasurf was compared to Survanta. A total of 3,098 patients were studied, 1,554 received Infasurf and 1,544 received an active control drug (Exosurf=978, and Survanta=566 patients). The 4 non-controlled, open label studies submitted by the sponsor have been reviewed and discussed individually in the previous section. None of them add new information to the present discussion.

Since the population involved in these three studies differed significantly in some relevant variables, i.e., birth weight, gestational age, respiratory status at entry into the study, etc., for some variables the studies were pooled by indication: for the prophylaxis (or prevention), and for the treatment (or rescue) of RDS; and the variables were presented as such.

Prophylaxis studies: Study 9101 SCT-P and Study 9201 ISCT-92 prophylaxis arm; involved 1,310 patients;

Treatment studies: Study 9101 SCT-T and 9201 ISCT-92 treatment arm; involved 1,788 patients.

Besides some differences in the definition of some of the variables studied, and in the method used to collect and analyze some of the data, the studies were deemed sufficiently similar to be able to generate meaningful data when combined in this safety database. Maybe one of the more obvious differences between the two controlled studies was the method of administration of Infasurf. In the SCT-P and T, it was given following the Exosurf labeling instructions: given through a side port in two aliquots. The prophylaxis trial provided for retreatment up to a total of 3 doses, and the treatment trial

up to 2 total doses given 12 hours apart. In the ISCT-92, Infasurf was given following the Survanta labeling instructions: through a feeding tube inserted just about the tip of the endotracheal tube, in four aliquots. Both, the prophylaxis and the treatment arm, could retreat up to a total of 3 doses at least 6 hours apart.

Pooling of all treated patients, however, of both prophylaxis and treatment populations, was also done for some particular variables, in an effort to obtain better estimates of adverse event incidence. These analysis will also be presented.

Because of the nature of the disease studied, it will be difficult to strictly separate some safety issues from efficacy outcomes, i.e., mortality and common complications encountered in the population studied. Thus, this section will review mortality, complications of prematurity and adverse events during administration of the surfactant as they relate in this NDA to measurements of safety. In the efficacy section they will be referred to and analyzed from the efficacy standpoint, to answer the question of the effectiveness of Infasurf related to active controls.

1. Demographic Characteristics

A. Prophylaxis Population

A total of 1,310 patients entered in the two randomized, double blinded, and well controlled studies. Six hundred fifty five patients were exposed to Infasurf and 655 patients received an active control drug (Exosurf=422 patients, Survanta=233 patients). TABLE 1 shows some of the demographic characteristics of the prophylaxis population studied.

TABLE 1. Demographic characteristics. -Prophylaxis population.

Parameter	Study 9101 SCT-P		Study 9201 ISCT-92 (Prophylaxis arm)	
	Infasurf	Exosurf	Infasurf	Survanta
Birth Weight (grams)				
N	431	422	224	233
Mean	895.7	899.8	886	878
Std. Dev.	236.0	241.9	234	238
Gestational Age (weeks)				
N	431	422	224	233
Mean	26.5	26.5	26.3	26.3
Std. Dev.	1.6	1.6	1.8	1.8
Sex (%)				
N	431	422	224	233
Males	222 (52)	236 (56)	117 (52)	113 (49)
Race (%)				
N	431	422	224	233
White	244 (57)	240 (57)	103 (46)	101 (43)
Apgar 1 minute				
N	429	420	224	233
Mean	4.5	4.4	4.2	4.1
Std. Dev.	2.3	2.4	2.4	2.3
Apgar 5 minute				
N	429	421	224	233
Mean	7.1	7.0	6.4	6.4
Std. Dev.	1.7	1.8	1.9	1.8

COMMENTS:
The patients included in the sample size of the prophylaxis trials present in general a balance in the demographic characteristics across the studies.

B. Treatment Population

A total of 1,788 patients entered in the two studies, 899 patients were exposed to Infasurf and 889 patients received and active control drug (Exosurf=556 patients, Survanta=333 patients). TABLE 2 shows some of the demographic characteristics of the treatment population studied.

TABLE 2: Demographic characteristics. - Treatment population

Parameter	Study 9101 SCT-T		Study 9201 ISCT-92 (Treatment arm)	
	Infasurf	Exosurf	Infasurf	Survanta
Birth Weight (grams)				
N	570	556	329	333
Mean	1648.2	1563.7	1171	1165
Std. Dev.	720.8	680.0	414	402
Gestational Age (wks)				
N	570	556	329	333
Mean	31.0	30.6	28.3	28.2
Std. Dev.	3.5	3.3	3.0	2.9
Sex (%)				
N	570	556	329	333
Males	327 (57)	347 (62)	189 (57)	191 (57)
Race (%)				
N	567	552	329	333
White	401 (71)	375 (68)	165 (50)	159 (48)
Apgar 1 minute				
N	559	543	329	333
Mean	5.5	5.3	4.3	4.2
Std. Dev.	2.4	2.6	2.4	2.5
Apgar 5 minute				
N	559	543	329	333
Mean	7.4	7.2	6.4	6.5
Std. Dev.	1.7	1.9	2.0	2.1
Respiratory status at entry (Mean ± St. Dev.				
N	570	556	329	333
FIO_2	0.75 ±0.21	0.74 ±0.21	0.74 ±0.22	0.75 ±0.23
PO_2	62.9 ±23.8	61.0 ±21.4	63 ±30	66 ±33
PCO_2	41.6 ±9.1	42.2 ±9.7	44 ±13	43 ±11
a/A Ratio	0.14 ±0.05	0.14 ±0.05	0.15 ±0.06	0.15 ±0.07

COMMENTS

The treatment population in the ISCT-92 was younger and lighter than the population in study 9101 SCT-T (the entry criteria in study ISCT-92 required patients to be <2,000 g of birth weight to be eligible, study SCT-T did not make such restriction), with lower Apgar scores at 1 and 5 min. However, the respiratory status at entry, is comparable in both studies. The study entry criterion for presence of RDS was the same: a CXR diagnostic of RDS and a/A $PO2 \leq 0.22$.

2. Mortality

Mortality was analyzed by cause as follows:

- RDS deaths - death primarily due to RDS and its complications, occurred at ≤14 days of age.
- Respiratory deaths - deaths due to respiratory causes other than RDS, and
- Total neonatal mortality - defined as all deaths, from any cause, that occurred during the hospital stay at 7 and 28 days, and to discharge.

TABLE 3 presents mortality analyzed by cause in the prophylaxis population, TABLE 4 presents the data in the treatment population. TABLE 5 presents the pooled data from all patients treated in the 3 controlled studies.

TABLE 3. Mortality by cause. - Prophylaxis populations.

Mortality by Cause	ITT Population (N=853)			ITT population (N=457)		
	Infasurf (N=431)	Exosurf (N=422)	p-Value	Infasurf (N=224)	Survanta (N=233)	p-Value
7 days	31 (7)	47 (11)	0.05	22 (10)	7 (3)	<0.01
28 days	52 (12)	68 (16)	0.1	26 (12)	15 (6)	0.07
Total Mortality (to Discharge)	77 (18)	82 (19)	0.56	40 (18)	25 (11)	0.03
Respiratory Mortality	15 (3)	18 (4)	0.6	14 (6)	9 (4)	0.29
RDS Mortality	7 (2)	23 (5)	0.004	10 (4)	0 (0)	<0.01
Survival to Discharge	354 (82)	340 (81)	0.56	184 (82)	208 (89)	0.03

COMMENTS

Infasurf treated patients had a statistically significantly lower incidence of RDS mortality and total mortality at 7 days when compared with Exosurf. The statistical significance was lost at 28 days and to discharge. In the ISCT-92 study, Survanta had statistically significantly lower incidence in total mortality at 7 days and to discharge, as well as in RDS mortality. Further discussion of the findings pertaining this variable and the explanation offered by the sponsor of an "unusual and unexpected survival rate of the <600 g population in the Survanta group, which drove the data to reach statistical significance" can be found in the section dedicated to the review of the ISCT-92 prophylaxis trial study. The improved survival found in the Survanta prophylaxis population can not be explained by an unbalance on any of the entry criteria or demographic characteristics. In fact, Survanta patients were lighter than their counterparts. The meaning and implication of these findings in the determination of overall safety of Infasurf need further internal discussion and will be presented to the Advisory Committee members for their recommendation.

TABLE 4. Mortality by cause. -Treatment populations.

Mortality by Cause	ITT Population (N=1126)			ITT population (N=662)		
	Infasurf (N=570)	Exosurf (N=556)	p-Value	Infasurf (N=329)	Survanta (N=333)	p-Value
7 days	34 (6)	34 (6)	0.91	36 (11)	34 (10)	0.80
28 days	47 (8)	58 (10)	0.21	50 (15)	45 (14)	0.58
Total Mortality (to Discharge)	52 (9)	69 (12)	0.07	63 (19)	58 (17)	0.62
Respiratory Mortality	9 (2)	16 (3)	0.16	23 (7)	16 (5)	0.25
RDS Mortality	23 (4)	23 (4)	1.00	20 (6)	26 (8)	0.45
Survival to Discharge	518 (91)	487 (88)	0.07	266 (81)	275 (83)	0.62

COMMENTS

The incidence of mortality was similar in all treatment groups by cause or age. There is a numerical trend favorable to Infasurf in total mortality to discharge related to Exosurf. In this study Survanta did not reach the spectacular difference in mortality found in the prophylaxis arm.

TABLE 5. Mortality . - Pooled populations.

Mortality by cause	ITT population (N= 3098)		
	Infasurf (N= 1554)	Exosurf (N= 978)	Survanta (N=566)
7 days	123 (8)	81 (8)	41 (7)
28 days	175 (11)	126 (13)	60 (11)
Total Mortality (to discharge)	232 (15)	151 (15)	83 (15)
Respiratory Mortality	61 (4)	34 (3)	25 (4)
RDS Mortality	60 (4)	46 (5)	26 (5)
Survival to Discharge	1322 (85)	827 (85)	483 (85)

COMMENTS

Mortality was similar across all treatment groups when analyzed by age and by cause of death, when all the treated patients of the 3 studies were combined. However, the question regarding the relevance of the difference in mortality found in a single, supportive, trial between Infasurf and Survanta in the total context of safety for Infasurf still remains open for discussion.

3. Causes of Mortality

The causes of neonatal death are presented in TABLE 6. It is a pool of the data of all the patients treated in the three controlled studies.

TABLE 6. Summary of causes of death for all treated patients in the controlled studies.

Cause of Death	Infasurf (N=1,554)	Exosurf (N=978)	Survanta (N=566)
RDS	60 (4)	46 (5)	26 (5)
Bacterial infection and septicemia	45 (3)	25 (3)	17 (3)
Chronic lung disease	19 (1)	14 (1)	9 (2)
Lung hypoplasia syndromes	8 (<1)	8 (1)	2 (<1)
Birth asphyxia and previable births	7 (<1)	3 (<1)	2 (<1)
Brain hemorrhage	23 (1)	16 (2)	4 (1)
Necrotizing enterocolitis	20 (1)	7 (1)	5 (1)
Congenital hydrops and/or ascites	3 (< 1)	2 (<1)	0 (0)
Congenital heart disease	4 (< 1)	1 (<1)	2 (<1)
Chromosomal abnormality syndromes	0 (0)	1 (<1)	0 (0)
Other congenital anomalies	1 (< 1)	1 (<1)	0 (0)
Renal failure	12 (1)	7 (1)	5 (1)
Pulmonary hemorrhage	14 (1)	9 (1)	5 (1)
Hepatic failure	2 (< 1)	2 (<1)	0 (0)
Pneumonia	4 (< 1)	3 (<1)	2 (<1)
Other causes	10 (1)	6 (1)	4 (<1)
TOTAL	232 (15)	151 (15)	83 (15)

COMMENT

The frequency of the different causes of death is similar across the treatments. Their combined incidence is similar to those of the individual studies analyzed separately by indication (prophylaxis and treatment) and when SCT-P and SCT-T where analyzed together. The results were also similar to this one when the two arms of the ISCT-92 (Infasurf-Survanta) were analyzed together.

4. Complications of Prematurity

The most common serious complications reported in the study populations were reviewed in this section: Brain hemorrhages (intraventricular hemorrhages [IVH] and periventricular leukomalacia [PVL]), air leaks (pneumothoraces, and parenchymal interstitial emphysema [PIE]), patent ductus arteriosus [PDA], sepsis, retinopathy of prematurity [ROP], and necrotizing enterocolitis [NEC].

In TABLES 7 and 8, the complications of prematurity are presented by the individual prophylaxis and treatment populations. The Infasurf prophylaxis data represents the combined results of the two controlled prophylaxis trials (SCT-P and the prophylaxis arm of the ISCT-92) and the treatment data the combined results of SCT-T and the treatment arm of ISCT-92. In TABLE 9 the prophylaxis and the treatment populations have been pooled together by drug products for a more in depth review of the incidence of complications. However, the comparison of all complications of prematurity between the treatment groups is difficult in this case because of a lack of uniform criteria across the studies in the definition and the analysis of some of the terms, e.g., PDA required ultrasound verification in the ISCT-92 and the denominator included only the number of patients evaluated; in the 9101 SCT-P trial the denominator included total number of patients in the trial, this yielded a comparable increment in the percentage of diagnosis of PDA in the Infasurf and Survanta-treated population in the ISCT-92 study. For this reasons, only brain hemorrhages and air leaks, which presented similar definitions and methods of analysis, will be pooled together. The rest of the complications of prematurity were analyzed in the individual study reports. It is noteworthy to comment here that even when the frequency of the other complications of prematurity was similar in all the treatment groups in the ITT population, in a subset analysis of patients <700 grams of the prophylaxis trial (SCT-P, Infasurf-Exosurf), Infasurf treated patients had a statistically significant increase in post hemorrhagic hydrocephalus ($p<0.05$) and sepsis ($p<0.01$), when compared to Exosurf treated patients.

TABLE 7. Complications of Prematurity. - Prophylaxis Population.

Safety Parameter	Infasurf (N=655)	Exosurf (N=422)	Survanta (N=233)
IVH only*	244/641 (38)	147/411(36)	71/227 (31)
PVL only*	19/641 (3)	19/411 (5)	3/227 (1)
IVH and PVL*	50/641 (8)	17/411(4)	13/227 (6)
IVH, PVL or both*	313/641 (49)	183/411(45)	87/227 (38)
IVH Grade I or II	206/294 (70)	112/164 (68)	73/84 (87)
IVH Grade III or IV	88/294 (30)	52/164 (32)	11/84 (13)
Air leaks (Overall):	76/655 (12)	79/422 (19)	24/233 (10)
Pneumothorax	44/655 (7)	36/422 (9)	14/233 (6)
Pulmonary interstitial emphysema	46/655 (7)	58/422 (14)	13/233 (6)

*As determined at study site. The Survanta trial did not have a central reader.

COMMENTS

With respect to cerebral hemorrhages, the pool of Infasurf prophylaxis patients presented an increase incidence of IVH across the studies. Infasurf presented more severe IVH (grades III and IV) and the combination of IVH and/or PVL with respect to Survanta, and more IVH and PVL combined with respect to Exosurf. In the individual studies, only the combined occurrence of IVH and PVL was statistically significant in favor of Exosurf. Regarding air leaks, Infasurf showed less air leaks overall and less PIE than Exosurf. The incidence of air leaks were similar between Infasurf and Survanta in the prophylaxis population.

TABLE 8. Complications of Prematurity. - Treatment Population.

Safety Parameter	Infasurf (N=899)	Exosurf (N=556)	Survanta (N=333)
IVH only*	214/821 (26)	142/507 (28)	116/295 (39)
PVL only*	16/821 (2)	11/507 (2)	2/295 (1)
IVH and PVL*	41/821 (5)	12/507 (2)	17/295 (6)
IVH, PVL or both*	270/821 (33)	165/507 (33)	135/295 (46)
IVH Grade I or II	170/254 (67)	109/154 (71)	104/133 (78)
IVH Grade III or IV	84/254 (33)	45/154 (29)	29/133 (22)
Air leaks (Overall):	130/899 (14)	137/556 (25)	59/533 (18)
Pneumothorax	64/899 (7)	66/556 (12)	34/533 (10)
Pulmonary interstitial emphysema	82/899 (9)	105/556 (10)	44/533 (13)

*As determined at study site. The Survanta trial did not have a central reader.

COMMENT

In the pooled treatment population, more Infasurf patients presented with severe IVH (grades III and IV) than Survanta treated patients. Survanta patients presented more IVH, PVL or both than Infasurf, more likely because Survanta also had more cases of IVH alone than Infasurf or Exosurf. It is noteworthy that Survanta had more cases of mild IVH (grades I or II) than Infasurf. In relation to air leaks, Infasurf tended to have less air leaks overall than Exosurf and Survanta.

TABLE 9. Complications of prematurity. Pooled data of all treated patients.

Safety Parameter	Infasurf (N=1554)	Exosurf (N=978)	Survanta (N=566)
IVH only*	458/1462 (31)	289/918 (31)	187/522 (36)
PVL only*	35/1462 (2)	30/918 (3)	6/522 (1)
IVH and PVL*	91/1462 (6)	29/918 (3)	30/522 (6)
IVH, PVL or both*	584/1462 (40)	348/918 (38)	222/522 (43)
IVH Grade I or 2	376/1462 (26)	211/918 (24)	177/522 (31)
IVH Grade III or IV	172/1462 (12)	97/918 (11)	40/522 (7)
Air leaks (Overall):	206/1554 (13)	216/978 (22)	83/566 (15)
Pneumothorax	108/1554 (7)	102/978(10)	48/566 (8)
Pulmonary interstitial emphysema	128/1554 (8)	163/978 (17)	57/566 (10)

*As determined at study site. The Survanta trial did not have a central reader.

COMMENT
In this analysis, where all patients were pooled by surfactant received, irrespective of the indication, the differences in the incidence of brain hemorrhages are markedly buffered. A positive trend is noticed in favor of Infasurf in the incidence of air leaks and PIE, especially against Exosurf.

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5. Adverse Events During The Administration of Surfactant.

As mentioned earlier in this section, the method of administration of the surfactants was different in the SCT trials (Infasurf-Exosurf) than in the ISCT-92 trial (Infasurf-Survanta).

SCT-P and SCT-T trials (Infasurf-Exosurf):

Dosage - Infasurf: 3 mL/Kg. (=100 mg of phospholipids/Kg. of body weight).
Exosurf: 5 mL/Kg. body weight.

In the prophylaxis trial the surfactant could be given up to a total of 3 doses.
In the treatment trial, the surfactant could be repeated once.
In both trials the minimum time interval between doses was 12 hours.

Administration - The total dose was given through a side-port adaptor connected to the endotracheal tube, in 2 aliquots. Each aliquot was given in small boluses over 1 - 2 minutes with the patient in the supine position, head midline. For the first prophylactic dose the patient was manually ventilated, and for all the treatment doses the patient was mechanically ventilated, while the surfactant was being instilled.

ISCT-92 (Infasurf-Survanta, prophylaxis and treatment arms):

Dosage - Infasurf: 4 mL/Kg. (The concentration of phospholipids was changed from the to-be-marketed product to provide 100 mg of phospholipids/Kg. of body weight).
Survanta: 4 mL/Kg. (100 mg of phospholipids/Kg. of body weight).

In both arms the surfactant could be given up to a total of 4 doses, at least 6 hours apart.

Administration - The total dose was given through a 5 French end-hole feeding tube inserted to the end of the endotracheal tube in 4 equal aliquots.

Each aliquot was given with the patient in 4 different positions. For the first dose the patient was manually ventilated, for the retreatment doses the patient was mechanically ventilated after each aliquot.

Due to the differences in the administration technique and in the events related, the summary of the adverse events reported during the administration of the surfactant on each trial are presented separately . TABLE 10 summarizes the adverse events reported in the SCT-P and SCT-T trials and TABLE 11 recounts the AE's from the two arms of the ISCT-92 trial.

TABLE 10. Adverse events during dosing. SCT-P and SCT-T populations

DOSING COMPLICATIONS	TREATED POPULATION (N=1979)	
	Infasurf (N=1001)	Exosurf (N=978)
Bradycardia	336 (34)	181 (18)*
Airway obstruction	385 (39)	214 (22)*
Reflux	208 (21)	209 (21)
Cyanosis	652 (65)	543 (56)
Reintubation	25 (3)	4 (<1)*
Manual ventilation	161 (16)	76 (8)*
Any	781 (78)	690 (71)*

*p≤0.01

TABLE 11. Adverse events during dosing. ISCT-92 population

DOSING COMPLICATIONS	TREATED POPULATION (N=1119)	
	Infasurf (N=553)	Survanta (N=566)
Bradycardia	83(15)	87(16)
Airway obstruction	18(3)	5(1)*
Extubated	8(1)	5(1)
Δ SBP > 5 mmHg	57(10)	55(10)
Suctioned within 1 hr	37(7)	17(3)*
Any	138(25)	140(25)

*p≤0.01 SBP= systolic blood pressure

COMMENT
Infasurf-treated patients presented a statistically significant increase in nearly all the adverse events reported during the administration of the surfactants in the SCT (Infasurf-Exosurf) trials. The data generated from the prophylaxis and treatment trials combined is similar with that obtained in each individual study. Patients in the Infasurf group developed statistically significantly more airway obstruction and bradycardia, and required more reintubations and manual ventilation than patients in the Exosurf group. Consistent with these findings are the results of the ISCT-92 trial, where Infasurf patients presented statistically significantly more airway obstruction and required more suctioning within one hour than Survanta patients. These adverse events were reported to be transient and without other sequelae derived from them.

6. REVIEWER'S COMMENTS ON INTEGRATED SUMMARY OF SAFETY

The highlights of the discussion on integrated safety were:
Mortality: - Infasurf was consistently the same or better than one of the controls and not consistently worse than another. When all the patients of the controlled studies were pooled, mortality was similar in all the treatment groups. On the other hand, the statistically significant higher mortality found in Infasurf in the prophylaxis arm of the ISCT-92 trial (Infasurf-Survanta) is of concern. Its impact in the determination of the overall safety of Infasurf would require further discussions. Of note is to say that the causes of death were similar in all the treatment groups.

Complications of prematurity: - All other complications besides brain hemorrhages and air leaks, had similar incidence in the ITT population of all treatment groups.

Air leaks: - Infasurf tended to have less patients with air leaks across all studies than controls, except in the prophylaxis arm of the ISCT-92, Infasurf-Survanta trial.

Brain hemorrhages: - Infasurf tended to have more incidence/more severe degrees of intracranial bleedings than the active control (Exosurf) in the pivotal studies. The same tendency can be seen when compared with Survanta, and when all patients were analyzed together.

Dosing complications: - Infasurf had consistently more adverse events during its administration than controls, with increased incidence of airway obstruction and suctioning within one hour of dosing in one trial, and increase incidence of airway obstruction, reintubation, bradycardia, and manual ventilation in the other two studies. The events were considered mild to moderate in nature.

In general, the data reviewed here identified some safety issues, like an increased

mortality of Infasurf patients in one of the supportive studies (the prophylaxis arm of ISCT-92 trial [Infasurf versus Survanta]), the increased incidence/severity of brain hemorrhages in general, and an increased incidence of "transient" adverse events during the administration of Infasurf, as of concern, and require to be addressed in the labeling, after further discussion by the Advisory committee members. However, considering the high morbi-mortality of the population studied, the questionable nature of the negative results vs. the benefits that Infasurf demonstrated to provide to the patients, the results of the trials indicate that Infasurf can be considered safe to be used in the prevention and treatment of RDS.

VI. Integrated Summary of Efficacy

The database of efficacy was generated mainly from the two pivotal studies, SCT-P and SCT-T, comparing Infasurf to Exosurf. The only other study submitted by the sponsor, considered adequate and well controlled, the ISCT-92, (Infasurf-Survanta), was also included. Additional data were provided from 4 other uncontrolled, non-randomized, open label studies and will not be discussed in this section. All the studies have been fully reviewed in previous sections. TABLE 1 and 2 summarizes the two pivotal studies.

TABLE 1. SCT-P study

Study Design # Sites	Treatment, Dose	Number patients Each Treatment	Gestational Age (GA) Mean ± SD (weeks)
Phase III, multicenter, masked, parallel group, active controlled study. 10 study sites	Infasurf: 3 mL/kg of 35 mg/mL x 3 doses, 12 hours apart each. Exosurf: 5 mL/kg x 3 doses, 12 hours apart each.	ITT Infasurf - 431 Exosurf - 422 TBW Infasurf - 250 Exosurf - 237	ALL PATIENTS Infasurf: GA: 26.5 ± 1.6 RACE: Cauc %: 56.6 Other %: 43.4 Exosurf: GA: 26.5 ± 1.6 RACE: Cauc %: 56.9 Other %: 43.1

TABLE 2. SCT-T TRIAL

Study Design	Treatment, Dose	Number patients Each Treatment	Gestational Age (GA) Mean ± SD (weeks)
Phase III, multicenter, masked, parallel group, active controlled study	Infasurf: 3 mL/kg of 35 mg/mL x 2 doses, 12 hours apart. Exosurf: 5 mL/kg x 2 doses, 12 hours apart	ITT Infasurf - 570 Exosurf - 556 TBW Infasurf - 190 Exosurf - 213	ALL PATIENTS Infasurf: GA: 31.0 ± 3.5 RACE: Cauc %: 70.7 Other %: 29.3 Exosurf: GA: 30.6 ± 3.3 RACE: Cauc %: 67.9 Other %: 32.1

These two pivotal studies were reviewed and discussed in detailed in a previous section. The major highlights of those discussions are presented below.

In the SCT-P (Prophylaxis trial), there were no between treatment group differences in surfactant administration variables including mean age at first dose (13.1 minutes for Infasurf, 15.8 minutes for Exosurf), duration of dosing (7.5 minutes for Infasurf, 7.8 minutes for Exosurf), and number of prophylactic doses received (2.6 for Infasurf, 2.7 for Exosurf).

In the SCT-T (Treatment trial), there were no between treatment group differences with respect to surfactant administration variables including: patient age at time of first surfactant dose (approximately 12 hours for the ITT populations and 7.5 hours for the TBW populations), duration of dose (approximately 13 minutes for both the ITT and TBW populations), and mean number of doses received (approximately 1.9 for both the ITT and TBW populations).

A. Primary Efficacy Variables

The primary variables of efficacy for the pivotal studies discussed in this section were: incidence of RDS (for the Prophylaxis study), incidence of bronchopulmonary dysplasia (BPD), mortality due to RDS (for both trials), and air leaks (for the Treatment trial). TABLE 3 shows the results of each variable by treatment group in the prophylaxis trial. TABLE 4 shows the results in the treatment trial.

B. Secondary Variables

Secondary variables of efficacy were: severity of RDS, total mortality, incidence of crossovers, total respiratory mortality, respiratory support required at 28 days.

TABLE 3. Efficacy-parameters. - Prophylaxis trial.

Parameter	ITT Population			TBW Population (700-1100 g)		
	Infasurf [N=431]	Exosurf [N=422]	p-Value	Infasurf [N=250]	Exosurf [N=237]	p-Value
RDS[1]	62/406 (15.3%)	183/389 (47.0%)	<0.001	36/233 (15.5%)	97/221 (43.9%)	<0.001
BPD[1a]	61/376 (16.2)	62/354 (17.5)	0.6	42/234 (17.9)	35/208 (16.8)	0.95
RDS Death[2]	7 (1.6)	23 (5.5)	0.004	0 (0.0)	8 (3.4)	< 0.01
Mortality to 7 days[b,†]	31 (7.2)	47 (11.1)	0.05	8 (3.2)	19 (8.0)	0.04
28 days[b]	52 (12.1)	68 (16.1)	0.10	15 (6.0)	29 (12.2)	0.03
At Discharge: Survival	354 (82.1)	340 (80.6)	0.56	222 (88.8)	203 (85.7)	0.27
Mortality[b]	77 (17.9)	82 (19.4)	0.56	28 (11.2)	34 (14.3)	0.27
Any Air Leak	42 (9.7)	65 (15.4)	0.01	22 (8.8)	34 (14.3)	0.05
Pneumothorax	23 (5.3)	30 (7.1)	0.29	11 (4.4)	18 (7.6)	0.13
PIE	23 (5.3)	52 (12.3)	<0.001	15 (6.0)	26 (11.0)	0.04

[1] The 95% Confidence Interval for difference between treatment group percents was 31.7 ± 6.1 (ITT) and 28.4 ± 8.0 (TBW Population)

[2] the 95% Confidence Intervals for differences between treatment group percents were 3.9 ± 2.5 (ITT Population) and 3.4 ± 2.3 (TBW Population)

[b] Any cause

[†] Denominators indicate survivors

TABLE 4. Efficacy variables. - Treatment Trial.

Parameter	ITT Population			TBW Population (700-1350 g)		
	Infasurf [N=570]	Exosurf [N=556]	p-Value	Infasurf [N=190]	Exosurf [N=213]	p-Value
BPD[1,a]	25/523 (4.8)	30/496 (6.0)	0.41	20/168 (11.9)	16/180 (8.9)	0.38
RDS Death[1]	23 (4.0)	23 (4.1)	0.95	14 (7.4)	16 (7.5)	0.95
Mortality to 7 days[b]	34 (6.0)	34 (6.1)	0.91	17 (8.9)	21 (9.9)	0.82
28 days[b]	47 (8.3)	58 (10.4)	0.21	22 (11.6)	33 (15.5)	0.32
At Discharge: Survival	518 (90.9)	487 (87.6)	0.07	163 (5.8)	171 (80.3)	0.17
Mortality[b]	52 (9.1)	69 (12.4)	0.07	27 (14.2)	42 (19.7)	0.17
Any Air Leak[a]	60 (10.5)	120 (21.6)	<0.001	28 (14.7)	71 (33.3)	<0.001
Pneumothorax	29 (5.1)	57 (10.3)	0.001	12 (6.3)	32 (15.0)	<0.01
PIE	39 (6.8)	94 (16.9)	<0.001	19 (10.0)	56 (26.3)	<0.001

[1]The 95% Confidence Interval for difference between treatment group percents was 0.1 ± 2.3 (ITT Population) and 0.1 ± 5.1 (TBW Population)
†Denominators indicate survivors with data
[b]Any cause

1. **Incidence of RDS**

Incidence of RDS was considered a measurement of efficacy in the prophylaxis trial, conducted in a population considered at high risk of developing respiratory distress syndrome. Its definition included a CXR positive for RDS (reticulo-granular infiltrates with or without air bronchograms), and an FiO2 ≥ 30% necessary to maintain the PaO2>50 torr or pulse oximetry >85% at the time of the CXR (16 to 36 hours).

The SCT-P, indicated that Infasurf was superior to Exosurf ($p<0.001$) in the prevention of RDS.

In the ISCT-92, (Infasurf-Survanta) prophylaxis arm, there was no statistically significant difference between Infasurf and Survanta ($p=0.55$).

2. **Incidence of BPD**

Chronic lung disease at 28 days was a primary endpoint in the prophylaxis and the treatment trials. Its definition included oxygen dependence and the Xray Score ≥ 4 on day 28.

The incidence of BPD was similar in all treatment groups of either study.

BPD is a parameter that has not been consistently effected by any surfactant treatment yet.

3. Mortality due to RDS

Mortality due to RDS was a primary efficacy endpoint in both, the prophylaxis and the treatment trials. It was defined as death, primarily due to RDS or to the complications of RDS (pneumothorax, air leaks, etc.), that occurred at or before 14 days (not associated with culture positive sepsis/pneumonia or with pulmonary hypoplasia).

In the prophylaxis trial (SCT-P), RDS death was statistically significantly lower in Infasurf patients than in the Exosurf group ($p=0.004$). In the treatment trial, (SCT-T) the incidence of RDS death was similar in both groups ($p=0.95$).

The pivotal studies showed that Infasurf was at least as effective as Exosurf in decreasing neonatal mortality due to RDS.

The ISCT-92 trial, prophylaxis arm, showed a statistically significant difference in RDS death in favor of Survanta ($p<0.01$), the treatment arm did not show a statistically significant difference in this endpoint between Infasurf and Survanta ($p=0.45$).

4. Incidence of RDS-related Air Leaks

These included pneumothorax and parenchymal Interstitial emphysema (PIE). This was a primary endpoint of the treatment trial.

Their incidence was analyzed based upon CXR's read at the sites and by a central radiologist reader (RRC). Even though they were numerically different, in both cases (when read at the sites and by the RRC), Infasurf-treated patients had statistically significantly less air leaks than Exosurf in both SCT trials:

In the prophylaxis trial, Infasurf had statistically significantly less air leaks in general ($p=0.01$) and less PIE ($p<0.001$) than Exosurf. In the treatment trial, Infasurf-treated patients had statistically significantly less air leaks (<0.001), pneumothoraces ($p=0.001$), and PIE ($p\leq0.001$) than the Exosurf-treated group.

The pivotal trials showed enough evidence to support that Infasurf was superior to Exosurf in decreasing the incidence of RDS-related air leaks.

In the ISCT-92 prophylaxis arm, there were no statistically significant differences in air leaks between Infasurf and Survanta.

5. Total Mortality

Neonatal mortality of any cause was a secondary endpoint in both trials. It was evaluated at 7 and 28 days and at discharge.

At 7 days: In the prophylaxis trial Infasurf had statistically significantly less mortality than Exosurf (p=0.05). In the treatment trial, the difference was not statistically significant. At 28 days and to discharge: There were no statistically significant differences in either SCT-trial between Exosurf and Infasurf.

The pivotal studies showed that Infasurf was at least as effective as Exosurf in improving neonatal mortality.

In the ISCT-92 trial, in the prophylaxis arm, mortality was statistically significantly lower in the Survanta treated group at 7 days ($p<0.01$) and to discharge ($p=0.03$). In the treatment arm, there were no statistically significant differences between both treatment groups.

6. REVIEWER'S COMMENTS ON INTEGRATED SUMMARY OF EFFICACY.

Efficacy is a matter of comparison of the outcome or effect of a new drug to that of a placebo, or, in some cases, to a second active drug already approved for that indication. The results of the comparison show if the new drug is better, same or worse than the control. The sponsors seeking approval of new drugs for indication of disease states with a high risk of serious morbidity or mortality, can not use a placebo as the comparator of efficacy when there is already an approved drug for that indication in the market. In these cases, the sponsor has to prove that it is more effective than, or at least as effective as, the approved drug, for a clinically relevant variable, where the active control has consistently shown (in adequate and well controlled studies), to be better than placebo. The population should be similar to the target population for the new drug. The sponsor planned to demonstrate that Infasurf is superior to Exosurf, a synthetic surfactant approved for the prevention and treatment of RDS.

Infasurf showed superiority to Exosurf in the pivotal study SCT-P (the prophylaxis study) in clinically relevant variables such as incidence of RDS, RDS deaths, total mortality at 7 days, and in the incidence of air leaks. In the second pivotal study, SCT-T (the treatment trial) Infasurf showed superiority in air leaks, and was comparable to Exosurf in all the other parameters.

Compared to the second surfactant already approved in the market, Survanta, Infasurf demonstrated statistically significant increase in the incidence of total mortality and mortality due to RDS in the prophylaxis trial. As discussed before (pages 84 - 86), the reason of the increased mortality in a single supportive trial is not completely clear to this reviewer and should be viewed with caution, possibly as an isolated event, especially because it failed to show reproducibility. The mortality results were similar in the treatment arm of the same trial.

7. CONCLUSION

From the above data we can conclude that the pivotal studies support the efficacy and safety of Infasurf for the prevention and treatment of Respiratory Distress Syndrome.

Further discussions with the Advisory Committee may elucidate the impact that the increased mortality found in Infasurf-treated patients in the prophylaxis arm of a supportive study (Infasurf - Survanta) should have in the labeling. Besides the difference in mortality, Infasurf and Survanta had comparable results in all the other clinically relevant parameters.

/S/

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05/22/96

/S/

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Concurrence by Deputy Director/Supervisor:
Yes____ **No**____
Signature/Date noted /S/ 5/7/96
Comments: see Supervisory NDA memo.

Concurrence by Team Leader:
Yes ✓ **No**____
Signature/Date /S/ 5/22/96
Comments:

Concurrence by Division Director:
Yes____ **No:**____
Signature/Date Noted /S/ 6/24/96
Comments: per Division Director's memo

Concurrence by Division Director:
Yes ✓ **No:**____
Signature/Date /S/ 5/24/96
Comments: