CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021746Orig1s000

MEDICAL REVIEW(S)

Summary Basis for Regulatory Action

Date	April 17, 2009
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	NDA 21-746
Applicant Name	Discovery laboratories, Inc.
Proprietary / Established (USAN) Names	Surfaxin lucinactant
Dosage Forms / Strength	Intratracheal Suspension (30 mg phospholipids/ml) 5.8 mL/kg every 6 hours, up to 4 doses
Proposed Indication(s)	Prevention of respiratory distress syndrome in premature infants
Action:	*Complete Response*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding Surfaxin and the reader should refer to the reviews in the action package for a more detailed discussion. Surfaxin has a long, tortured history exemplified by this being the fourth review cycle for this product. Dr. Durmowicz has a summary of the history regarding the multiple review cycles in his review, and I will not repeat it here, but will focus on the last major outstanding issue. As noted in Dr. Durmowicz's review, the safety and efficacy of the product tested in the original package has been established and I will not review previous decisions made in that regard. What is at hand for this review is whether the sponsor has developed an adequate bioassay. A trustworthy bioassay is imperative for this type of product, and this one in particular as I will discuss below, as the bioassay is used to determine the potency and release specifications of new batches of drug.

Respiratory Distress Syndrome (RDS) is limited mainly to premature infants. Use of surfactant type agents has revolutionized the treatment of these patients and has greatly reduced the morbidity and mortality associated with RDS. The currently available agents are derived from animal products and have a good track record, while this product is composed of four synthetic compounds which are synthetic 21-amino acid peptide (sinapultide), dipalmitoylphosphatidylcholine (DPPC), sodium salt of palmitoylphosphatidylglycerol (POPG), and palmitic acid (PA). It is important to note that these are synthetic components as this product seems to have less stability than the naturally derived lung surfactants. Early breakdown of these synthetic components affects the (b) (4) structure of the compound, the (b) (4) structure being thought as critical to the activity of this type of product in RDS. Therefore, it is imperative that the biological activity (evaluation of intact (b) (4) structure) of this product is documented prior to release. Measurement of biological activity is also crucial for expiry dating, assuring the shelf-life of the product. During the development of this product, the sponsor failed to develop a validated bioassay study during the original clinical

trial, despite our explicit advice, as recorded in pre-NDA meeting minutes dated June 13, 2003. This in and of itself may not have been a problem, but the applicant did not save any of the original batch, or it expired during development as the drug has very limited shelf life. The drug product potency/biological activity came to play during the NDA review (multiple cycles) as the sponsor has had major CMC deficiencies that have led to major manufacturing changes, such that there has been a major problem linking the current product to that tested in the efficacy trials. Not anticipating the need for access to any of the original batches has been a major oversight on the sponsor's part and has limited options that can be used to link the product used in the clinical trial to the present product. The Division and the sponsor have struggled as to how to overcome this hurdle without conducting another trial. It was discovered that a published study (*Pediatrics*, vol. 117:295-303) used the original batches in a lamb animal study. It was decided that the only path forward, short of repeating a clinical trial or trials, was for the sponsor to use the information in this published study as a means to bridge the results from the lamb study to some other bioassay model (usually rabbit), or to further develop the lamb model (which would be very unwieldy). The purpose of this application was the sponsor's attempt to make a convincing argument that they had successfully bridged the results from the published lamb study to a rabbit bioassay so that we could have confidence that they could establish the efficacy of their product and also provide adequate expiration dating.

The sponsor was able to repeat the original fetal lamb studies using comparable methodology and demonstrated similar results between the batches used in the clinical trials to the new batches. However, they were not able to link the results from the lamb studies to the proposed rabbit bioassay. Particularly concerning was that the rabbit assay was not as sensitive and did not seem to be able to predict loss of potency in the product as the lamb assay could. This is demonstrated in the series of tables below from Dr Pei's review. The first table demonstrates that the lamb studies conducted for the sponsor were able to predict surfactant activity based on expiry dating.

Table 1 Mean Lung Compliance before and after Lucinactant Treatment in Pre-term Lambs

Lot # [a]	N	Compliance (ml/cm H_2O/kg) [b]		% of baseline [b]	Net Increase
		Base line	Treatment [c, d]	compliance	(%) [d]
T8004	5	0.079 ± 0.009	0.185 ±0.365	233.3 ± 26.4	133
T8005	5	0.103 ± 0.049	0.228 ± 0.103	223.7 ± 7.1	123
T8006	5	0.073 ± 0.019	0.164 ± 0.043	225.7 ± 1.5	125
Mean		0.085 ± 0.031	0.193 ± 0.065	227.6 ± 14.4	127
T7002	3	0.079 ± 0.003	0.130 ± 0.022	162.7 ± 21.2	63
T7003	3	0.071 ± 0.005	0.117 ± 0.013	164.0 ± 10.4	64
Mean				163.4 ± 15.0	63

a. Lots T8004, T8005 and T8006 were within the expiry date while Lots T7002 and T7003 were beyond the expiry date.
b. Reported values
c. Measured at 30 minutes after the lucinactant treatment without adjusting the ventilator settings.
d. Calculated values. Increase% = % of baseline – 100.

As can be seen, Lots T7002 and T7003 are expired and demonstrated decreased activity compared to the Lots still within their expiry date. The next table from Dr. Pei's review addendum compares these results to those of the literature report.

Table 8 Effect of Expiry Status on Lucinactant Efficacy in Pre-Term Lambs

Lot No./ Grouped	Manu-facturing Date	Time of Testing	Expiry Status at Time of Testing	Mean Lung Compliance	
				Percent of Baseline	Net Increase (%) [a]
T7002	1/23/07	Jul-2008	Yes	163.4 ± 15.0%	63% [b]
T7003	1/31/07				
T7002	1/23/07	Sep-2007 [c]	No	226.3 ± 70.3% [d]	126%
T7003	1/31/07				
T8004	5/21/08	Jul - Aug 2008	No	227 ± 14.4%	127% [b]
T8005	7/16/08				
T8006	7/31/08				
N/A	N/A	Literature	No	262.5% [e]	162.5%

a. Derived by subtracting 100 from the percent of baseline values.
b. Source: Table 7, page 11 of the current review.
c. Report date. The report did not provide the experiment date.
d. Source: Vol. 1, p 154 of the 17-OCT-2008 supplement submission.
e. Reported by Gastiasoro-Cuesta et al. (*Pediatrics*, 117:295-303, 2006).

This would seem to indicate that when Lots T7002 and T7003 were within their expiry, they demonstrated activity as did Lots T8004-6. This table also demonstrates that the activity levels for these lots were similar to those demonstrated in the published study. Upon expiration, with degradation of the (b) (4) structure, the activity of lucinactant decreased as we would expect.

The next table from Dr. Pei's review was a demonstration of the rabbit assay comparing expired to unexpired lucinactant. Note that the rabbit assay is not able to predict decreases in lucinactant activity based on expiration dating.

Table 2 Mean C_{RS}/kg in Treatment Groups (% of Control mean)

Lot #	Low Dose		High Dose		*p* – value [b]	
	Lucinactant (5.8 ml/kg)	Beractant [c] (4.0 ml/kg)	Lucinactant (8.0 ml/kg)	Beractant (5.6 ml/kg)	Lucinactant (5.8 vs. 8.0)	Beractant (4.0 vs. 5.6)
T7002 [a]	455 ± 116	1176 ± 133	287 ± 70	1294 ± 112	0.431	0.302
T7003 [a]	551 ± 114	1182 ± 208	389 ± 57	1316 ± 224	0.093	0.492
Mean	503	1179	338	1305	-	-
T8004	509 ± 56	1187 ± 112	451 ± 29	1269 ± 42	0.186	0.296
T8005	596 ± 138	1186 ± 255	571 ± 56	1267 ± 226	0.783	0.702
T8006	442 ± 51	1112 ± 127	408 ± 103	1358 ± 402	0.632	0.368
	516 ± 103	1162	477	1298	-	-

Average	511	1168	441	1301	-	-

a. Expired lots.
b. These p–values reflect the statistical difference between the low and high dose groups for each drug.
c. Lot # for beractant was 54790Z7.

This final table from Dr. Pei's review combines the findings from this submission regarding the rabbit and lamb assays.

Table 3 Results of the Lamb and Rabbit Assays

Lot	Expiry status	Mean Increase in Compliance (%) [a]				
		Rabbit [b]				Lamb [c]
		Lucinactant		Beractant		Lucinactant
		5.8 ml/kg	8.0 ml/kg	4.0 ml/kg	5.6 ml/kg	5.8 ml/kg
T7002, T7003	Yes	403	238	1079	1205	63
T8004, T8005, T8006	No	416	377	1062	1198	127
Mean	-	411	341	1068	1201	-

a. Changes in lung compliance 30 minutes after intratracheal instillation of 5.8 ml/kg of lucinactant. These numbers were obtained by subtracting 100 from the reported % of control.
b. Increases over negative (air) control in specific dynamic lung compliance C_{RS}/kg. The data was normalized by subtracting 100% from the reported data (Table 3, page 6).
c. Increases (%) over base line in lung compliance in lambs. (Source: Table 7, page 11). The compliance was measured by ml/cm H_2O/kg.

This table clearly demonstrates that the rabbit assay is not as sensitive as the lamb assay in predicting decreases in lucinactant activity. As stated above, this is particularly concerning with this drug as we know that degradation occur, and probably has an effect on the (b) (4) structure such that the product will not be as effective. If the bioassay proposed by the sponsor is not able to adequately determine this degradation of activity, we cannot have confidence in the efficacy of the product or its expiry dating.

Conclusions and Recommendations

This drug is being used in Respiratory Distress Syndrome (RDS), a life-threatening condition found in premature infants, for which surfactant type products have been proven to be life saving. It is critical that the activity and potency of such products are established before they are released. This submission has not adequately addressed the deficiency of validating an *in vivo* rabbit fetal model and has not provided a sufficient link of the rabbit model to the lamb model. To resolve the CMC deficiencies, the sponsor will need to validate the rabbit model, or develop the lamb model to the point of assuring reliability, or conduct clinical trials while simultaneously developing an appropriate model. Dr. Durmowicz has also outlined some drug impurity issues that the sponsor will also need to address (although these do not seem to be as major of a problem as the one outlined above). Until these deficiencies have been resolved, I recommend that the action on this application is a Complete Response (CR).

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Curtis Rosebraugh
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MEDICAL OFFICER

Cross-Discipline Team Leader Review

Date	April 14, 2009
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 21-746, N000
Applicant	Discovery Laboratories, Inc.
Date of Submission	October 17, 2008
PDUFA Goal Date	April 17, 2009
Proprietary Name / Established (USAN) names	Surfaxin/lucinactant
Dosage forms / Strength	Intratracheal Suspension (30 mg phospholipids/mL) Dosing Regimen: 5.8 mL/kg q 6 hr, up to 4 doses
Proposed Indication(s)	1. Prevention of respiratory distress syndrome in premature infants
Recommended:	*Complete Response*

1. Introduction

This is the fourth review cycle for Surfaxin (lucinactant) Intratracheal Suspension (NDA 21-746), which was originally submitted by Discovery Laboratories on April 13, 2004. The original application included the results of a single pivotal study (study KL4-IRDS-06) which established the efficacy and safety of lucinactant for the proposed indication, "the prevention of RDS in premature infants". The clinical recommendation for the original submission was Approval; however, there were and continued to be have been major CMC deficiencies that led to Approvable actions on February 11, 2005, March 31, 2006, and May 1, 2008. These have included drug substance related impurities for (b) (4) that exceed the qualification threshold of 0.15% recommended by the ICH guidance Q3A and major deficiencies related to inadequate specifications for release and stability, inadequate information on the manufacturing process, inadequate stability data, inadequate acceptance criteria for impurities, and inadequate validation of the lucinactant bioassay to be used for lot release testing. In this application, the Applicant submits responses to the eighteen outstanding CMC and microbiology deficiencies outlined in the May 1, 2008 Approvable letter. This review will focus on continued potential deficiencies, most notably, the lack of a valid bioassay to demonstrate biological activity of the drug.

2. Background

Respiratory Distress Syndrome (RDS) is a clinical condition found almost exclusively in premature infants characterized by inadequate production of endogenous pulmonary surfactant that is required to reduce surface tension at the pulmonary alveolar air/liquid interphase. Lack of endogenous surfactant results in greatly increased work of breathing, hypoxemia, and eventual alveolar collapse with resultant respiratory failure and the need for mechanical ventilation. Surfactant replacement therapies, in which non-native surface active agents are

instilled into the lungs of premature infants to prevent and/or treat RDS have been developed and were approved by the FDA in the 1990s (Exosurf 1990, Survanta 1991, Infasurf 1998, and Curosurf 1999). The use of these agents has resulted in greatly reduced morbidity and mortality from RDS. The initial product marketed, Exosurf, was completely synthetic while the other product are derived from animal (bovine or porcine) lung surfactant and standardized for protein and phospholipid content. Initial concerns over potential immunogenicity and transmission of infectious diseases for the animal-derived products have not been realized in the approximately 19 year history of use of their use.

Because these drugs are locally active at the alveolar air/liquid interphase and their activity is [redacted] (b) (4) of the peptides in the drug monolayer that is formed at the site of action, drug lots of surfactant products are subject to a bioassay (typically performed in rat or rabbit pup lungs) prior to lot release in order to demonstrate biological activity in reducing surface tension with a resultant increase in lung compliance. These bioassays should be developed at or before the time that pivotal clinical studies are performed in order that the assay procedure can be linked and thereby validated, to the performance of the clinical lots demonstrated to be effective in the clinical studies conducted to support approval of the surfactant product. One of the major problems with the rabbit model bioassay proposed by the Applicant for the determination of biological activity for Surfaxin has been that it was not developed until after the pivotal clinical trials were conducted and therefore has not been able to be linked to the biological activity and subsequent clinical efficacy demonstrated in the pivotal clinical trial. This lack of a validated bioassay that is able to be linked to the clinical efficacy of the drug lots used in the pivotal clinical study is exacerbated by the significant changes made in the manufacture of Surfaxin since the clinical trials were conducted for the RDS indication and remains a major issue that needs to be resolved prior to approval.

This issue has been conveyed to and discussed with the Applicant on multiple occasions during the clinical development of Surfaxin. For example in the original Approvable letter conveyed on February 11, 2005, comment 12c specifically stated to "Include an internal reference standard of Surfaxin (e.g., the batch used in the pivotal clinical trials, or an equivalent batch of proven potency)" in the analytical method for testing of the biological activity of the drug product. The Applicant subsequently acknowledged that no batches used in the clinical trials were available to be used as an internal standard to validate the proposed bioassay however, an animal study was conducted with the clinical trial material in a fetal lamb model of RDS which demonstrated some degree of biological activity (approximately a 150% increase in lung compliance; Pediatrics 2006, vol 117:295-303). The Division at a meeting on December 21, 2006 stated that the lamb study appeared to provide some evidence that lots used in the clinical studies had bioactivity and agreed to allow the lamb model to be used as a bridge to the efficacy demonstrated in the clinical lots of Surfaxin provided that currently manufactured lots of Surfaxin were found to demonstrate a similar degree of biologic activity when administered to fetal lambs in a manner comparable to the methods used in the published study. The Division then stated that since the lamb model demonstrated the bioactivity of the batches used in pivotal clinical trials, to be validated, the rabbit model should show comparable bioactivity to the lamb model. The Division suggested that the Applicant perform a side by side comparison of the lamb and rabbit bioassays ensuring that the lamb

assay be carried out as outlined in the journal article. The results, if successful in demonstrating comparability of the proposed rabbit bioassay to the published lamb study, could be used to link the current drug batches to the clinical batches. Additional discussions on what would be needed to "validate" the proposed rabbit bioassay by linking it to the results of the lamb studies and, thereby, the drug product shown to be efficacious in the clinical trials occurred during a teleconference with the Applicant on June 18, 2008, and is captured in the meeting minutes of that meeting (response and discussion to Applicant question 1a).

3. CMC/Device

The Sponsor has been successful in repeating the original fetal lamb study using comparable methodology and demonstrating that the new clinical batches have a similar degree of biological activity as demonstrated in the original study (studies performed by (b) (4) (b) (4) to support the third and current NDA submissions). The critical unresolved issue as alluded to above is linking the proposed rabbit bioassay to the studies conducted in fetal lambs, i.e., demonstrating that the proposed rabbit bioassay is a comparable method to demonstrate biological activity, or lack thereof, as has been demonstrated in the fetal lamb studies.

The current submission fails to demonstrate that the rabbit assay, unlike the studies performed in fetal lambs, can serve as a method which is able to adequately detect changes in biological activity of Surfaxin, i.e., to be able to differentiate between active and inactive drug (see the Pharmacology/Toxicology consult to the CMC review discipline by Luqi Pei Ph.D. dated 3/4/2009, for a detailed review on this subject). This is demonstrated in data submitted by the Applicant in the current submission. While studies in the fetal lamb are able to distinguish the differences in biological activity of Surfaxin lots that are current from those that have expired (with a known diminution in surface tension lowering activity that is noted from stability testing), the proposed rabbit assay cannot distinguish any differences between active and expired lots of Surfaxin. The following table reproduced as Table 8 from Dr. Pei's consultative Pharmacology Toxicology review addendum, demonstrates the ability of the lamb studies to distinguish between expired and unexpired lots of Surfaxin.

Table 8 Effect of Expiry Status on Lucinactant Efficacy in Pre-Term Lambs

Lot No./ Grouped	Date of Manufacture	Time of Testing	Expiry Status at Time of Testing	Mean Lung Compliance	
				Percent of Baseline	Net Increase (%) [a]
T7002 T7003	1/23/07 1/31/07	Jul-2008	Yes	163.4 ± 15.0%	63% [b]
T7002 T7003	1/23/07 1/31/07	Sep-2007 [c]	No	226.3 ± 70.3% [d]	126%
T8004 T8005 T8006	5/21/08 7/16/08 7/31/08	Jul - Aug 2008	No	227 ± 14.4%	127% [b]
N/A	N/A	Literature	No	262.5% [e]	162.5%

a. Derived by subtracting 100 from the percent of baseline values.
b. Source: Table 7, page 11 of the current review.
c. Report date. The report did not provide the experiment date.
d. Source: Vol. 1, p 154 of the 17-OCT-2008 supplement submission.
e. Reported by Gastiasoro-Cuesta et al. (*Pediatrics*, 117:295-303, 2006).

Note that the unexpired lots of Surfaxin manufactured in 2007 and 2008 possessed biological activity comparable to that observed in the previously mentioned lamb study published in the journal Pediatrics that used the same actual clinical lots of drug as those used in the pivotal clinical study (126 and 127% vs 162% increases in lung compliance, respectively). Also note that this lamb model could detect the loss of approximately one half the biologic activity of the now expired lots of Surfaxin manufactured in 2007 and tested in 2008 compared to the activity of the same lots studied one year previously (63% vs 126% increases in lung compliance, respectively). This substantial loss of activity seems to be proportional to the increasing amounts of decomposition products arising from the peptide over time (b) (4)

In contrast, the proposed rabbit bioassay was unable to detect any difference in biologic activity, as determined by per cent change in lung compliance between the unexpired lots of drug and those from older expired lots in which we know from results of the lamb studies and in vitro testing that decreases in biologic activity and increases in measured surface tension have occurred (increases in rabbit lung compliance were 403% and 411% in the expired and the current unexpired lots of Surfaxin, respectively, Pharm/Tox consultative review by Luqi Pei, Ph.D., Table 10). An additional issue with the rabbit bioassay was in the analysis of the data obtained. Data were transformed during the analysis and that transformation significantly impacted the interpretation of the results, i.e., lots that would have failed the specification for biological activity passed when the data were transformed (see Dr. Pei's consultative review dated March 4, 2009).

Another CMC deficiency besides the validation of the rabbit bioassay also remains (comment #11c, from the May 1, 2008 AE letter). The Applicant's qualification data in ferrets do not support the proposed acceptance criteria for the (b) (4) impurity in the drug product. The Applicant will therefore need to tighten the acceptance criteria to not more than (b) (4), or provide adequate safety data to qualify this impurity.

There were ten microbiology deficiencies outlined in the May 1, 2008 AE letter that the Applicant has adequately addressed in the current NDA submission (see microbiology review by Vinayak B. Pawar, Ph.D dated March 24/2009.

4. Nonclinical Pharmacology/Toxicology

There are no outstanding clinical pharmacology issues with this application other than the Pharmacology/toxicology consultative review to the CMC discipline by Dr. Luqi Pei noted in the Section 3, CMC/Device, above.

5. Clinical Pharmacology/Biopharmaceutics

There are no outstanding clinical pharmacology issues with this application.

6. Clinical Microbiology

Clinical microbiology is not applicable to this application. Microbiological testing deficiencies detected during the manufacturing process are captured in the CMC section.

7. Clinical/Statistical- Efficacy

The initial NDA submission submitted by Discovery Laboratories on April 13, 2004, for Surfaxin® (lucinactant) Intratracheal Suspension for the proposed indication of "prevention of RDS in premature infants" demonstrated sufficient efficacy for approval. In that submission there was a single pivotal study upon which clinical support for the indication rested, study KL4-IRDS-06. A second study, KL4-IRDS-02, was positioned by the Applicant as being supportive, but the Division considered its support to be limited because of design weaknesses and because it was not completed. Study KL4-IRDS-06 was a multicenter, multinational, randomized study conducted outside the United States that compared Surfaxin to Exosurf (a synthetic surfactant no longer marketed due to lack of efficacy compared to animal surfactant extract preparations) in a superiority design. A second active comparator, Survanta (a marketed lung surfactant prepared from bovine lungs), was included as a reference drug arm. In this study, Surfaxin was demonstrated to be superior to the active comparator, Exosurf, on both co-primary endpoints, the incidence of RDS at 24 hours and RDS mortality at 14 days. Specifically, the incidence of RDS was about 17% less in patients treated with Surfaxin than with the active comparator Exosurf, and RDS-related mortality was approximately half the rate in Surfaxin patients (4.7 vs. 9.6%). Results were consistent across population subgroups based on birth weight, gender, and race.

Additional follow-up data (review of the long-term follow-up for 394 patients who received Surfaxin in the pivotal study, KL4-IRDS-06) included in a complete response received October 6, 2005 failed to show any significant changes in mortality or neurologic complications between treatment groups.

For a more in depth discussion of the clinical program see the initial clinical review of NDA# 21-746 by J. Harry Gunkel, MD, dated January 14, 2005, the subsequent joint complete response review by J. Harry Gunkel, MD and Anthony G. Durmowicz, MD, dated March 10, 2006, and the review by Anthony G. Durmowicz, MD, dated March 19, 2008.

8. Safety

In reviewing the safety of Surfaxin compared to other active comparator surfactants (Survanta and Curosurf) used in the pivotal clinical trials in this critically ill population, it is clear that patients who received Surfaxin had a higher incidence of prospectively defined negative reactions to dosing (dose interruption, endotracheal tube obstruction, ETT reflux, pallor, etc.) than those who received other surfactant products. While this issue was not addressed by the Applicant, the most obvious likelihood is that the larger dose volume of Surfaxin per kg of patient weight compared to other marketed surfactant products is responsible. This information has been added to the proposed product label.

Subsequent clinical submissions have consisted of safety updates for ongoing studies involving Surfaxin; however, none were conducted in the same study population for which this NDA applies (premature infants at risk for RDS). Thus, while much of the safety data available for these studies is generally not relevant to the indication for this NDA, there was one notable finding of increased severe adverse events, including an increase in deaths, in adults with ARDS who received Surfaxin in study KL4-ARDS-04. Information about the increase in severe adverse events, including death, in adults with ARDS who received Surfaxin has been included in the proposed product label.

9. Advisory Committee Meeting

An Advisory Committee meeting will not be assembled for this NDA submission.

10. Pediatrics

The proposed indication is in a narrow niche of the general pediatric population, premature infants at risk for RDS. Because this disease entity does not exist outside the premature infant population, no additional studies in other pediatric populations are required.

11. Other Relevant Regulatory Issues

In accordance with Good Review Management Practices, the Division held an informal telecon with the Applicant on March 4, 2009, to give an update on the progress of the NDA review during which the Division stated that we continued to have concerns over the ability of the rabbit bioassay to discriminate between active and inactive drug product as described earlier in this review. As a result the Applicant submitted two unsolicited documents to the NDA received March 13 and 30, 2009 containing additional information regarding the biological activity test and a testimonial from the inventors of lucinactant in an attempt to support their proposed biological activity testing methodology. While the documents were submitted too late in the review cycle for a thorough review by all disciplines, I do not believe their contents would substantially alter the Division's view of the inadequacy of the rabbit bioassay to determine active from inactive drug product.

12. Labeling

During the previous (third) review cycle the Division performed a thorough review of the product label, comments were communicated to the applicant, and many changes were made to the original labeling proposed by the Applicant including the addition of (b) (4) (b) (4) the increases risk of death observed when lucinactant was administered to the lungs via flexible bronchoscopy to adults with ARDS. There are still some minor areas of the label that have not been agreed upon. These will be resolved with the Applicant in a subsequent cycle before the application is approved.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action is a Complete Response. Continued CMC deficiencies, specifically the inability to ensure the biological activity of the drug product using a validated bioassay and the need to tighten acceptance criteria for drug impurities, preclude approval of Surfaxin for the prevention of respiratory distress syndrome in premature infants. To support approval of Surfaxin, the Applicant will need to demonstrate that each drug lot of drug product meets the standards of biological activity as determined by a validated bioassay that has been adequately linked to the drug product used in the clinical trials conducted to support its safety and efficacy. This may be done by validating the fetal rabbit assay, developing and demonstrating that the lamb model is a reliable bioassay, or by conducting the necessary clinical trials and nonclinical studies to validate any other bioassay to assess Surfaxin's biological activity. In addition, the Applicant will need to tighten the acceptance criteria for drug impurities.

- Risk Benefit Assessment

Administration of exogenous surfactant products are potentially life-saving treatments for the prevention and treatment of RDS in premature infants. Currently there are three marketed products approved for this indication in the United States, all of which are derived from animal lung surfactants. While Surfaxin has the theoretical advantage inherent in a completely synthetic surfactant replacement product, the lack of the proposed rabbit bioassay to differentiate lots of drug that possess adequate biological activity from lots shown to possess significantly diminished activity places critically ill premature infants at undue risk that any Surfaxin drug product administered may not possess adequate biologic activity to prevent RDS. In addition, initial concerns over potential immunogenicity and transmission of infectious diseases for the already approved animal-derived surfactant products have not been realized in the approximately 19 year history of use of their use. The long history of use and excellent safety record of the natural surfactant products greatly outweighs the risk of use of a potentially inactive/inferior synthetic product.

- Recommendation for Postmarketing Risk Management Activities

Because of the Complete Response action, there are no recommendations for other post-marketing study commitments.

- Recommendation for other Postmarketing Study Commitments

Because of the Complete Response action, there are no recommendations for other post-marketing study commitments.

- Recommended Comments to Applicant

The following comments should be conveyed to the Applicant:

1. Comment #11c, from our letter dated May 1, 2008, remains as deficiency. The provided qualification data for study in ferrets do not support the proposed acceptance criteria for the (b) (4) impurity in the drug product. Tighten the acceptance criteria to not more than (b) (4), or provide adequate safety data to qualify this impurity.

2. You have not adequately addressed Comment 14 of the Approvable Letter issued on May 1, 2008 and the request in the Question 1a discussion section of the minutes of the June 18, 2008 telephone conference. Comment 14 requests that you tighten the acceptance criteria for the drug product biological activity and validate the fetal rabbit biological activity assay. Question 1a requests that you repeat a lamb study and compare it with results from the fetal rabbit bioassay in an attempt to validate the bioassay as a valid method to demonstrate biological activity of Surfaxin

To address the above deficiencies, conduct one of the following options:

- Continue to try to validate the fetal rabbit assay by linking it to the results of fetal lamb studies. Demonstrate the rabbit bioassay's ability to differentiate lucinactant activity between the expired and unexpired batches or lots as was observed with the lamb model.

Or

- Develop and demonstrate that the lamb model is a reliable bioassay for testing lucinactant activity. This assay should then be used to assess the potency and release specifications of drug lots.

Or

- Conduct necessary clinical trials and nonclinical studies to validate any other bioassay to assess lucinactant potency and specifications prior to release.

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/s/

Anthony Durmowicz
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Badrul Chowdhury
4/16/2009 01:42:13 PM
MEDICAL OFFICER
I concur

SUMMARY REVIEW OF REGULATORY ACTION

Date:	April 23, 2008
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	21-746
Applicant Name:	Discovery Laboratories
Date of Submission:	November 1, 2007 (original submission was on April 13, 2004)
PDUFA Goal Date:	May 1, 2008
Proprietary Name:	Surfaxin
Established Name:	Lucinactant
Dosage form:	Intratracheal suspension
Strength:	(b) (4) sinapultide, 22.5 mg/mL DPPC, 7.5 mg/mL POPG, and 4.05 mg/mL palmitic acid
Proposed Indications:	Prevention of Respiratory Distress Syndrome (RDS) in premature infants at high risk of RDS
Action:	Approvable

Discovery Laboratories submitted the original 505(b)(1) new drug application (NDA 21-746) on April 13, 2004, for Surfaxin (lucinactant) Intratracheal Suspension for the prevention of (b) (4) respiratory distress syndrome (RDS) in premature infants. The clinical program conducted by the applicant and submitted with the original application to show efficacy and safety of Surfaxin consisted of one pivotal study. The results of the study, along with supporting clinical data, were deemed to be adequate for approval of the application in the original review cycle. There were no major deficiencies from other review disciplines, except CMC. There were major CMC deficiencies that precluded approval of the application in the original review cycle. The applicant went through subsequent review cycles and the application remained approvable due to continued major CMC deficiencies. The CMC deficiencies are still not resolved and the action on this cycle will also be APPROVABLE.

The CMC review has identified numerous deficiencies in the drug product and drug substance. There are many drug substance related impurities for (b) (4) (b) (4) that exceed the qualification threshold of 0.15% recommended by the ICH guidance Q3A. There are numerous major drug product related deficiencies such as, inadequate specifications for release and stability, inadequate information on the manufacturing process, inadequate stability data, inadequate acceptance criteria for impurities, and inadequate validation of the lucinactant bioassay to be used for release testing. In addition the applicant has not addressed deficiencies identified by the microbiology review. A final office of compliance recommendations have not been issued yet for this review cycle.

During this review cycle various disciplines of the Division did a thorough review of the product label and the comments were communicated to the applicant. The applicant has responded to the comments and agreements have been reached for some areas of the label. There are still some areas of the label that have not been agreed upon. These will be resolved with the applicant in a subsequent cycle before the application is approved.

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/s/

Badrul Chowdhury
4/23/2008 01:50:12 PM
MEDICAL OFFICER

Curtis Rosebraugh
4/23/2008 01:53:41 PM
MEDICAL OFFICER
A agree with Dr. Chowdhury's review and it shall serve as the office decisional memo

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-746
Submission Code	N000
Letter Date	October 31, 2007
Stamp Date	November 1, 2007
PDUFA Goal Date	May 1, 2008
Reviewer Name	Anthony G. Durmowicz, M.D.
Review Completion Date	March 19, 2008
Established Name	Lucinactant
(Proposed) Trade Name	Surfaxin®
Therapeutic Class	Lung surfactant
Applicant	Discovery Laboratories, Inc.
Priority Designation	Standard
Formulation	Intratracheal Suspension (30 mg phospholipids/mL)
Dosing Regimen	5.8 mL/kg q 6 hr, up to 4 doses
Indication	Prevention of respiratory distress syndrome in premature infants
Intended Population	Premature Neonates

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The clinical recommendation is for Approval for Surfaxin® intratracheal suspension for prevention of respiratory distress syndrome (RDS) in premature (b) (4) This decision is founded in the previously demonstrated effectiveness of Surfaxin® in preventing neonatal respiratory distress syndrome (RDS) and deaths related to RDS and the lack of any unexpected safety concerns upon review of both previous and this current NDA submission by the Applicant.

This is the third review cycle for Surfaxin® (lucinactant) Intratracheal Suspension (NDA 21-746), which was originally submitted by Discovery Laboratories on April 13, 2004. The original application included the results of a single pivotal study (study KL4-IRDS-06) which established the efficacy and safety of lucinactant for the proposed indication, "the prevention of RDS in premature infants". The clinical recommendation for the original submission was Approval; however, there have been substantial CMC deficiencies that led to an Approvable action on February 11, 2005, for the original submission and an Approvable action on March 31, 2006, for the first complete response. The current (second) complete response submitted on October 31, 2007, contains no additional clinical data from the original program, but includes a safety update from clinical trials ongoing or initiated since the time of the previous complete response.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Risk Management Plan originally proposed by the Applicant was previously judged to be satisfactory (see Section 8.7 of the original NDA clinical review by J. Harry Gunkel dated February 11, 2005). (b) (4)

1.2.2 Required Phase 4 Commitments

Since the recommended action for this drug product is Approvable due to CMC deficiencies, no Phase 4 commitments are required at this time.

1.2.3 Other Phase 4 Requests

A comment to the Applicant was conveyed in the initial Approvable letter dated February 11, 2005, that encouraged the Applicant to further explore other (smaller) doses of Surfaxin. Smaller doses may be equally effective and also reduce the relatively high risk of negative reactions to dose administration compared to the two marketed surfactants used as comparators in clinical trials.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

NDA 21-746 was submitted by Discovery Laboratories on April 13, 2004, for Surfaxin® (lucinactant) Intratracheal Suspension. The proposed indication was "the prevention of RDS in premature infants." In the submission there was a single pivotal study upon which clinical support for the indication rested, study KL4-IRDS-06. A second study, KL4-IRDS-02, was positioned by the Applicant as being supportive, but the Division considered its support to be limited because of some design weaknesses and because it was not completed. Features of the two studies are shown in the Table 1 below.

Table 1: Surfaxin® Clinical Studies

Study	Design	Test Products/ Therapies	N	Endpoints
KL4-IRDS-06 – Major Efficacy Study **54 centers in Europe and Latin America**	•Multicenter Prevention •Neonates 600-1250g •Randomized, double-blind, event-driven, active-controlled ▪ Adjudication Committee determined causes of death ▪ Evaluations at 24 hr, 14 & 28 days; 36 weeks post-conceptional age; 6 and 12 months corrected age	Surfaxin 175 mg/kg up to 4x Exosurf 67.5 mg/kg up to 3x (Comparator) Survanta 100 mg/kg up to 4x (Reference)	527 509 258	•Co-Primary: RDS at 24 hr RDS-deaths at 14 days •Secondary RDS severity Air leaks No. of surfactant doses BPD Duration of oxygen, ventilation, hospitalization Concurrent diagnoses
KL4-IRDS-02 **35 centers in US, N America, Europe**	•Multicenter Prevention •Neonates 600-1250g •Randomized, double-blind, active-controlled ▪No Adjudication Committee ▪ Evaluations at 24 hr, 14 & 28 days; 36 weeks post-conceptional age; 6 and 12 months corrected age	Surfaxin 175 mg/kg up to 3x Curosurf 175 mg/kg x 1; 100 mg/kg up to 2x	124 128	•Primary: Alive without BPD at 28 days •Secondary All-cause mortality RDS severity Air leaks No. of surfactant doses Duration of oxygen, ventilation, hospitalization Concurrent diagnoses

The demonstration of efficacy was provided by study KL4-IRDS-06, a multicenter, multinational, randomized study conducted outside the United States that compared Surfaxin® to Exosurf in a superiority design. A second active comparator, Survanta, was included for reference. In this study, Surfaxin® was demonstrated to be superior to the active comparator, Exosurf, on both co-primary endpoints, the incidence of RDS at 24 hours and RDS mortality at 14 days. Specifically, the incidence of RDS was about 17% less in patients treated with Surfaxin® than with the active comparator Exosurf, and RDS-related mortality was approximately half the rate in Surfaxin® patients (4.7 vs. 9.6%). Results were consistent across population subgroups based on birth weight, gender, and race.

On February 11, 2005, the Division took an Approvable action on the application. The clinical recommendation was Approval, but there were substantial CMC deficiencies that resulted in the Approvable action.

Discovery submitted a proposed complete response to the Approvable letter on July 29, 2005, but the Division notified the Applicant on August 16, 2005, that the submission was not considered a complete response because of unaddressed, persisting CMC deficiencies. Discovery followed with another complete response submission, received on October 6, 2005. The Division notified the Applicant on October 20, 2005, that the submission was considered a complete response, and set a PDUFA goal date of April 6, 2006. The clinical section of the complete response consisted mostly of updates of portions of the clinical section of the original NDA which included:

- Amended final study reports of clinical studies KL4-IRDS-06 (the single pivotal study) and KL4-IRDS-02 to include some new data
- Final 6- and 12-month follow-up reports for study KL4-IRDS-06
- Amended final 6- and 12-month follow-up reports for study KL4-IRDS-02
- Updated Integrated Summary of Safety

The single clinical deficiency noted in the initial approvable letter was the lack of assessment for immunogenicity during clinical trials. This deficiency was adequately addressed in the complete response received on October 6, 2005 (lack of immunogenicity in animal studies and the inability of premature neonates to form an adequate immune response).

In addition, review of the long-term follow-up for 394 patients who received Surfaxin in the pivotal study, KL4-IRDS-06, failed to show any significant changes in mortality or neurologic complications. Data submitted for the KL4-IRDS-02 study did not contradict the results of KL4-IRDS-06 and no unexpected safety concerns were seen.

While clinical data reviewed from the complete response were consistent with those evaluated in the initial review and the clinical recommendation remained Approval for the proposed indication, CMC problems sufficient to withhold approval continued to exist including:

- Inadequate DMFs (Drug Master Files)
- Inadequate stability data

- Lack of adequate impurity profiles for drug substances and drug product
- Deficient biological activity data and method
- Inadequate proposed specifications for drug substances and drug product
- Issues with GMP compliance at drug manufacturing sites

As a result of these serious CMC deficiencies, the Division took a second Approvable action on March 31, 2006.

The current, (officially the second) complete response submission, dated October 31, 2007, was received on November 1, 2007. This submission contains no additional data from studies conducted for the "prevention of RDS" indication that is the focus of this NDA but includes a safety update from clinical trials which were either ongoing or initiated since the time of the previous complete response. It should be noted that the safety data available for these studies is generally not relevant to the RDS prevention indication for this NDA as the disease indications, patient populations, drug doses, and modes of delivery are all quite different from the proposed indication (ARDS and asthma in adults, (b) (4)

1.3.2 Efficacy

The data reviewed as part of this complete response did not assess efficacy for the following reasons. Data submitted with the original NDA submission received on April 13, 2004 demonstrated that Surfaxin was efficacious in the prevention of RDS in premature neonates. Additional follow-up data included in a complete response received October 6, 2005 did not contradict the initial determination, and the study data included in this response does not contain any additional efficacy data for the proposed indication. See the brief summary above, the initial clinical review of NDA# 21-746 by J. Harry Gunkel, MD, dated January 14, 2005, and the subsequent complete response review by J. Harry Gunkel, MD and Anthony G. Durmowicz, MD, dated March 10, 2006 for the full evaluation of efficacy.

1.3.3 Safety

The original clinical review of safety was performed by J. Harry Gunkel, M.D., at the time of the original NDA submission (document date April 13, 2004) and may be found in his review dated January 14, 2005. In his review there were two concerns regarding safety that were identified; the possibility for increased infection in infants receiving Surfaxin and the definite increased incidence of negative reactions to dose administration (dose interruption, endotracheal tube obstruction, pallor, etc.) compared to other surfactants used in the clinical trials. The analysis of the possibility for increased infection was primarily driven by a comparison of the number of patients who died with a diagnosis of neonatal sepsis. There was a slightly higher number of patients who received Surfaxin (23) compared to Exosurf (18), 4.4% vs 3.5%, respectively, who died due to infections in the single large efficacy study, KL4-IRDS-06, however, there were no differences in infection adverse events, serious adverse events, or the incidence of acquired sepsis (Table 33, original clinical review by J. Harry Gunkel, MD, p. 74). Nor were there any differences noted for study KL4-IRDS-02 between Surfaxin and the marketed product Curosurf.

Thus, the signal for increased infection is not that strong. In addition, any analysis of the sepsis data was confounded by the lack of any objective criteria required for the diagnosis of sepsis to be made. Establishing the presence of sepsis, by either the Adjudication Committee or investigator did not require the presence of positive cultures; it could be based on "substantial clinical evidence of infection." The absence of rigorous, objective diagnostic criteria for sepsis makes it difficult to conclusively attribute cause to the drug.

Regarding negative reactions to drug administration, it is clear that patients who received Surfaxin had a higher incidence of prospectively defined negative reactions to dosing than those who received other surfactant products (see Table 2 below). However, the higher frequency of negative reactions to dose administration did not appear to compromise the patients' eventual outcomes (Section 7.1.3.3.2 original NDA clinical review, pp. 67-69). While this issue was not addressed by the Applicant, the most obvious likelihood is that the larger dose volume per kg of weight of Surfaxin is responsible. (b) (4)

An additional safety review was performed at the time of the first Complete Response to an Approvable letter dated February 11, 2005 in a joint review by J. Harry Gunkel, M.D. and Anthony Durmowicz, M.D., that included updates on the long-term follow-up (6 and 12 month) for the pivotal and "supportive" studies, KL4-IRDS-06 and 02, respectively. Review of the long-term follow-up for 394 patients who received Surfaxin in KL4-IRDS-06 failed to show any significant changes in mortality or neurologic complications. In addition, data submitted for the supportive study, KL4-IRDS-02, did not uncover any unexpected safety concerns.

The safety data in this submission includes a safety update from clinical trials which were either ongoing or initiated since the time of the previous Complete Response. It should be noted that the safety data available for these studies is generally not relevant to the indication for this NDA (prevention of RDS in premature (b) (4)) as the disease indications, patient populations, drug doses, and modes of delivery are all quite different from the proposed indication (ARDS and asthma in adults, (b) (4)
However, there was one notable finding of increased severe adverse events, including an increase in deaths, in adults with ARDS who received Surfaxin in study KL4-ARDS-04. From a safety perspective, information about the increase in severe adverse events, including death, in adults with ARDS who received Surfaxin should be included in the product label.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Several persistent nonclinical and CMC deficiencies outlined in the initial Approvable action dated February 11, 2005, remain unresolved and continue to preclude approval. They are briefly summarized below.

3.1 CMC

Dr. Eugenia Nashed has performed the CMC review of all three submissions and has noted that significant problems still exist that will preclude approval of the application in this review cycle.

These include inadequate stability data, inadequate impurity profiles for drug substances and drug product, biological activity data and method that continue to be deficient, and inadequate proposed specifications for drug substances and drug product. Also, in the past there have been major issues with GMP compliance at drug manufacturing sites with four previous inspections of the Totowa, NJ site (February 2005, October 2005, February 2006, and April 2006) revealing serious deficiencies. Although the Applicant indicated the facilities were ready for inspection when this complete response was submitted, the Applicant stated in a communication dated December 20, 2007, that the current manufacturing facility will be closed and not available for inspection at least until February 25, 2008 (over half way through the 6-month review period). Because of this delay, a determination regarding resolution of manufacturing processes cannot be made at the time of this review.

3.2 Animal Pharmacology/Toxicology

Dr. Huiqing Hao has performed the Pharm/Tox review of all three submissions to date. There was a previous recommendation by the Pharm/Tox team for an Approvable action pending resolution of problems with validation of the test method for Surfaxin bioactivity and impurity qualifications as mentioned above. These issues have not been adequately addressed during this review cycle (see Dr. Hao's most recent review from March, 2008). Regarding the validation study, use of a lucinactant dose higher than the proposed clinical dose, lack of the previously agreed upon inclusion of a positive control, lack of justification for what change in compliance is considered a positive result, and inadequate number of lots tested (one, when we asked for at least three) remain deficiencies. For impurity qualifications, all impurities at, or above 1.0% need to be identified, characterized, and qualified and impurities at, or above 0.5% should be fully identified and characterized with at least minimal identification for impurities at, or above 0.2%.

7 INTEGRATED REVIEW OF SAFETY

The original clinical review of safety was performed by J. Harry Gunkel, M.D., at the time of the original NDA submission (document date April 13, 2004) and may be found in his review dated January 14, 2005. Regarding safety, the review noted an increase in pre-determined, prospectively collected negative reactions to dosing in patients who received Surfaxin compared to comparator surfactants (see Table 2 below). This information will be required to be added to the final product label. An additional safety review was performed at the time of the first Complete Response to an Approvable letter dated February 11, 2005 in a joint review by J. Harry Gunkel, M.D. and Anthony Durmowicz, M.D., that included updates on the long-term follow-up (6 and 12 month) for the pivotal and "supportive" studies, KL4-IRDS-06 and 02, respectively. Review of the long-term follow-up for 394 patients who received Surfaxin in KL4-IRDS-06 failed to show any significant changes in mortality or neurologic complications. In addition, data submitted for the supportive study, KL4-IRDS-02, did not uncover any unexpected safety concerns. The review of safety for this, the second complete response, includes a safety update from clinical trials which were either ongoing or initiated since the time of the previous complete response. It should be noted that the safety data available for these studies is generally not relevant to the indication for this NDA (prevention of RDS in premature neonates) as the disease indications, patient populations, drug doses, and modes of delivery are all quite different from

the proposed indication (ARDS and asthma in adults, (b) (4) (b) (4) Each of these studies will be briefly summarized below with pertinent safety issues discussed if identified.

Table 2: Negative Reactions to Dosing in Surfaxin Controlled Clinical Trials

	Efficacy Study (KL4-IRDS-06)			Supportive Study (KL4-IRDS-02)	
	Surfaxin (N=524)	Exosurf (N=506)	Survanta (N=257)	Surfaxin (N=119)	Curosurf (N=124)
Total Doses Administered	994	1038	444	174	160
	Total # of Events (Events per 100 doses)				
Dose Interruption	87 (8.8)	46 (4.4)	30 (6.8)	7 (4.0)	2 (1.3)
Pallor	88 (8.9)	46 (4.4)	38 (8.6)	18 (10.3)	7 (4.4)
ETT Reflux	183 (18.4)	161 (15.5)	67 (15.5)	47 (27.0)	31 (19.4)
ETT Obstruction	122 (12.3)	21 (2.0)	19 (4.3)	27 (15.5)	1 (0.6)
# of events reported as an adverse reaction	140	89	61	13	7

From: Table 2.2.5.1A, Module 5, vol 1, page 104.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.9 Safety Update

A safety update has been submitted within the Integrated Summary of Safety (ISS) that includes a summary of safety data from clinical trials which were either ongoing or initiated since the time of the first Complete Response received on October 6, 2005. None of the studies contains data for the indication proposed in this NDA. Rather, the studies are generally Phase 1 or 2 trials that explore other indications such as asthma or ARDS in adults (b) (4) The update includes:

- (b) (4)

(b) (4)

- KL4-ASTH-01 Study: This was a Phase 1, randomized, single-blind, placebo-controlled study was designed to assess the safety and deposition characteristics of aerosolized radio-labeled lucinactant in 6 healthy adult volunteers and 9 adult subjects with mild-persistent asthma. Healthy subjects were first each administered a low dose (target dose of 12.5 mg) of radiolabeled lucinactant to determine lung deposition patterns and in vivo deposition rates. Subsequently, subjects with mild-persistent asthma were randomized to receive lucinactant or placebo to assess the safety and the nebulization time relationship to the amount of drug delivered. In this arm, subjects received 20-minute nebulizations (target doses of 25 to 50 mg) in the morning and evening of both regimens in a crossover manner. The few adverse events reported for this study are not relevant to the proposed neonatal RDS indication, however, it should be noted that 6/15 subjects had AEs of wheezing during the study and 1/9 subjects with mild persistent asthma was withdrawn from the study due to wheezing and low FEV1 after receiving both placebo and active drug.
- KL4-ARDS-04 Study: This was the fourth and largest open label study conducted by the Applicant for the indication of treatment of ARDS in the adult population. It was ongoing at the time of the first complete response but has now been completed. It was designed as a multicenter, 2-part, open label study. Part A was for dose-escalation using 4 regimens to assess the tolerability and safety of lucinactant by segmental bronchoalveolar lavage of varying concentrations and volumes. Part B was the controlled, randomized, open-label part of the study to evaluate the efficacy and safety of lucinactant by segmental bronchoalveolar lavage compared with standard of care treatment. From Part A, the two highest dosing regimens were chosen to proceed into Part B compared to standard of care. The dosing regimen was rather complex. For Part B (the "controlled" open label part) 19 pulmonary subsegments were lavaged via flexible bronchoscopy twice with 50 mL of lucinactant (one at 10 mg/mL and the other at 20 mg/mL concentration). The treatments were repeated 48 hours after the first treatment with a subset of these patients (38) going on to receive 2 additional bolus treatments of lucinactant instilled via endotracheal tube at 48 hour intervals. A total of 124 patients (22 in Part A and 102 in Part B with 66 receiving lucinactant and 36 standard of care) were enrolled at the time the study was terminated on February 10, 2006. The safety of lucinactant when delivered at very high doses directly into pulmonary subsegments to adults with ARDS is not relevant to the neonatal indication proposed in this application as the disease, dose, and delivery of the drug are markedly different. However, similar to the (b) (4) study described above, it should be noted that this reviewer's interpretation of the safety of lucinactant for adults with ARDS differs from that of the Applicant. While the Applicant stated in the summary that lucinactant was "generally safe and well tolerated and that there were no unexpected safety concerns or patterns of adverse events" noted, there were very significant differences between those receiving lucinactant and those receiving standard of care for many adverse events, including death (see Table 3 below).

Table 3: Selected Adverse Events/Serious Adverse Events in Study KL4-ARDS-04 Noted to be Greater in the Lucinactant Group *(Source: Tables 2.11.2.2A, D, and E; Module 5, Vol. 1, pages 242, 246, and 248, respectively)*

Adverse Event Preferred term	**Lucinactant N=88 (%)**	**Standard of Care N=36 (%)**
Anemia NOS	21 (23.9)	5 (13.9)
Bradycardia NOS	7 (8.0)	1 (2.8)
Multi-organ failure	6 (6.8)	1 (2.8)
Bacteremia	4 (4.5)	0 (0)
MRSA infection	6 (6.8)	1 (2.8)
Sepsis	9 (10.2)	1 (2.8)
Oxygen saturation decreased	18 (20.5)	0 (0)
LFTs abnormal	7 (8.0)	1 (2.8)
Hypernatremia	9 (10.2)	1 (2.8)
Renal Failure NOS	11 (12.5)	3 (8.3)
Hypoxia	17 (19.3)	2 (5.6)
Pneumothorax	19 (21.6)	5 (13.9)
Respiratory acidosis	10 (11.4)	2 (5.6)
Respiratory failure	4 (4.5)	1 (2.8)
Hypotension NOS	17 (19.3)	5 (13.9)
Anoxic encephalopathy	2 (2.3)	0 (0)
Pulmonary Embolism	2 (2.3)	0 (0)
Death*	18 (20.5)	5 (13.9)

*Deaths reported as SAEs: Lucinactant: 7 (8.0%) SOC: 1 (2.8%)
** If the same AE occurred more than once in the same patient, only one occurrence was counted.

Reviewer's Comment: The AE profile of patients who received lucinactant is quite poor compared to those who received standard of care. This is likely due to the volume and method of administration of lucinactant; (b) (4) *From a safety perspective, information about the dramatic increase in severe adverse events, including death, in adults with ARDS who received Surfaxin should be included in the product label.*

- (b) (4)

Table 4: Selected Adverse Events that Occurred in ≥ 10% of Infants in any Treatment Group that were higher in the Lucinactant Treatment Groups *(Source: Table 2.11.4.5 A; Module 5, Vol. 1, pages 279-280)*

Adverse Event Preferred term	**Lucinactant 90 mg/kg N=47**	**Lucinactant 175 mg/kg N=45**	**Air Sham Placebo N=44**
Bradycardia NOS	20 (42.5)	16 (35.6)	8 (18.2)
Hypoxia	4 (8.5)	6 (13.3)	2 (4.6)
Neonatal hypoxia	25 (53.2)	18 (40.0)	7 (15.9)
Neonatal respiratory failure	1 (2.1)	7 (15.6)	2 (4.6)
Bronchopulmonary dysplasia (BPD)*	34 (72.3)	39 (86.7)	37 (84.1)

* BPD was the primary efficacy endpoint yet AEs for BPD were no different between treatment groups.

In summary, from a clinical standpoint the risk/benefit of lucinactant for the indication of prevention of RDS in premature neonates has already been judged as acceptable based on review of previous NDA submissions. The studies submitted in this safety update, all of which were for different indications or used different dosing methods or regimens, revealed no new safety issues that alter that conclusion. However, the finding of increased severe adverse events in adults with ARDS who received Surfaxin should be added to the label to warn against its use for that indication.

9 OVERALL ASSESSMENT

9.2 Recommendation on Regulatory Action

The clinical recommendation is for Approval for Surfaxin® intratracheal suspension for prevention of RDS in premature neonates. This decision is founded in the previously

demonstrated effectiveness of Surfaxin® in preventing neonatal respiratory distress syndrome (RDS) and deaths related to RDS and the lack of any unexpected safety concerns upon review of both prior and this current NDA submission by the Applicant.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The Risk Management Plan originally proposed by the Applicant was previously judged to be satisfactory (see Section 8.7 of the original NDA clinical review by J. Harry Gunkel dated February 11, 2005). (b) (4)

9.3.2 Required Phase 4 Commitments

Since the recommended action for this drug product is Approvable due to CMC deficiencies, no Phase 4 commitments are required at this time.

9.3.3 Other Phase 4 Requests

A comment to the Applicant was conveyed in the initial Approvable letter dated February 11, 2005, that encouraged the Applicant to further explore other (smaller) doses of Surfaxin. Smaller doses may be equally effective and also reduce the relatively high risk of negative reactions to dose administration compared to the two marketed surfactants used as comparators in clinical trials.

9.4 Labeling Review

Because of major CMC deficiencies that precluded approval, only general labeling comments were submitted to the Applicant in the previous two Approvable letters; many of which have not been fully addressed in this submission. Despite the continuing CMC deficiencies noted during review of the current submission, DPAP will extensively revise the label and convey the revised label to the Applicant for discussion. It should be noted that since the original label was submitted prior to the PLR going into effect that the label continues to use the old format.

9.4.1 Trade Name

The proposed product name, Surfaxin, was initially reviewed by the Division of Medication Errors and Technical Support (DMETS) in October, 2004 (ODS consult # 04-0194) and was re-

reviewed in November, 2005 (ODS consult # 04-0194-1). At those times DMETS continued to not recommend the use of the proprietary name, Surfaxin because of the sound-alike similarities with the word "surfactant" which is the class of drugs that Surfaxin belongs to. The DPAP continues to disagree with that recommendation primarily because of the very specific way and conditions under which the drug is administered, i.e., via an endotracheal tube in either the delivery room or in a neonatal intensive care unit by the health care provider who ordered it. At the time of finalization of this review, the DMETS review for this review cycle has not been received.

9.4.2 Package Insert

The Division of Drug Marketing, Advertising, and Communication has also reviewed earlier versions of the proposed Surfaxin label, carton, and container submitted during the two previous review cycles (comments dated March 14, 2006 and February 1, 2006). Their review for the (b) (4)

As mentioned above, despite two previous review cycles, many of the general labeling comments previously conveyed to the Applicant have not been fully addressed in the most recent proposed label. The proposed label (b) (4) For this cycle, DPAP will take the lead in extensively revising the label with the intention of submitting it to the Applicant. Specific labeling comments include the following:

In the CLINICAL PHARMACOLOGY SECTION:

- (b) (4)

1 PAGE OF DRAFT LABELING HAS BEEN WITHHELD IN FULL AS b4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

(b) (4)

9.5 Comments for the Action Letter

We continue to encourage you to consider additional dose-ranging clinical studies with Surfaxin. The additional information could help to determine whether negative reactions to dose administration could be reduced without affecting efficacy.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Anthony Durmowicz
3/19/2008 03:39:38 PM
MEDICAL OFFICER

Sally Seymour
3/19/2008 04:20:19 PM
MEDICAL OFFICER
I concur.

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-746	**TRADE NAME:**	Surfaxin
APPLICANT/SPONSOR:	Discovery Labs	**USAN NAME:**	lucinactant
MEDICAL OFFICER:	Anthony G. Durmowicz, M.D.		
TEAM LEADER:	Sally Seymour, MD	**DRUG CLASS:**	surfactant
MEETING DATE:	NA	**ROUTE:**	Intra-tracheal

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
September 10, 2007	September 11, 2007	General Correspondence	Structure and content of safety update for NDA resubmission

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW:

Background/Review: Discovery Labs originally submitted NDA 21-746 on April 24, 2004 for lucinactant intra-tracheal suspension for use in respiratory distress syndrome (RDS) in premature infants. The initial submission and a subsequent resubmission dated October 5, 2005 were judged as Approvable on February 11, 2005 and March 31, 2006, respectively. From a clinical standpoint, the program was adequate thus far; however, there were many CMC issues which precluded approval of the application. Safety updates associated with these two applications were submitted on September 30, 2004 and July 29, 2005, respectively. At the time of the March 31, 2006, Approvable action, Discovery was advised to request feedback from DPAP on the extent and format of the safety update to be included in Discovery's next resubmission of NDA 21-746. Since the time of the last safety update dated July 29, 2005, several studies, all for different indications (but several in infants/children) have been completed. These include studies KL4-ARDS-04 and KL4-ASTH-01 in adults with ARDS and asthma, (b) (4) In this General Correspondence, Discovery proposes to submit an ISS that does not duplicate information supplied in previous NDA 21-746 submissions but will instead include all available information from completed studies and will reference information from earlier submissions when necessary. (b) (4)

The request by Discovery to submit only new safety information which has been submitted previously is acceptable. Reasons for this are that from a clinical standpoint the risk/benefit of lucinactant has already been judged as acceptable in previous NDA submissions and that the additional studies conducted/completed since the last safety update were all for other indications. (b) (4) Discovery should include CRFs for those subjects in the NDA resubmission. In addition, Discovery should submit safety data for all lucinactant studies ongoing at the time of the NDA resubmission.

Comment for the Sponsor:
Your request to submit only new safety information which has not been submitted previously is acceptable (b) (4) Include CRFs for those subjects in the NDA resubmission. In addition, we request you submit safety data for all lucinactant studies ongoing at the time of the NDA resubmission.

OUTSTANDING ISSUES:

None

RECOMMENDED REGULATORY ACTION: NONE

OTHER ACTION: ____ **COMMENTS SENT TO SPONSOR:** X

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/s/

Anthony Durmowicz
10/16/2007 07:58:19 AM
MEDICAL OFFICER

Sally Seymour
10/16/2007 08:00:40 AM
MEDICAL OFFICER
I concur.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE DIRECTOR'S DECISIONAL MEMORANDUM

Date: Friday, March 31, 2006
NDA: 21-746
Sponsor: Discovery Laboratories, Inc.
Proprietary Name: Surfaxin (luminactant) Intratracheal Suspension
Author: Robert J. Meyer, MD, Director, ODE II

Brief Summary:

This is a brief decisional memorandum on the second cycle review of the NDA for Surfaxin, from Discovery Laboratories. As stated in my memo of February 09, 2005, the deficiencies following the first cycle review were entirely CMC (although labeling has not been finalized), and these issues were myriad and substantive.

The resubmission was received on October 11th, 2005. While it was reasonably clear on its face that this resubmission would not be satisfactory, it was considered a complete response as the sponsor at least addressed all the outstanding comments, if not satisfactorily.

As per the CMC/ONDQA review by Dr. Nashed and colleagues, most of the outstanding issues have not been satisfactorily addressed and the sponsor still has yet to demonstrate they can reliably manufacture a sterile, reasonably pure, consistent product. In addition, there are outstanding unacceptable DMFs and a withhold recommendation on the EER. Note that the inspectors could not inspect the main production facility earlier in this review cycle due to it not being ready. The facility is currently undergoing inspection, though it is not currently producing product. The results are unlikely to be available by the action date, so presumably the withhold recommendation would stand.

Planned Action:

This NDA remains satisfactory with regard to the demonstration of safety and efficacy for Surfaxin, but the sponsor still cannot demonstrate that Surfaxin can be satisfactorily and reliably manufactured. Therefore, I plan to take yet another approvable action with still extensive CMC deficiencies to be transmitted to the sponsor (letters have been issued to the unsatisfactory DMF holders). There will be a comment in the action letter making clear that satisfactory inspections will be needed prior to approval. Finally, I believe we should meet with the sponsor, if possible, and strongly encourage them to use outside consultants, if necessary, to move their CMC forward for this product.

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/s/

Robert Meyer
3/31/2006 09:22:44 AM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-746	**TRADE NAME:**	Surfaxin
APPLICANT:	Discovery Laboratories, Inc.	**USAN NAME:**	Lucinactant
MEDICAL OFFICER:	J. Harry Gunkel, M.D.		
	Anthony G. Durmowicz, M.D.		
TEAM LEADER:	Peter Starke, M.D.	**CATEGORY:**	Lung surfactant
PDUFA DATE:	April 6, 2006	**ROUTE:**	intratracheal

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
October 5, 2005	October 6, 2005	NDA 21-746, N000-BZ	Complete response to action letter
December 9, 2005	December 12, 2005	NDA 21-746, N000-BM	Annotated amended study reports

RELATED APPLICATIONS

Document Date	Application Type	Comments
April 13, 2004	NDA 21-746, N000	Original NDA submission

REVIEW SUMMARY: This clinical review pertains to a complete response submission, received on October 6, 2005 for Surfaxin® (lucinactant) Intratracheal Suspension, Discovery Laboratories, Inc., for the proposed indication of prevention of RDS in premature infants. The Division took an approvable action on the initial NDA submission (dated April 13, 2004) on February 11, 2005. At that time there were many serious CMC deficiencies. There was a single clinical deficiency in the initial submission, a request to justify why immunogenicity assessments were not performed during the clinical program. This deficiency has been adequately addressed as is discussed below in Section 3.1. The remainder of this clinical review deals with updates (6 and 12 month long-term follow-up) for the pivotal and "supportive" studies, KL4-IRDS-06 and 02, respectively. Review of the long-term follow-up for 394 patients who received Surfaxin in KL4-IRDS-06 failed to show any significant changes in mortality or neurologic complications. Data submitted for the KL4-IRDS-02 study did not contradict the results of KL4-IRDS-06 and no unexpected safety concerns were seen. Thus, clinical data reviewed are consistent with that evaluated in the initial review and the clinical recommendation remains approval for the proposed indication. General labeling comments were submitted to the Applicant during the first review cycle, most of which were not addressed by the Applicant in this submission. Given the continuing extent of CMC deficiencies that preclude approval during this cycle, clinical comments refer the Applicant to the initial labeling comments, specifically (b) (4)

The majority of the review of this NDA complete response submission was performed by Dr. J. Harry Gunkel. Dr. Anthony Durmowicz subsequently reviewed and concurred with Dr. Gunkel's preliminary review, finalized it, and entered it into DFS. As such this is a joint review.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: ____ **FILEABLE** ____ **NOT FILEABLE**

X **APPROVAL** ____ **APPROVABLE** ____ **NOT APPROVABLE**

Referential Notation: Brackets [ ] in this review contain references to source material. Roman numerals refer to the volume number of the IND submission, while the Arabic numerals refer to page numbers within that volume. Textual descriptions and dates refer to FDA reviews, correspondence, or meeting minutes; for example, [Medical Officer's review 12/21/98].

1. INTRODUCTION AND BACKGROUND

NDA 21-746 was submitted by Discovery Laboratories on April 13, 2004, for Surfaxin® (lucinactant) Intratracheal Suspension. The proposed indication was ***"the prevention of RDS in premature infants."*** On February 11, 2005, the Division took an approvable action on the application. The clinical recommendation was Approval, but there were substantial CMC deficiencies that resulted in the approvable action.

Discovery submitted its proposed complete response to the approvable letter on July 29, 2005, but the Division notified the Applicant on August 16, 2005, that the submission was not considered a complete response because of several unaddressed, persisting CMC deficiencies. Discovery followed with another complete response submission, received on October 6, 2005. The Division notified the Applicant on October 20, 2005, that the submission was considered a complete response, and set a PDUFA goal date of April 6, 2006.

This is the clinical review of the complete response. The deficiencies noted in the approvable letter were from the CMC discipline except for one, noted below, so the clinical section of the complete response consists mostly of updates of portions of the clinical section of the original NDA. Those updates had been submitted in the July 29, 2005, submission (volumes 2-153), along with a response to the single clinical deficiency. For that reason, the clinical section of the October complete response submission simply references the earlier July 29 submission. That reference is appropriate and acceptable.

The single clinical deficiency in the approvable letter was stated, "*We note that no assessment of immunogenicity was performed during the clinical studies. Submit an adequate justification of why immunogenicity assessments were not performed during the clinical program or, alternatively, submit adequate immunogenicity assessment data from Surfaxin use*." The Applicant's response is discussed in Section 2.1 below.

Otherwise, the clinical portion of the complete response has four components:

- Amended final study reports of clinical studies KL4-IRDS-06 and KL4-IRDS-02 to include some new data
- Final 6- and 12-month follow-up reports for study KL4-IRDS-06
- Amended final 6- and 12-month follow-up reports for study KL4-IRDS-02
- Updated Integrated Summary of Safety

These four components were agreed upon by the Division in a fax to the Applicant dated May 11, 2005. The Applicant also included an updated Integrated Summary of Efficacy in the submission, which it intends to provide support for its responses to several comments made by the Division about the proposed labeling (refer to Section 3 below).

As originally submitted, the Applicant provided no indications of how the original study reports had been amended. In response to a request from the Division to facilitate review, the Applicant provided that information in a submission dated December 9, 2005. In that submission, an Executive Summary enumerated the changes that were made in the reports. In addition to the summary, the submission also included versions of the amended study reports for KL4-IRDS-06, KL4-IRDS-02, and the Integrated Summary of Efficacy in which the amendments were noted using the "Track Changes" function of Microsoft Word. The annotated versions of the reports were used extensively for this review.

2. NONCLINICAL SUMMARY

There continue to be several persistent nonclinical deficiencies in this submission that are briefly summarized below.

2.1 CMC:

Dr. Eugenia Nashed has performed the CMC review of both submissions and has noted that significant problems exist that will preclude approval of the application in this review cycle. These include one DMF (Drug Master File) that remains inadequate, inadequate stability data, impurity profiles for drug substances and drug product that have not been worked out, biological activity data and method that are deficient, and proposed specifications for drug substances and drug product that are inadequate. In addition, there have been major issues with GMP compliance at drug manufacturing sites. Currently, the only drug product manufacturing site (Laureate Pharma, recently purchased by Discovery Laboratories, Inc.), has a WITHHOLD APPROVAL status (dated Feb 6, 2006).

Previous lots of drug product have failed final lot testing procedures. The Applicant submitted an SOP (MIC-1035) dated May 01. 2003, which did not address issues of (b) (4) handling of containers, including sampling and dispensing of raw materials. Materials submitted during this review cycle continue to ignore these issues; the Applicant still needs to provide a validated procedure or SOP to address bioburden control during transportation of the processed raw material between facilities.

2.2 Pharm/Tox: Dr. Huiqing Hao performed the Pharm/Tox review of both submissions to date. The recommendation by the Pharm/Tox team is for an approvable action pending resolution of problems with validation of the test method for Surfaxin bioactivity and impurity qualifications as mentioned in the CMC section above.

Thus, there continue to be multiple CMC issues that need to be rectified prior to the drug being approved as a prophylaxis therapy for RDS.

3. CLINICAL INFORMATION

3.1 Immunogenicity Assessment

The active ingredient of Surfaxin is sinapultide, a synthetic 21-amino acid residue peptide. In its response to the deficiency cited in Section 1 above, the Applicant stated its belief that clinical evaluation is not warranted and provided the following information.

The Applicant performed pre-clinical immunotoxicity studies in guinea pigs, which showed no evidence of immune response. The results were summarized by the Applicant as: "It is unlikely that a totally water-insoluble peptide such as KL4, or fragment of KL4 would induce an immune response since presentation to the T-cell and B-cell normally required (sic) that the peptide be in an aqueous medium. KL4 exists in a lipid environment, in the acyl side chains of a phospholipid layer."

The Applicant's rationale for not performing clinical assessments has merit. In addition to the results of the preclinical study, premature neonates are immunologically immature and mount very poor immune responses; hence the rationale for delaying many immunizations until children reach 6-8 weeks of age. The other approved surfactant products containing naturally sourced animal protein(s) performed similar preclinical assessments. Survanta also included blood sampling in the clinical studies to detect antibodies to bovine surfactant-associated proteins and none was found.

The lack of immunogenicity assessments is acceptable for the (b) (4) RDS indication. In response to the Division's request, the Applicant added the following statement to its description of the clinical studies in the proposed package insert: "*No clinical immunogenic assessments were performed.*" (b) (4) Inexplicably, that statement has been removed from the revised package insert provided in the complete response. It should be reinstated.

The immunogenicity issue will have to be re-addressed for an adult indication, because the adult immune system is quite different and adult patients will require larger doses.

3.2 Amended Final Study Reports

KL4-IRDS-06 was the single pivotal study upon which clinical support for the indication rested. KL4-IRDS-02 was a study that was positioned by the Applicant as being supportive, but the Division considered its support to be limited because of some design weaknesses and because it was not completed. Features of the two studies are shown in the Table below.

Table 1: Surfaxin Clinical Studies

Study	Design	Test Products/ Therapies	N	Endpoints
KL4-IRDS-06 – Major Efficacy Study **54 centers in Europe and Latin America**	•Multicenter Prevention •Neonates 600-1250g •Randomized, double-blind, event-driven, active-controlled • Adjudication Committee determined causes of death • Evaluations at 24 hr, 14 & 28 days; 36 weeks post-conceptional age; 6 and 12 months corrected age	Surfaxin 175 mg/kg up to 4x Exosurf 67.5 mg/kg up to 3x (Comparator) Survanta 100 mg/kg up to 4x (Reference)	527 509 258	•Co-Primary: RDS at 24 hr RDS-deaths at 14 days •Secondary RDS severity Air leaks No. of surfactant doses BPD Duration of oxygen, ventilation, hospitalization Concurrent

				diagnoses
KL4-IRDS-02 **35 centers in US, N America, Europe**	•Multicenter Prevention •Neonates 600-1250g •Randomized, double-blind, active-controlled ▪No Adjudication Committee ▪ Evaluations at 24 hr, 14 & 28 days; 36 weeks post-conceptional age; 6 and 12 months corrected age	Surfaxin 175 mg/kg up to 3x Curosurf 175 mg/kg x 1; 100 mg/kg up to 2x	124 128	•Primary: Alive without BPD at 28 days •Secondary All-cause mortality RDS severity Air leaks No. of surfactant doses Duration of oxygen, ventilation, hospitalization Concurrent diagnoses

There were several important time points in the studies at which patients were evaluated for study outcomes. As shown in the Table, the co-primary efficacy endpoints in the pivotal study were the incidence of RDS at 24 hours of age and the incidence of RDS-related death at 14 days of age. The updates to the clinical data that were provided in this complete response focused on three of the other time points: 36 weeks post-conceptional age, 6 months corrected age and 12 months corrected age.

Development is sometimes delayed in neonates who are born prematurely, as is the postnatal maturation of some physiological processes. To try to find a common point in time to assess premature neonates, it has become common practice to evaluate them when they would have reached full term in utero; i.e., about 36 weeks after conception. This is the purpose of the 36 week post-conceptional age evaluation. At the time the NDA was submitted, data at 36 weeks post-conceptional age was not yet available for all patients in the studies; therefore, the amended study reports submitted in the complete response bring those evaluations to completion.

The amended study reports provide no new information that substantively alters the conclusions and recommendations of the initial clinical review. The changes in data are relatively minor; i.e., they consisted of changes of one or two patients in the N's in various treatment groups in various analyses. In no case did these changes alter the outcomes of the primary or secondary endpoints, nor did they change any results of statistical testing from significance to non-significance or vice versa.

3.3 KL4-IRDS-06 Follow-up Reports

In the NDA, the report of the 6-month follow-up portion of KL4-IRDS-06 was complete. The 12-month follow-up portion was still in progress so an interim report was provided in the NDA. In this complete response, final follow-up reports are provided. Some minor amendments of 6-month data were made, which like the amendments of the early portion of the study, did not alter the overall conclusions or produce any notable new findings.

The 12-month follow-up assessments are now complete. They are more meaningful than the 6-month assessments, which were performed by telephone interview only. The 12-month assessments, on the other hand, were obtained at clinical visits by investigators and included physical examinations.

Data from an additional 394 patients at 12 months are available for this final report. All patients are accounted for and very few (16 total) were lost to follow up. There are no changes of clinical or regulatory significance from the interim 12-month follow-up report in the original NDA to this updated final report. Some notable results are briefly summarized here.

Table 2 shows the disposition of patients in KL4-IRDS-06 through 12 months corrected age. The population used for the long-term follow-up analyses were treated patients, as opposed to randomized patients, so those are the numbers used in the Table. In fact, only six total patients were randomized but not treated (3 Surfaxin and 3 Exosurf).

Table 2: Disposition of Patients at 12 Months Corrected Age, KL4-IRDS-06

	Surfaxin	Exosurf	Survanta
Total in study	524	506	258
Alive	376	350	178
Dead	140	146	73
Lost to follow-up	5	8	3
Withdrawn consent	3	2	4
Source: NDA 21-746, N000-BM, December 9, 2005, p 192			

RDS-related survival at 14 days was one of the co-primary efficacy endpoints for this application, but survival throughout the study period is an outcome of interest. Mortality at each of the important evaluation times in the study is shown in the next Table.

Table 3: Mortality Through 12 Months Corrected Age, KL4-IRDS-06

	Surfaxin (N=524)	Exosurf (N=509)	Survanta (N=258)	Surfaxin vs. Exosurf
	N (%)			
Day 14	84 (16.03)	83 (16.40)	48 (18.60)	0.643
Day 28	100 (19.08)	106 (20.95)	61 (23.64)	0.307
36 weeks PCA	111 (21.18)	119 (23.52)	68 (26.36)	0.248
6-months corrected	136 (25.95)	150 (29.64)	78 (30.23)	0.086
12-months corrected*	148 (28.24)	156 (30.83)	80 (31.01)	0.228
*includes lost to follow-up and those who withdrew consent, See Table 2 PCA=post-conceptional age Source: NDA 21-746, N000-BM, December 9, 2005, p 198				

As noted, the 12-month evaluation included a physical examination which was to specifically encompass neurologic findings. It should be noted, however, that there was no requirement by protocol that the neurologic examination be conducted by a neurologist or individual specially trained in neurologic evaluation of premature neonates. The study report does not specify who conducted the exams except that study investigators were almost universally neonatologists.

Taking that caveat into account, some neurologic findings at 12 months are of note and are summarized in Table 4. It is important to note that the results shown in Table 4 are the *observed* findings. The Applicant's primary presentation of the data ascribed the worst outcome for patients who died or were lost to follow-up at 12 months. That is a reasonable analytical approach, but in a population with a high mortality such as this one, it does not provide an accurate sense of how common neurologic deficits actually were in survivors. That is, the imputed rate of cerebral palsy, for example, included the nearly 30% non-survivors. An estimation of the actual numbers of affected survivors is critical because evaluating a therapy that beneficially affects early mortality might have limited value if survivors were disproportionately impaired. The figures in the Table therefore indicate the actual number of patients who were observed to have the finding.

Table 4: Neurologic Findings at 12 Months Corrected Age, KL4-IRDS-06 - Observed

Neurologic Finding	Surfaxin (N=524)	Exosurf (N=508)	Survanta (N=258)	Surfaxin vs. Exosurf
	N (%)			
Gross tone or reflex abnormality	30 (7.11)	45 (11.25)	25 (12.25)	0.094
Cerebral palsy*	16 (3.79)	23 (5.75)	13 (6.37)	0.203
Hydrocephalus	7 (1.66)	10 (2.50)	4 (1.96)	0.317
Deafness	10 (2.38)	7 (1.75)	1 (0.49)	0.436
Blindness	8 (1.90)	10 (2.50)	2 (0.98)	0.323
Seizures requiring anticonvulsants	7 (1.66)	7 (1.75)	5 (2.45)	0.333
Gross motor delay	30 (7.11)	42 (10.50)	15 (7.35)	0.105
Other gross neurologic findings	22 (5.21)	18 (4.50)	6 (2.94)	0.408
NDA 21-746, N000-BZ, July 29, 2005, vol 49, pp133-135				

* Criteria used to arrive at a diagnosis of cerebral palsy were not specifically defined

In general, these neurologic findings provide encouragement that the improved RDS survival attributed to Surfaxin did not result in more impaired survivors. It should be noted that using the imputed results resulted in two differences that were statistically significant: gross tone or reflex abnormality and gross motor delay. As the Table indicates, these were no longer significant when the observed figures were used. The Applicant (b) (4) stating that "*There were no differences between the Surfaxin, Exosurf, and Survanta treatment groups on physical examination and gross abnormal neurological findings at 12-months corrected age*."

The proportion of Surfaxin-treated patients who had unilateral or bilateral deafness was higher than in the other treatment groups. This had also been noted in the interim report in the NDA, but the discrepancy is less in this final report than it had been in the interim report *[Medical Officer's Review, DFS, 1/14/05, pp 89, 91]*.

3.4 Amended KL4-IRDS-02 Follow-up Reports

As noted in Section 2.2, the Applicant considers study KL4-IRDS-02 to be supportive, but the Division did not attribute great weight to it. In general, its results supported and did not contradict the results of the pivotal study KL4-IRDS-06, and it produced no unique or unexpected safety concerns. The amended reports of the early phase of the study and the follow-up phases produced no new information to alter this judgment.

3.5 Updated Integrated Summary of Safety

Similarly, the results in the updated integrated safety summary submitted in this complete response did not alter the safety profile of Surfaxin that was generated from review of the original NDA. There were minor changes in data but none substantively altered any conclusions, nor do they warrant any additions or deletions to product labeling for neonatal RDS.

The same is true for the updated results for the Applicant's programs in progress in neonatal meconium aspiration syndrome and adult respiratory distress syndrome.

4. PRODUCT NAME

The proposed product name, Surfaxin, was initially reviewed by the Division of Medication Errors and Technical Support (DMETS) and the Division of Drug Marketing, Advertising, and Communication (DDMAC) in October, 2004 (ODS consult # 04-0194) and was re-reviewed in November, 2005 (ODS consult # 04-0194-1). DMETS continues to not recommend the use of the proprietary name, Surfaxin because of the sound-alike similarities with the word "surfactant" which is the class of drugs that Surfaxin belongs to. While respecting their expertise, the DPAP continues to disagree with that recommendation primarily because of the very specific way and conditions under which the drug is administered, i.e., via an endotracheal tube in either the delivery room or in a neonatal intensive care unit by the health care provider who ordered it. Further, a possible mistake would not be a safety issue as the neonate would receive a drug of the same class. In addition, hospital will likely have only one type of surfactant available for use due to formulary considerations and if more than one is available the neonatology staff will have decided before the birth of the child what surfactant would be used in that specific case.

5. LABELING

The initial approvable letter included numerous comments about the clinically relevant sections of the proposed package insert. In this complete response, the Applicant has not complied with many of the comments. Two particular issues persist and remain problematic. They are briefly discussed below. They are more comprehensively addressed in the Medical Officer review of the original NDA *[Medical Officer's Review, NDA 21-746, N000, 1/14/05]*.

5.1 Prevention vs. Rescue Indication

The approach to surfactant therapy in neonatal RDS has involved two strategies, which evolved into different indications even though they are both for premature neonates. The indication proposed for Surfaxin and which received the approvable action is for *prevention* of RDS. In this strategy, surfactant is administered within minutes of birth or as soon as feasible to prevent the development of RDS. Because this is a preventive approach, it has been used only in those neonates whose risk for RDS is greatest; i.e., at least 50%. Generally, these are patients born before about 32 weeks gestational age and less than 1250 grams birth weight. The other strategy is the *treatment or "rescue"* indication for neonates who did not receive prophylaxis and develop RDS requiring mechanically assisted ventilation during the first day of life.

As noted, the clinical support for the NDA rested primarily in the single pivotal prevention study KL4-IRDS-06, with some minimal support from prevention study KL4-IRDS-02. The program also included a small prevention study of 11 patients, KL4-IRDS-05. (b) (4)

5.2 Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is a chronic inflammatory and fibrotic disease of lungs that occurs in premature neonates. It is caused by injury to fragile immature lungs from exposure to high ambient oxygen, the barotrauma of mechanically assisted ventilation, and the inflammatory processes that ensue from both. As a major morbidity of neonatal RDS, all surfactant studies evaluate BPD incidence and severity. (b) (4)

(b) (4)

(b) (4)

A definition commonly used for BPD is the prolonged requirement for supplemental oxygen beyond the neonatal period, usually at 36 weeks post-conceptional age. This is a problematic criterion, however, from a regulatory standpoint because the use of oxygen is often based on clinical judgment only. That is, one practitioner may administer oxygen at 32%, for example, while another administers 28%. Both are probably clinically acceptable, but one would define the presence of BPD and the other would not. Recognizing this conundrum, some investigators recently began advocating a "physiologic definition" of BPD. This would require patients to be tested under safe, closely monitored conditions, to determine their actual physiologic requirement for oxygen by slowly withdrawing oxygen until certain criteria were met. This approach is slowly gaining acceptance, but a diversity of opinion remains. (b) (4) In addition, by definition, BPD is a chronic condition and approving a therapy for it ought to include evaluation of chronic morbidities; i.e., increased hospitalizations or clinic visits, more frequent respiratory illnesses or allergies, malnutrition, delayed development, etc. The Applicant did not specifically address any of these areas.

The clinical comment for the Applicant will refer to label comments given during the first review cycle, and specifically mention the issues discussed above.

6. SUMMARY AND DISCUSSION

This clinical review pertains to a complete response submission, received on October 6, 2005 for Surfaxin® (lucinactant) Intratracheal Suspension, Discovery Laboratories, Inc., for the proposed indication of prevention of RDS in premature infants. While there were many serious CMC deficiencies in the initial submission, many of which are still unresolved, there was a single clinical deficiency, a request to justify why immunogenicity assessments were not performed during the clinical program. This

deficiency has been adequately addressed during this review cycle. The remainder of this clinical review deals with updates (6 and 12 month long-term follow-up) for the pivotal and "supportive" studies, KL4-IRDS-06 and 02, respectively. Review of the long-term follow-up for 394 patients who received Surfaxin in KL4-IRDS-06 failed to show any significant changes in mortality or neurologic complications. Data submitted for the KL4-IRDS-02 study did not contradict the results of KL4-IRDS-06 and no unexpected safety concerns were seen. Thus, clinical data reviewed are consistent with that evaluated in the initial review and the clinical recommendation remains approval for the proposed indication. General labeling comments were submitted to the Applicant during the first review cycle, most of which were not addressed by the Applicant in this submission. Given the continuing extent of CMC deficiencies that preclude approval during this cycle, clinical comments refer the Applicant to the initial labeling comments, specifically those dealing with a (b) (4)

7. COMMENTS TO APPLICANT

Please refer to the comments regarding labeling in the approvable letter from DPAP dated 2/11/05 (comments 28-36) and revise draft labeling accordingly. In particular, (b) (4)

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/s/

Anthony Durmowicz
3/8/2006 11:35:56 AM
MEDICAL OFFICER

Peter Starke
3/10/2006 05:10:15 PM
MEDICAL OFFICER
I concur.

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-746	**TRADE NAME:**	Surfaxin®
APPLICANT/SPONSOR:	Discovery Laboratories, Inc.	**USAN NAME:**	Lucinactant
MEDICAL OFFICER:	J. Harry Gunkel, M.D.		
TEAM LEADER:	Peter Starke, M.D.	**CATEGORY:**	Lung surfactant
DUE DATE:	N.A.	**ROUTE:**	Intratracheal suspension

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
April 8, 2005	April 11, 2005	N000-BM	General Correspondence re: approvable letter

RELATED APPLICATIONS

Document Date	Application Type	Comments
April 13, 2004	NDA 21-746	Original NDA

REVIEW SUMMARY: Discovery Laboratories has submitted a General Correspondence to NDA 21-746 requesting Division review of its plans for responding to the safety update requirement of the NDA approvable letter of February 11, 2005 (21 CFR 314.50 (d)(5)(vi)(b)). Discovery plans to include four components in the update, as follows.

1. Amended reports of pivotal study KL4-IRDS-06 and supporting study KL4-IRDS-02, adding new follow-up data, if any, affecting the status of patients at 36 weeks post-conceptional age.

2. Final reports of 6- and 12-month follow-up assessments for KL4-IRDS-06.

3. Amended final reports of 6- and 12-month follow-up reports for KL4-IRDS-02.

4. Updated Integrated Summary of Safety to include all data from all neonatal RDS studies, and updated data from studies of meconium aspiration syndrome and acute respiratory distress syndrome (ARDS).

(b) (4)

The proposed items 1-4 above are acceptable to the Division. The Division does not concur with (b) (4) (b) (4) The following comment should be sent to the Sponsor.

"Your proposed safety update submission, as described in items 1 through 4, is satisfactory and acceptable to the Division. (b) (4) **In addition, provide a tabular listing of all case report forms submitted to this NDA at any time and indicate the location (submission date, volume of submission, page number)."**

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

OTHER ACTION: X **COMMENTS TO SPONSOR**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Gunkel
4/19/05 09:29:43 AM
MEDICAL OFFICER

Peter Starke
4/19/05 03:52:00 PM
MEDICAL OFFICER
I concur with this review and the comments to the sponsor.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE DIRECTOR'S DECISIONAL MEMORANDUM

Date: Wednesday, February 09, 2005
NDA: 21-746
Sponsor: Discovery Laboratories, Inc.
Proprietary Name: Surfaxin (luminactant) Intratracheal Suspension
Author: Robert J. Meyer, MD, Director, ODE II

Introduction:

Respiratory Distress Syndrome (RDS) of the newborn is a lung disease manifested primarily in premature infants with inadequate maturation of the pulmonary system and specifically of alveolar surfactant. It has become standard of care to either treat or prevent this syndrome with exogenous surfactant. The surfactants currently approved and available in the US are all of animal origin, with two bovine-derived products (Infasurf and Survanta) and one porcine-derived product (Curosurf). This application is for a novel, totally synthetic surfactant with an artificial polypeptide that was designed to mimic the action of one of the native surfactant-related proteins, called Sp-B. This protein, amongst other activities, is thought to enhance the surface spreading of the surfactant phospholipids and thereby is believed to play a critical role in the efficacy of these phospholipids in reducing alveolar surface tension and preventing atelectasis. The artificial polypeptide is called sinapultide by the sponsor and represents a construct of 21-amino acids formed from repeating sequences of lysine and leucine.

Due to there being available therapies for RDS that improve mortality, designing studies that would convincingly show assay sensitivity and also a clear benefit for Surfaxin was a challenge. The sponsor eventually, with FDA concurrence, settled on a study design whereby the drug was primarily tested for superiority against an approved but no longer U.S. marketed surfactant – Exosurf. Like Surfaxin, this drug is wholly synthetic, but in addition to phospholipids, this protein-free surfactant contains colfosceril palmitate, cetyl alcohol, and tyloxapol, none of which clearly mimic Sp-B. There are in vitro data that suggest Exosurf has poorer surface tension lowering capabilities than the animal-derived products[1]. There are also some in vivo data in animals and in humans that bear out the in vivo relevance of such observations.[2] Therefore, it was felt that, by its containing the Sp-B protein mimic sinapultide, Surfaxin might be able to show superiority to an existing, approved product. By conducting a successful superiority trial, efficacy would be assured. Additionally, the FDA felt a comparator arm to a bovine-derived product would

[1] J Biomater Appl. 2000 Oct;15(2):140-59
[2] Am J Respir Crit Care Med. 1996 Feb;153(2):820-8; Arch Pediatr. 1996 Feb;3(2):165-75

be useful, not for inferential statistical purposes, but for qualitative comparisons to assure that Surfaxin did not appear to be inferior to the currently marketed surfactant products. The basis of the submission is a single RCT with the above basic design. FDA agreed to this given the known efficacy of surfactants and the in vitro, preclinical and early clinical work with Surfaxin.

CMC: Unfortunately, the CMC submission in support of this application is substantially deficient at this point in time. There are numerous outstanding DMF deficiencies as well as a paucity of data on the attributes and the stability of the product produced by the facility eventually identified by the sponsor. The drug product is to be sterile (as it is distilled directly down endotracheal tubes into the infant's lungs) and consists of a suspension of the synthesized phospholipids DPPC (dipalmatylpalmitoylphosphatidylcholine), POPG (palmatoyloleoylphosphatidylglycerol), PA (palmitic acid), and the sinapultide. The final ten milliliter vials contain (b) (4) suspension of 0.8 mg/mL of sinapultide, 22.5 mg/mL of DPPC, 7.5 mg/mL of POPG, and 4.05 mg/mL of PA. Notably, the CMC deficiencies include important microbiologic concerns about the ability of the production facility (Laureate Pharma) to produce the Surfaxin with assured sterility, as it is not clear proper media fill runs have been done to demonstrate sterility. The myriad identified CMC issues will need to be addressed prior to the drug being approved for RDS.

EERs: Though no final recommendation is yet made, it appears that at least one of the facilities inspected may result in a withhold recommendation (the final drug product producer – Laureate), as the district offices issued an "unacceptable" recommendation for this site and found gross GMP violations.

Pharm/Tox: Surfaxin was demonstrated to be pharmacologically active by in vitro assays and in vivo studies. In vitro, Surfaxin importantly decreases surface (air-liquid) tension in standard in vitro assays. In vivo, Surfaxin increases pulmonary compliance in premature rabbits, and improved lung expansion and other respiratory and pulmonary parameters in premature monkeys. Surfaxin also showed salutary effects in animal models of ARDS (such as endotoxin instillation in the lung).

Considering the proposed use of this product – that being a short-term and often single dose use in premature infants - the toxicology program was fairly small and focused on acute toxicities. Surfaxin was studied in rabbits, dogs and cats in short-term trials (<=14 days). The common toxicity findings of these studies were respiratory distress after dosing (large quantities were given), increased lung weights and lung inflammation (macrophages, neutrophils, mononuclear cells, and eosinophils at alveolar and/or bronchioalveolar and/or perivascular regions). All of the toxicities were partially or completely reversible.

Clinical: While the sponsor performed several studies in the RDS indication, only one of these is satisfactory in terms of its design, conduct and results to support approval (study KL4-IRDS-06), which I will refer to as study 06. This single study was a multicenter,

multinational, properly masked RCT of Surfaxin vs. Exosurf as a preventative for RDS in premature infants. A Survanta arm was also included at a 1:2:2 randomization to Surfaxin and Exosurf. The study was conducted primarily in Eastern Europe and Latin America. Neonates between 600 and 1250 grams were eligible for enrolling and the drug was to be given between 15 – 30 minutes of birth as a preventive measure. The trial enrolled approximately 1280 patients. There were co-primary endpoints of RDS at 24 hours (adjudicated) and RDS-related deaths by day 14 (also adjudicated). Secondary endpoints were numerous and included: air leaks, development of bronchopulmonary dysplasia (BPD), need for repeat doses, duration of ventilation and oxygen supplementation, severity of RDS, and occurrence of concurrent diagnoses. Initially, the sponsor had proposed to include air-leaks in the first week amongst a composite primary endpoint, but this was removed with FDA concurrence prior to the blind being broken.

The results of trial 06 essentially establish the efficacy of Surfaxin in that the drug was shown to be statistically superior to Exosurf on the primary endpoints and looked comparable in most regards to Survanta (qualitatively better in many measures, worse in some). See the Medical Officer's memo for details. Essentially, the rate of adjudicated RDS in the 527 babies given Surfaxin was 39.1% and the RDS-related mortality at 14 days was 4.7%. For Exosurf, the 509 babies showed an RDS rate at 24 hours of 47.2% and a 14-day RDS related mortality of 9.6% (more than double the mortality rate for Surfaxin). The respective percentages for the 258 Survanta babies were 33.3% and 10.5%. All cause mortality at 14 days was similar across groups, with 15.9, 16.0 and 18.6% respectively for Surfaxin, Exosurf and Survanta. This study showed convincing superiority of the study drug over Exosurf on RDS endpoints and supports its clinical comparability to Survanta on those same endpoints.

The sponsor started a European/North American study (study 02), which was a positive-control "non-inferiority" study of Surfaxin vs. Curosurf (the porcine-derived product) in infants with similar entry criteria to study 06. This study was stopped prematurely due to business reasons and the FDA did not consider this study to be an adequate designed study for making statistical inferences. That said, the study did enroll over 240 infants prior to termination and provides some useful data for comparing Surfaxin with an animal derived product in a qualitative sense. The designated primary endpoint for Study 02 was being "alive and without BPD" at day 28. Of the 119 Surfaxin babies, 37.8% met this endpoint, as opposed to 33.1% of the Curosurf babies. All other endpoints also showed comparable results between the two treatments, though, of course, no firm conclusions on their comparison can be reached.

As for safety, the AEs and other events recorded for the Surfaxin treated babies in the total database are as might be expected for an exogenous surfactant and are substantially similar to the approved comparator agents. The primary medical officer raised two safety issues that stood out for him, that of potential renal effects and that of excess infections. The former he rightfully dismisses as likely spurious, and perhaps reflect that Surfaxin babies survived longer and in greater numbers, allowing for the development of other complications of critically ill preemies. The primary medical officer feels infections may be have some relation to Surfaxin therapy (though not of sufficient concern to preclude

an approval recommendation on his part). This observation would be critically important if true, as it would raise questions about whether some attribute of Surfaxin therapy or the product itself predisposes to infection. However, looking at the same data in the Medical Officer Review, I do not feel convinced there is a signal of excess infections with Surfaxin compared to other surfactant treatments. The most striking imbalance in the database is from meconium aspiration studies, where the control is standard of care (i.e., no instillation of surfactant at all). In these circumstances there are clearly more infections with Surfaxin than SOC. However, this finding alone only suggests exogenous surfactant administration can lead to infections, not that this drug specifically is an issue relative to other surfactants. In the comparative trials (Studies 06 and 02), there really is no clear monotonous signal of an excess occurrence of any manifestation of infection (sepsis, pneumonia or otherwise) with Surfaxin that is not seen with the other agents. I refer the reader to the data for RDS trials in the MO Review Table 33 in the ISS. These data show that many of the apparent discrepancies in one study are offset by findings in the other and/or in other categorizations of infections. Therefore, I conclude that there is no clear signal of excess infections with Surfaxin to suggest that it is worse than any other exogenous surfactant in this regard.

Statistics: The statistical review (Sue Jane Wong) provided input throughout the development of this drug and has an important historical perspective on the salient issues. Her review was able to replicate the sponsor's findings and indeed shows statistical superiority of the drug over Exosurf. However, if one uses CRF data instead of adjudicated data, the superiority for the drug over Exosurf on RDS mortality at 14-days does not remain. It must be kept in mind, however, that the adjudication was pre-planned and well-conducted, and therefore there is no reason to discount the data based on the adjudicated assignment of cases.

DSI: Four clinical study sites were inspected by DSI and no important deficiencies or discrepancies were found.

Labeling/Nomenclature: Given the extent of the CMC deficiencies, substantive labeling comments will not be given in this cycle. The name "Surfaxin" was found satisfactory by DDMAC, but not by DMETS. DMETS expressed concern over the sound alike characteristics of the name with respect to comparisons to Survanta or "surfactant" itself. The division leadership disagrees with DMETS, pointing out that there would be little serious consequence to an inadvertent switch of one surfactant for another. Additionally, many hospitals may only carry one particular surfactant on their formularies. I believe the name "Surfaxin" is acceptable, as I agree with the DPADP director in this regard.

Planned Action:

This NDA is satisfactory to establish the safety and efficacy of Surfaxin, but has not yet demonstrated that Surfaxin can be satisfactorily and reliably manufactured. Therefore, I plan to take an approvable action with extensive CMC deficiencies to be transmitted to the sponsor (as well as to various DMF holders).

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/s/

Robert Meyer
2/9/05 04:15:09 PM
MEDICAL OFFICER

DIVISION DIRECTOR'S MEMORANDUM

Date: February 8, 2005

To: NDA 21-746

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Surfaxin (lucinactant) Intratracheal Suspension

Applicant: Discovery Laboratories, Inc.

Administrative and Introduction

Discovery Laboratories submitted a 505(b)(1) new drug application (NDA 21-746) on April 13, 2004, for Surfaxin (lucinactant) Intratracheal Suspension for the prevention of (b) (4) respiratory distress syndrome (RDS) in premature infants. The PDUFA due date of this application is February 13, 2005. Surfaxin, like other surfactants for the prevention or treatment of neonatal RDS, has an orphan drug designation. The applicant requested a Priority Review of this application, which was denied because the data presented by the applicant did not demonstrate significant advantage of Surfaxin over other marketed surfactants. In addition, the applicant only submitted 3 months stability data with the original application, which is inadequate to support a meaningful approval given the timetable of a priority review.

Surfaxin is a new molecular entity by virtue of the constituent sinapultide, a unique synthetic peptide of 21 lysine and leucine residues. Natural mammalian lung surfactant contains at least four constituitive proteins designated surfactant-associated proteins A, B, C, and D (abbreviated SP-A, SP-B, SP-C, and SP-D). Of the four proteins, SP-B appears to play a major role in reducing alveolar surface tension. Sinapultide is intended to mimic the structural and functional properties of SP-B. Surfaxin also contains phospholipids intended to mimic the characteristics of the phospholipids in native surfactant, since SP-B activity depends on the presence of surface active phospholipids.

Neonatal RDS develops when birth occurs prematurely before full development of the pulmonary surfactant system. Without surfactant, the lungs collapse at the end of expiration resulting in generalized atelectasis, which leads to respiratory failure accompanied by several complications. In untreated patients, neonatal RDS results in high morbidity and mortality. Over the past decade several exogenous surfactants have been developed to prevent and treat neonatal RDS (Table 1). Of the four surfactants approved in the United States, Survanta, Infasurf, and Curosurf are animal derived, and Exosurf is synthetic. Surfaxin, the subject of this application, is a synthetic surfactant.

Historically, the use of surfactant in the management of neonatal RDS involved two strategies, prevention and treatment. In the prevention strategy, surfactant is

administered as soon as feasible after birth in high-risk premature infants (generally 32 weeks or less of gestational age and 1250 gm or less of body weight) to prevent the development of neonatal RDS. In the treatment strategy, surfactant is administered to neonates who did not receive preventive surfactant and developed RDS during the first day of life. Of the four surfactants approved in the United States, Exosurf, Survanta, and Infasurf have both prevention and treatment indications, and Curosuf has only the treatment indication (Table 1). The applicant is seeking only a prevention indication for Surfaxin. (b) (4) Up to three additional doses are proposed to be given at minimum six hour intervals if RDS develops. Since the strategy is prevention, it is likely that some infants will receive Surfaxin who would not have developed RDS.

The clinical program conducted by the applicant to show efficacy and safety of Surfaxin consisted of one pivotal study. The results of the study, along with supporting clinical data, support the efficacy and safety of Surfaxin. But there are major CMC deficiencies that will preclude approval of this application in this review cycle.

Table 1. Surfactant Products in the United States

Product	NDA number Approval date	Product Information	Indication
Exosurf*	NDA 20-044 August 1990	**Synthetic** Colfosceril palmitate 67.5 mg/mL; tyloxapol; cetyl alcohol	Prevention Treatment
Survanta	NDA 20-032 July 1991	**Bovine** Phospholipids 25 mg/mL; SP-B <0.2 mg/mL	Prevention Treatment
Infasurf	NDA 20-521 July 1998	**Bovine** Phospholipids 35 mg/mL; SP-B 0.26 mg/mL	Prevention Treatment
Curosurf	NDA 20-744 November 1999	**Porcine** Phospholipids 80 mg/mL; SP-B 0.3 mg/mL	Treatment
Surfaxin	NDA 21-746 Pending	**Synthetic** Phospholipids 30 mg/mL; sinapultide 0.8 mg/mL	Prevention
* Not marketed in the United States anymore			

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The drug product is an aqueous suspension of sinapultide, a synthetic peptide of 21 lysine and leucine residues and a mixture of synthetic phospholipids (dipalmitoyl-phosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol (POPG), and palmitic acid (PA)). As mentioned above, sinapultide is designed to simulate the nature and function of SP-B. (b) (4) to mimic the behavior of the in vivo environment responsible for lowering surface tension in the lungs. The drug product is sterile-filled to 10 mL sterile glass vials and contains 0.8 mg/mL of sinapultide, 22.5 mg/mL of DPPC, 7.5 mg/mL of POPG, and 4.05 mg/mL of PA, in 8 mL per vial. This corresponds to a concentration of 30 mg of total phospholipoids per 1 mL of drug product suspension. The commerical drug product will be manufactured by Laureate Pharma, Totowa, NJ, for Discovery Laboratories.

The CMC team and the consulting Microbiology team have identified several major deficiences that will preclude approval of this application, and I concur with their assessment. Major approvability issues are briefly summarized below. Detailed review of the issues can be found in Dr. Nashed's CMC review, and in Dr. Pawar's Microbiology Review.

There are serious microbiology deficiencies in the NDA and DMFs supporting manufacturing and controls for all four drug substances and drug product. The submitted data do not assure sterility during the drug product manufacture, and there are contradictory results between the media fill data submitted to the NDA and to the DMF. Assurance of sterility is critical for this drug product because it is intended to be administered intratracheally into immature lungs. In addition to the microbiology deficiencies, there are other substantial CMC deficiencies regarding characterization and release of drug substances, drug product controls, inadequate impurity profiles, and lack of adequate supporting stability data. Several DMFs are also deficient. The drug product manufacturing site, Laurette Pharma at Totowa, NJ, and the drug product testing site, Discovery Labs at Doylestown, PA, have a "withhold approval" recommendation from the Field Inspectors because of serious GMP violations. Of note, a previous drug manufacturing site (b) (4) which produced drug product that was used in clincial studies, also had "withhold" recommendations due to GMP violations.

Clinical and Statistical

The applicant conducted four studies with Surfaxin in patients with neonatal RDS, of which one study (Study KL4-IRDS-06) was considered as pivotal and two studies (Study KL4-IRDS-02, Study KL4-IRDS-05) were supportive. Studies KL4-IRDS-06, KL4-IRDS-02, and KL4-IRDS-05 used the prevention strategy, which is relevant to the proposed indication. A fourth study (KL4-IRDS-01) used the treatment strategy and is therefore not relevant to the proposed indication, but was the only study that used a range of doses of Surfaxin.

The doses and dosing regimens for the lung surfactant products including Surfaxin have mostly been derived empirically. This applicant selected an initial clinical dose of 133 mg/kg phospholipids based on results of primate studies. Later primate studies showed that a higher dose of 200 mg/kg produced more consistent and longer-lasting effects. A clinical dosing study (Study KL4-IRDS-01) then compared the two doses, but the study was in the treatment strategy and only eight patients received the lower dose. The dose selected for further development was 175 mg/kg with no clear rationale.

As mentioned above, the clinical program included one pivotal study, and other studies primarily provided supportive safety data. This was acceptable to the Division because of the nature of the indication and the difficulties in doing RDS studies given approved, lifesaving therapies already on the market. The single study was carefully designed in consultation with the division and the Office of Biometrics and considerations were given to eliminate potential biases. The applicant and the Division had multiple interactions during the development program of Surfaxin where the design of the pivotal study was

discussed. In subsequent sections of this document, brief comments are made on studies that have bearing on the approvability of this application. Detailed review of the clinical program and the regulatory history that summarizes the interaction between the applicant and the Division can be found in Dr. Gunkel's excellent medical review and in Dr. Starke's medical team leader memorandum.

Study KL4-IRDS-06

This was a multi-center, double-blind, active-controlled parallel group study conducted in premature neonates between 600 grams and 1250 grams birth weight. The study was conducted in 54 centers in Europe (Hungary, Poland, and Russia) and in Latin America (Brazil, Chile, Ecuador, Mexico, Panama, and Uruguay). Infants satisfying the entry criteria were randomized at a ratio of 2:2:1 to Surfaxin, Exosurf, and Survanta. Exosurf was considered the primary comparator, with Survanta included as a reference product. The hypothesis was that Survanta would be more effective than Exosurf, since the latter does not include an SP-B mimetic peptide. Patients were stratified within each category by birth weight. The first dose of surfactant was given between 15 and 30 minutes after birth and up to three subsequent doses could be given at 6 hour intervals if certain predefined criteria consistent with development of RDS were met. The study had two evaluation phases: the first phase was through 36 weeks post-conceptional age, hospital discharge, or death, whichever occurred later, and the second phase consisted of follow-up evaluations at 6 and 12 months corrected age. There were co-primary efficacy endpoints – incidence of RDS at 24 hours, and RDS-related death at 14 days. Both endpoints were adjudicated by a seven-member adjudication committee. The adjudication committee decisions were used in the primary analyses. Secondary endpoints included all-cause mortality, occurrence of air leaks, development of bronchopulmonary dysplasia (BPD), severity of RDS, number of surfactant doses, duration of oxygen supplementation, ventilation, hospitalization, and occurrence of concurrent diagnoses. The presence of air-leak at 7 days was initially a part of the composite co-primary endpoint, but it was later removed from the co-primary endpoint by the applicant prior to unblinding of the efficacy data with the Division's concurrence. There were challenges in defining the co-primary endpoints and substantiating them in the clinical setting, but the applicant adhered to the agreed upon processes and carried them out with due diligence. Safety was assessed through adverse event reports, assessment for any negative reactions to dose administration, use of concomitant medications, physical examinations, and vital signs. An event driven design was used to estimate the sample size based on published incidences of RDS and death for Exosurf-treated patients. With this scheme, 400 RDS events and 66 RDS-death events were estimated to be needed and this was anticipated to require 600 patients in the Surfaxin and Exosurf groups.

Results of the primary efficacy variable and selected secondary efficacy variables are shown in Table 2. Surfaxin was statistically significantly superior to Exosurf on the primary efficacy variables, and the secondary efficacy variables mostly tended in favor of Surfaxin. The results were consistent across populations based on birth weight, gender, and race. Importantly, Surfaxin appeared similar to Survanta on these endpoints, helping to assuage concerns that this artificial product might be inferior to a naturally-derived

surfactant. Curiously, the non-RDS related death rate tended to be higher in the Surfaxin group compared to the other groups. This increase was primarily due to deaths from renal failure and from sepsis (Table 2). These two causes of death are difficult to relate to Surfaxin from a physiological or pharmacologic standpoint. It was reassuring that two other causes of death, intraventicular hemorrhage and pulmonary hemorrhage, which are considered to be physiologically related to RDS, favored Surfaxin. In the decisions of the adjudication committee, these two causes of death were frequently not counted under RDS-related death.

There were two safety issues that were of concern. The first was the suggestion of higher rates of infection related events in Surfaxin treated patients including death from sepsis as discussed above. The second was negative reactions related to the administration of Surfaxin, which included obstruction of the endotracheal tubes and interruption and discontinuation of dosing. These reactions occurred most likely because the volume of Surfaxin was relatively larger compared to other surfactants. These reactions related to administration of Surfaxin have important clinical implications.

Table 2. Efficacy results, n (%)

	Surfaxin (n=527)	**Exosurf (n=509)**	**Survanta (n=258)**	**p-value**	
				vs Exosurf	**vs. Survanta**
RDS at 24 hr	206 (39.1)	240 (47.2)	86.3 (33.3)	0.005	0.108
RDS-related mortality through 14 days	25 (4.7)	49 (9.6)	27 (10.5)	0.001	0.001
Air leak at 7 days	80 (15.2)	89 (17.5)	35 (13.6)		
All cause mortality, day 14	84 (15.9)	86 (16.0)	48 (18.6)		
Alive and no BPD at 36 wk	313 (59.4)	274 (53.8)	144 (55.8)		
BPD at 36 wk	212 (40.2)	229 (45.0)	110 (42.6)		
Non-RDS related mortality	59 (11.2)	37 (7.3)	21 (8.1)		
Renal failure	7 (1.3)	1 (0.2)	0 (0)		
Sepsis	23 (4.4)	18 (3.5)	4 (1.6)		
Intraventicular hemorrhage	17 (3.2)	28 (5.5)	18 (7.0)		
Pulmonary hemorrhage	15 (2.8)	12 (2.4)	11 (4.3)		

Study KL4-IRDS-02

This was a multi-center, double-blind, active-controlled parallel group study conducted in premature neonates between 600 grams and 1250 grams birth weight. The study was conducted in centers in US, Canada, UK, and several European countries. Infants satisfying the entry criteria were randomized to Surfaxin or Curosurf. Patients were stratified within each category by birth weight. The first dose of surfactant was given between 15 and 30 minutes after birth and up to two subsequent doses could be given at 6 hour intervals if certain predefined criteria consistent with development of RDS were met. The study had two evaluation phases: the first phase was through 36 weeks post-conceptional age, hospital discharge, or death, whichever occurred later, and the second phase consisted of follow-up evaluations at 6 and 12 months corrected age. The primary efficacy endpoint was the incidence of being alive without BPD at 28 days of age. Investigators determined whether BPD was present according to predefined criteria. Secondary endpoints included RDS at 24 hours, RDS related mortality at 14 days, all-

cause mortality, occurrence of air leaks, bronchopulmonary dysplasia (BPD), severity of RDS, number of surfactant doses, duration of oxygenation, ventilation, hospitalization, and occurrence of concurrent diagnoses. Safety was assessed through adverse event reports, negative reactions to dose administration, concomitant medications, physical examination, and vital signs. The study was of non-inferiority design with a non-inferiority margin of -14.5% and a sample size of 248 patients per group was determined to be needed for the study. The selection of the non-inferiority margin is questionable because the margin was set based on results of only one limited treatment study comparing Curosurf to placebo and the primary endpoint was different than the one used in this study (Pediatrics 1988; 82:683-691). Therefore, the validity of the study for assessing definitive efficacy was questioned by the Agency even prior to its conduct. Of note, this study was terminated prematurely for business reasons, which further weakens its contribution to the efficacy assessment.

Results of the primary efficacy variable and selected secondary efficacy variables are shown in Table 3. Efficacy conclusions from this study are very limited because of reasons stated above. Surfaxin was generally well tolerated in this study.

Table 3. Efficacy results, n (%)

	Surfaxin (n=119)	**Curosurf (n=124)**
Alive without BPD at 28 days	45 (37.8)	41 (33.1)
RDS at 24 hr	22 (18.5)	19 (15.3)
All cause mortality at 14 days	13 (10.9)	17 (13.7)
Non-RDS related mortality	12 (10.1)	17 (13.7)
Air leak at 7 days	11 (9.2)	9 (7.3)
Alive and no BPD at 36 wk	77 (64.7)	84 (67.7)

Study KL4-IRDS-05

This was a single-center open-label study conducted in 11 premature neonates in Ecuador to examine the logistics and feasibility of proceeding to larger studies. All patients were treated with 175 mg/kg of Surfaxin, half of the patients were to receive the doses in two half-dose aliquots and half of the patients were to receive the doses in four quarter-dose aliquots. Patients in the study were followed through 28 days and there was no long-term follow-up.

Summary of efficacy and safety findings:

The efficacy and safety results of the single pivotal study KL4-IRDS-06 and supportive data from other studies support approval of Surfaxin for the prevention of neonatal RDS in premature infants. Efficacy results of study KL4-IRDS-06 were persuasive, and efficacy data from study KL4-IRDS-02 was not contradictory. The major safety concern with Surfaxin is the possibility of increased infection and more frequent negative reactions to dose administration compared to other surfactants. These safety concerns do not override the beneficial effects of the drug, given the outcome results. Informaiton about both safety issues can be included in the product labeling and can be followed up

post-approval. Specifically the applicant will be asked to incorporate postmarketing surveillance plans to monitor the risk of infection-related events, and explore efficacy of lower doses that can reduce negative reactions to dose administration without affecting efficacy.

The Division requested that the applicant conduct an assessment of anti-surfactant antibodies in a subset of infants in the pivotal study. The applicant did not perform this assessment. The lack of this assessment will not preclude approval of this application, because premature infants are unlikely to mount a vigorous immune response. However, the package insert should contain a statement that no clinical immunogenicity was assessed.

Animal Pharmacology and Toxicology

The animal pharmacology and toxicology studies conducted by the applicant for Surfaxin were somewhat limited because of the nature of the drug product and the proposed indication (i.e., this drug is only to be administered acutely). Animal pharmacology studies demonstrated reduced surface tension in ex vivo systems; and increased lung compliance and expansion, improved gas exchange, and reduced ventilatory pressures in premature animal models. Animal toxicology studies were conducted in neonatal rabbits, neonatal dogs, and neonatal cats. All studies were characterized by respiratory distress, and early deaths in rabbits from respiratory distress. Histopathology in repeat dose studies showed evidence of lung inflammation with lung histiocytosis and inflammatory cell infiltrates. NOAELs could not be established because the findings of lung inflammation occurred in all doses. Clinical studies were allowed to proceed because of the intended clinical benefit. Reproductive and carcinogenicity studies were not performed for this product. The applicant performed animal immunotoxicity studies in guinea pigs, which showed no evidence of hypersensitivity response. These animal pharmacology and toxicology studies were reviewed in detail by Dr. Hao and were found to be adequate to support approval.

Clinical Pharmacology and Biopharmaceutics

There were no clinical pharmacology studies conducted for this Surfaxin because this is a "topically" applied and locally active drug product that does not appreciably gain entry into the systemic circulation.

Data Quality, Integrity, and Financial Disclosure

DSI audited four study sites that participated in the pivotal study KL4-IRDS-06, the adjudication process of study KL4-IRDS-06, and the laboratory that conducted the animal toxicology study. The clinical study sites were selected because of high enrollment, high number of deaths, and/or inconsistencies in the cause of death determined by the investigator and the adjudication committee. Sites were selected to evenly represent the European and Latin American countries. The DSI audit concluded that all sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. Minor deviations were noted in some sites, but

these were not of a magnitude that would impact the conclusions of the studies. During review of the submission, no irregularities were found that would raise concerns regarding data integrity. Despite some history of ethical issues in discussion leading up to the pivotal trials, no important ethical issues were found in the final program. All studies were performed in accordance with accepted clinical standards. The applicant submitted acceptable financial disclosure statements. None of the disclosures raise questions about financial conflict of interest.

Pediatric Considerations

Surfaxin is proposed to be indicated for a condition restricted to premature infants; therefore, there are no further pediatric considerations for this application.

Product Name

The proposed product name Surfaxin was reviewed by the Division of Medication Errors and Technical Support (DMETS), and the Division of Drug Marketing, Advertising, and Communication (DDMAC). DMETS does not recommend the use of the propriety name Surfaxin because of the sound alike similarity of the name Surfaxin and the word surfactant, which is the name of this class of drug. I disagree with the recommendation, because a possible mistake would not be a safety issue as the patient will receive a drug of the same class. Furthermore, such an error is somewhat unlikely, because a delivery room will likely have one specific surfactant available for use because of formulary considerations, and if more than one surfactant is available for use, it is likely that the health care team will have decided before delivery of the baby on the surfactant that will be used in a specific case. My assessment on the propriety name is the same as that of the medical team leader, but differs from the medical reviewer. DDMAC has determined that the proprietary name is acceptable from a promotional perspective.

Labeling

The label has been reviewed by various disciplines of this Division and by DDMAC. Detailed label negotiation was not done with the Applicant because the application is not heading towards an approval action. The comments on the label are captured in various discipline reviews, specifically in the clinical reviews. I generally concur with the comments captured in these reviews. Some of the broader comments will be transmitted to the Applicant in the action letter. There are some major problems with the proposed label that are worth noting. (b) (4)

[redacted]

(b) (4)

Action

The submitted clinical data support the approval of Surfaxin (lucinactant) Intratracheal Suspension for the prevention of neonatal RDS in premature infants, but there are several major CMC deficiencies as discussed above that will preclude approval of this application in this cycle. The applicant will need to resolve the CMC deficiencies before the application can be approved. The product label will also need substantial revision as discussed above. I recommend an APPROVABLE action for this application.

There are two unresolved clinical issues that will need to be addressed by the applicant. First, the applicant did not investigate the immunogenicity assessment for anti-surfactant antibodies in the pivotal study. Second, there is virtually no dose-ranging information in the clinical program and the proposed dose entails administration of a large volume of the drug product that was noted to cause negative reactions in patients. While these are not approvability issues, the applicant should be asked to address these. It is possible that these issues can lead to phase 4 commitment studies.

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/s/

Badrul Chowdhury
2/8/05 09:51:37 AM
MEDICAL OFFICER

CLINICAL TEAM LEADER MEMORANDUM

Date: January 14, 2005

To: NDA 21-746

From: Peter Starke, MD
Medical Team Leader
Division of Pulmonary and Allergy Drug Products, HFD-570

Product: Surfaxin® (lucinactant) Intratracheal Suspension

Applicant: Discovery Laboratories, Inc.

Re: First cycle clinical review
PDUFA date February 11, 2005

Administrative and Introduction

This is a clinical team leader memorandum for NDA 21-746 from Discovery Laboratories, Inc. for a drug product with the established name of Lucinactant and a proposed trade name of Surfaxin®. Surfaxin is a peptide-containing pulmonary surfactant. It differs from other surfactants in that it is composed of phospholipids, a fatty acid, and a synthetic peptide, sinapultide, which is unique to this product. Sinapultide is a peptide of 21 lysine and leucine residues developed to specifically mimic the structural and behavioral properties of SP-B, one of the four proteins identified in natural mammalian lung surfactant. Lung surfactants act locally at the alveolar-air interface to reduce surface tension on the alveolar surface and prevent the lungs from collapse at the end of expiration.

The proposed indication is "for the prevention of Respiratory Distress Syndrome (RDS) in premature infants." Because it is intended to prevent RDS, a disease that begins in the first hours after birth, the first Surfaxin dose would be given as soon as possible after birth, preferably within 30 minutes. Up to three additional doses would be given at minimum 6-hour intervals if RDS develops. Dosing is intended to be confined to the first 48 hours of life. Since the incidence of RDS decreases with increasing gestational age, the appropriate patient population is neonates born prematurely enough to have a high likelihood (≥50% risk) of developing RDS and therefore with best chance to benefit from a prevention approach. The proposed population group for Surfaxin is therefore appropriate: neonates of birth weights 600-1250 grams and less than 32 weeks gestational age. As with any preventive strategy, some patients will inevitably be treated who would never have developed RDS.

The Applicant is seeking only a prevention, not a treatment, indication. Surfaxin has not been evaluated for the treatment or "rescue" of infants who develop RDS. Four surfactants have been approved in the United States for treatment of NRDS (Exosurf, Survanta, Infasurf, Curosurf), of which three are also approved for the prevention indication (Exosurf, Survanta, Infasurf). Surfaxin is the only one of the surfactants that contains a synthetic peptide. The other surfactants are extracts of mammalian lungs

(Survanta, Infasurf, Curosurf) or a combination of non-peptide ingredients (Exosurf). Of note, Exosurf, the primary comparator to Surfaxin in the major efficacy study (KL4-IRDS-06), is no longer marketed in the United States. It was at the time the Surfaxin clinical program was developed.

There is an extensive history of interactions between the sponsors of the IND for Surfaxin and the Division, which will not be discussed in detail here. Please refer to the excellent Medial Officer review by Dr. Gunkel for details. However, there was agreement between the sponsor and the Division that the application would contain a single major efficacy study of a superiority design, with Exosurf as the primary comparator, and a natural surfactant (Survanta) as a reference. Initial agreed-upon co-primary endpoints were incidence of RDS at 24 hours and the composite endpoint of RDS-related deaths by 14 days and/or air leak by 7 days. Subsequently, the Sponsor chose to change the composite endpoint to a non-composite one by dropping the air leak endpoint, thus leaving the endpoints to be the incidence of RDS at 24 hours and RDS-related deaths by 14 days. It is important to note that final agreement on these endpoints was not reached with the Division until the pivotal efficacy study had begun, indeed not until after all patients had been enrolled, but before any results or treatments were revealed.

The applicant is also studying Surfaxin for treatment of meconium aspiration syndrome (MAS), asthma, and adult respiratory distress syndrome (ARDS). Information from studies for these indications was reviewed as part of the safety review.

Consultations were provided for this application by the Division of Scientific Investigations (DSI), the Division of Drug Marketing, Advertising, and Communication (DDMAC), and the Division of Medication Errors and Technical Support (DMETS).

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

Surfaxin is a peptide-containing pulmonary surfactant formulated as an opaque off-white suspension for intratracheal instillation. It is composed of phospholipids, a fatty acid, and the synthetic peptide, sinapultide. The specific composition per mL is 30 mg phospholipids (22.5 mg dipalmitoylphosphatidylcholine, 7.5 mg palmitoyloleoyl-phosphatidylglycerol), 4.05 mg palmitic acid, and 0.801 mg sinapultide. The proposed packaging is in glass vials containing (b) (4) of product. It is stored refrigerated and warmed to room temperature before use.

Dr. Eugenia Nashed has performed a comprehensive CMC review. Her review details the significant issues and problems that will preclude approval of the application in the first review cycle. The following briefly summarizes the findings.

- Three of four DMFs (Drug Master File) supporting the drug substance are inadequate.
- Only 6 months of stability have been submitted.
- The proposed method for biological activity testing is inadequate.
- There are inadequate methods and specifications for an impurity profile.
- This drug product (b) (4) rather, the manufacturing process must be sterile, a process that relies heavily on the presence of Good

Manufacturing Procedures (GMP). Basic microbiology information, especially media fill, for this sterile fill drug product was only submitted to the appropriate DMF in December, 2004. A microbiological consultation is pending.

The major area of concern had been and continues to be in the GMP compliance of the manufacturing and testing sites and processes. This is an issue that directly impacts clinical issues, since infection-related mortality within the first two weeks of life (with a potential but clinically unsubstantiated concern for sterility of the drug product) was an important safety consideration for this drug product. Manufacture was transferred from a previous site (b) (4) because of repeated instances of GMP noncompliance. Of note, the (b) (4) site was the site of manufacture for the batches used in the clinical trials for this drug product. The current site (Laureate Pharma) has also been cited for numerous GMP violations and a repeat inspection is in progress. Final testing of the product is in the hands of the Applicant and numerous issues have been identified at their site, including out-of-specification results, lack of written SOPs, lack of adequately validated methods, and lack of appropriate documentation. Site inspections have not been completed as of the time of this memorandum.

In summary, the CMC review has identified numerous issues that result in inadequate assurance that drug product can be manufactured reliably and consistently with the quality necessary for marketing. These deficiencies preclude approval on this cycle.

Pharmacology and Toxicology

Dr. Huiqing Hao performed the Pharmacology and Toxicology review and recommends an Approval. The following briefly summarizes the findings.

Preclinical pharmacology studies demonstrated reduced surface tension in ex vivo systems, and increased lung compliance and expansion, improved gas exchange, and reduced ventilatory pressures in premature animal models. Toxicology studies were performed in neonatal rabbits, neonatal dogs, and neonatal cats. All studies were characterized by early deaths due to respiratory distress. Histopathology in all repeat dose studies showed evidence of lung inflammation with lung histiocytosis and inflammatory cell infiltrates, especially macrophages. NOAELs could not be established because the findings of lung inflammation were universal. Clinical studies have proceeded and approval is recommended because of the intended clinical benefit.

Carcinogenicity studies were not performed for this product.

The Applicant performed pre-clinical immunotoxicity studies in guinea pigs, which showed no evidence of an immune response. Although the Division requested assessment of anti-surfactant antibodies in a subset of infants in the pivotal study, this was not performed. The lack of clinical immunogenicity assessment is acceptable for the NRDS indication, since premature neonates are immunologically immature and mount very poor immune responses. However, the package insert should contain a statement that no clinical immunogenicity assessment was performed.

Dr. Hao has recommended some modifications to the proposed package insert in describing mechanism of action and results of mutagenicity testing.

Clinical Pharmacology and Biopharmaceutics

Since this is a topically applied and locally active drug product, there were no clinical pharmacology studies for this application.

Clinical and Statistical

The development plan for this product consisted of the four studies in patients with neonatal RDS, as shown in Table 1 below. Of the four studies, three used an RDS prevention design strategy and one used a rescue strategy. Of the three prevention studies, only one study, KL4-IRDS-06, was considered pivotal from an efficacy perspective. KL4-IRDS-02 was considered by the Applicant to be supportive; however, its usefulness is severely restricted by significant flaws in study design. Among others, these flaws include use of Curosurf in a dose and dosing frequency not specified in the Curosurf label. KL4-IRDS-05 had too few patients be meaningfully interpretable. While only KL4-IRDS-06 and KL4-IRDS-02 were evaluated for efficacy, in his excellent review Dr. Gunkel evaluated all studies from a safety perspective, including MAS and ARDS studies.

Of note, the dose of Surfaxin chosen to be administered appears to have been picked arbitrarily, and no dose-ranging was ever carried out. In the whole development program, only eight patients received a lower dose, and this was in a rescue study design. Other limitations include the fact there are practically no Black patients in the entire clinical program, and the difficulties with interpretability for a US population with regard to differences in clinical practice in the neonatal intensive care nursery for studies performed in different parts of the world.

Table 1. Table of Neonatal RDS Studies

Study	Centers	Design	Test Products/ Therapies	N	Endpoints	Status
KL4-IRDS-06 **Pivotal Efficacy Study**	54 US, Europe, Latin America	•Prevention •Neonates 600-1250g •Randomized, double-blind, event-driven, active-controlled	Surfaxin 175 mg/kg up to 4x Exosurf 67.5 mg/kg up to 3x (Comparator) Survanta 100 mg/kg up to 4x (Reference)	527 509 258	•Co-Primary: RDS at 24 hr RDS-deaths at 14 days •Numerous secondary •6- & 12-month corrected age follow-up	Complete (12-month follow-up ongoing)
KL4-IRDS-02	35 US, N America, Europe	•Prevention •Neonates 600-1250g •Randomized, double-blind, active-controlled	Surfaxin 175 mg/kg up to 3x Curosurf 175 mg/kg x 1; 100 mg/kg up to 2x	124 128	•Primary: Alive without BPD at 28 days •Numerous secondary •6- & 12-month corrected age follow-up	Complete
KL4-IRDS-05	1 Ecuador	•Prevention •Neonates 600-1250g	Surfaxin 175 mg/kg up to 4x: 2 half-doses		Numerous - similar to “06” and “02” studies	Complete

Study	Centers	Design	Test Products/ Therapies	N	Endpoints	Status
		•Open-label, uncontrolled •Evaluate two ½-doses vs. four ¼-doses	4 quarter-doses	9 2		
KL4-IRDS-01	6 US	•Rescue •Neonates 750-1750 g •Open-label, uncontrolled	Surfaxin 133 mg/kg or 200 mg/kg up to 2x	8 39	Efficacy endpoints not defined. Info collected about ventilation requirements, RDS, BPD, death	Complete

Medical Officer Review of NDA 21-746, Dr. J. Harry Gunkel, Table 3

Study KL4-IRDS-06

The pivotal efficacy and safety study, KL4-IRDS-06, was a large, multicenter, randomized, active controlled study conducted in Eastern Europe and Latin America. As noted above, co-primary and secondary endpoints were discussed extensively with the Division, and although one of the co-primary endpoints was changed at the last moment, they were agreed upon.

Methodology

Premature neonates between 600 and 1250 grams birth weight were randomized immediately after birth to receive one of three surfactants: Surfaxin, Exosurf, or Survanta. Patients were stratified for randomization into three birth weight strata. The first dose of surfactant was given between 15 and 30 minutes after birth and up to three subsequent doses could be given at 6 hour intervals if the following criteria for respiratory distress were met: the patient continued to require mechanical ventilation with MAP ≥6 cm H_2O and FiO_2 ≥30% to maintain PaO_2 between 50 and 80 mmHg or an oxygen saturation between 88 and 95% and a chest radiograph consistent with RDS. Procedures were used to mask the treatments to caregivers.

The study had two evaluation phases. The first was through 36 weeks post-conceptional age (PCA), hospital discharge, or death, whichever occurred later. The second phase consisted of follow-up evaluations at 6 and 12 months corrected age.

The co-primary efficacy endpoints were incidence of RDS at 24 hours and RDS-related death at (through) 14 days, both per an independent Adjudication Committee. Secondary endpoints included all-cause mortality; occurrence of air leaks; severity of RDS; number of surfactant doses; incidence of bronchopulmonary dysplasia (BPD); duration of oxygen, ventilation and hospitalization; and the occurrence of concurrent diagnoses. Safety was assessed through adverse events reports, negative reactions to dose administration, concomitant medications, and physical examination and vital signs.

The primary comparison was a superiority comparison to Exosurf, one of the first approved surfactants, and one which previously was shown to have efficacy against placebo including on mortality endpoints. It was not possible to include a placebo control group because the approved surfactants beneficially affect survival or other clinically important outcomes and withholding them would be unethical. Randomization was in a 2:2:1 ratio, with a Survanta arm included as a reference. An event driven design

was used to estimate sample size based on published incidences of RDS and death for Exosurf-treated patients. With this schema, 400 RDS events and 66 RDS-death events would be needed and this was anticipated to require 600 patients in the Surfaxin and Exosurf groups.

Efficacy

There were 524, 506, and 258 treated patients in the Surfaxin, Exosurf, and Survanta groups, respectively. Demographics were similar for all three treatment groups. The study won on both co-primary endpoints, as shown in Table 2. These analyses were confirmed by the FDA statistician.

Incidence of RDS at 24 hours is a reasonable endpoint, and Surfaxin won on this co-primary endpoint in comparison to Exosurf, although it did not fare numerically as well as Survanta. RDS is a well-established clinical syndrome and the diagnostic criteria are relatively straightforward. The endpoint of RDS was used with all other surfactant products for the prevention indication. For the pivotal study, diagnostic criteria included a positive chest x-ray (per the Adjudication Committee) and ≥30% FiO_2 at 24 ±4 hours. Of concern, all that was needed was at least one FiO_2 measurement ≥30% to qualify, but this is considered a minor flaw in the study design. In order to place the incidence of RDS into perspective, historical results for other surfactants (based on their package inserts) are shown in Table 3. The results for Surfaxin compare reasonably favorably.

Surfaxin also won on the co-primary endpoint of RDS-related mortality through 14 days, as per the Adjudication Committee findings. This endpoint, however, is a little less clear-cut. Despite the difference in RDS-related mortality, there was no difference between treatment groups in all-cause mortality at any time point in the study. The difference is the incidence of non-RDS-related mortality (all the deaths besides those RDS-related) within the first 14 days, which was significantly higher in Surfaxin patients than Exosurf patients. Dr. Gunkel performed multiple evaluations to assess how realistic, reproducible, and meaningful this finding was, both from an efficacy and from a safety point of view. Please see his review and the safety section below for further details. Note, however, that it is quite reasonable for the applicant to have selected the RDA-related mortality endpoint, because surfactant treatment does not deal with the rest of organ systems that are immature in these sick neonates.

Analyses of results for subgroups of males, females, white, non-white, 600-800 grams, 801-1000 grams, and 1001-1250 grams were generally consistent with the primary and secondary efficacy and safety findings. However, Black patients were under-represented.

In this study, there was no evidence that Surfaxin is superior in any complication of prematurity, RDS, or mechanical ventilation, save the two primary endpoints. For secondary endpoints, there were no treatment differences for number of surfactant doses, severity of RDS, duration of supplemental oxygen, mechanical ventilation, or hospitalization. Three secondary endpoints are important to note: air leak at 7 days, alive with no evidence of BPD at 36 weeks, and mortality beyond 14 days. Air leak at 7 days is considered important since it was one of the original composite co-primary endpoints. The percent alive without evidence of BPD at 36 weeks is a time that is generally accepted to be the earliest that one can establish this diagnosis, and therefore is considered clinically meaningful. Both of these secondary endpoints are shown in Table

2. These two endpoints lend credence to the efficacy of the drug product. Mortality before and after 14 days is important because of the mortality safety concerns uncovered in the review of this drug product, as discussed below. (b) (4)

Interpretability and applicability of results is, of course, a major concern for studies performed in very ill patients who are treated in ex-US centers which may have different care regimens than those in the US. Dr. Gunkel compared outcomes for various endpoints to previously published studies at US centers. He noted that the experience in KL4-IRDS-06 for death, pneumothorax, and NEC was not much different from the North American reports. The striking difference was in the incidences of severe IVH which was much higher in patients in KL4-IRDS-06. However, this difference was noted reasonably equally across all three treatment groups.

Safety

The second endpoint of incidence of RDS-related mortality through 14 days raises both efficacy and safety issues. While the incidence of all-cause mortality at 14 days was numerically similar to that of Exosurf and Survanta, the Adjudicated results for this endpoint had lower mortality for Surfaxin than either of the other treatments, and consequently higher incidence of non-RDS related mortality during this 14-day time period. Dr. Gunkel looked into this issue quite closely, as the issue leads to implications regarding efficacy on the one hand, and issues of safety on the other. The difference in mortality spans a number of diagnoses. The actual cause of death is often quite hard to determine in a very sick baby who may have multiple concurrent problems that may be life-threatening. Nevertheless, renal disease and sepsis appear to be slightly numerically higher in frequency in this sub-group, but the numbers are quite small, so interpreting the results is problematic.

Review of the Adjudicated results for mortality by 14 days did not reveal any apparent bias on the part of the Adjudication Committee. However, careful review did lead to the suspicion that much of the lower 14-day RDS-related mortality in the Surfaxin group, and consequent concern for an increase in non-RDS related mortality, may have been the result of a quirk in the Adjudicated results. This statement applies to all deaths in the Surfaxin treatment group except those due to infection/sepsis, as differences between treatment groups for this type of diagnosis cannot be as easily explained. One possibility considered is that Surfaxin, by improving respiratory-related deaths, unmasks other lethal events in this highly ill premature population. The review team could not come to a firm conclusion regarding this hypothesis, and ultimately felt that the data neither supported nor contradicted this possibility. Another possibility considered was that Surfaxin somehow is related to increased incidences of various non-RDS related mortality during the first 14 days after treatment. After careful consideration, the review team felt that of all the diagnoses, only an increased incidence of infection-related mortality by 14 days might be possibly related to Surfaxin treatment. Each of those issues is addressed below.

When one looks at the Adjudicated results for babies for whom RDS was or was not diagnosed at 24 hours, in the Surfaxin group there are more babies without a diagnosis of RDS who died of IVH or pulmonary hemorrhage (both diagnoses that the review team

felt are intimately related to RDS) than in the other two treatment groups. Since these diagnoses had been adjudicated by the committee as not RDS related, this supported the possibility of a quirk in the adjudicated 14-day mortality results that both gave Surfaxin the statistical efficacy advantage and also created the issue with safety concerns.

Regarding renally related mortalities, specific assessment of these events suggested that this diagnosis was often the terminal event of multiple lethal events, implying that there was no specific relationship between administration of Surfaxin and this type of death event.

If one eliminated any differences between treatment groups for IVH, pulmonary hemorrhage, or renally-related 14-day mortality, from an efficacy perspective the implication is that the co-primary endpoint of RDS-related mortality by 14 days was likely not as robust as the numbers appear to show. However, one is still left with a higher incidence of infection-related mortality within the first 2 weeks of life in the Surfaxin treatment group. Therefore, Dr. Gunkel carefully evaluated this issue of infection and sepsis, within the perspective that the overall mortality through 14 days was numerically similar for all three treatment groups. Although RDS-relatedness was not assessed, the increased incidence did not continue beyond the 14-day timepoint. Beyond 2 weeks, Surfaxin actually has a slight numerical mortality advantage, with no differences in sepsis or renal mortality.

Sepsis in the premature neonate is a clinical diagnosis, overlapping many other more objective diagnoses. Since no diagnostic criteria were used to establish the diagnosis in this study, the presence of sepsis is therefore a rather subjective assessment. Note that the drug product for the clinical trials was from (b) (4), a site that has had GMP issues. If one were to suspect some form of contamination of the drug product, it is not borne out in the clinical trials in the sense that there did not appear to be a higher incidence of positive blood cultures, or cultures of a specific type, in the Surfaxin group. Indeed, the total AEs and for sepsis/infection events for the whole study (not just the first two weeks) did not differ between treatment groups. Safety review of the ARDS and MAS studies also revealed some similar trends for sepsis/infection events. The bottom line is that the issue of increased incidence of sepsis/infection-related mortality in the Surfaxin-treated group within the first two weeks cannot be fully resolved with the information provided in the NDA. While it is not a strong enough safety signal to warrant prevention of an approval, the label should adequately present the potential for an increased risk within the context of the overall mortality in the first two weeks, which is similar to the other two surfactants.

There is also an issue re higher incidence of adverse events shortly after administration of Surfaxin than for either of the other drug products, leading to the suspicion that the Surfaxin dose may be higher than clinically necessary. The volume of Surfaxin administered is minimally larger than other surfactants, and this may or may not be the reason for the higher incidence of AEs. Increased reactions included pallor, obstruction of the ETT, and interruption or discontinuation of dosing, events with important clinical implications. These findings need to be included in product labeling.

Finally, in the patients evaluated so far, there is a slight difference in reports of deafness at 6 months: 4 Surfaxin patients (1.08%), 2 Exosurf patients (0.57%), 0 Survanta or

Curosurf patients. This trend needs to be followed up in the assessment of the 12-month data, and should also be included in the labeling.

Table 2 Primary Endpoints, Key Mortality and Secondary Endpoints (N, %)

	KL4-IRDS-06					KL4-IRDS-02	
	Surfaxin N=527	Exosurf N=509	Survanta N=258	Surfaxin vs. Exosurf	Surfaxin vs. Survanta	Surfaxin N=119	Curosurf N=124
Primary Endpoints							
RDS at 24 Hours by AC[a]	206 (39.1)	240 (47.2)	86 (33.3)	OR=0.679 (0.519-0.888) P=0.005	OR=1.319 (0.941-1.849) P=0.108	22 (18.5)	19 (15.3)
RDS-related Mortality by AC[a]	25 (4.7)	49 (9.6)	27 (10.5)	OR=0.417 (0.246-0.707) p=0.001	OR=0.347 (0.183-0.658) p=0.001	NA	NA
Other 14-day Mortality Endpoints							
All-cause Mortality[b]	84 (15.9)	86 (16.0)	48 (18.6)			13 (10.9)	17 (13.7)
Non-RDS-related Mortality[c]	59 (11.2)	37 (7.3)	21 (8.1)			12 (10.1)	17 (13.7)
Selected Secondary Endpoints[d]							
Air Leak at 7 Days[e]	80 (15.2)	89 (17.5)	35 (13.6)			11 (9.2)	9 (7.3)
Alive No BPD at 36 wks PCA	313 (59.4)	274 (53.8)	144 (55.8)			77 (64.7)	84 (67.7)

a Co-primary efficacy endpoint for KL4-IRDS-06. Applicant's primary analysis based on AC results. Source: Source: M5, v 56, sec 5.3.5.3, p 42 and M5, v 56, sec 5.3.5.3, p 46

b Secondary endpoint. Source: M5, v 56, sec 5.3.5.3, p 92

c FDA analysis

d Source: M5, v 56, sec 5.3.5.3, Tables 2.2.2.1E, 2.2.2.3A, 2.2.2.3[E]

e Results for air leak are shown not imputed for death

Medical Officer Review of NDA 21-746, Dr. J. Harry Gunkel, Tables 9, 12, and 14

Table 3. Incidence of RDS in Exosurf and Survanta Package Inserts (%)

	Exosurf Study A[a] (700-1350 g)		Exosurf Study B[a] (700-1100 g)		Survanta Study A[b] (600-1250 g)		Survanta Study B[b] (600-1250 g)		Published Study[c] (<29 wks gestation)	
	Exo	Pbo	Exo	Pbo	Surv	Pbo	Surv	Pbo	Exo	Infa
Incidence of RDS (%)	42	46	55	55	27.6	63.5	28.6	48.3	42	16

Exo=Exosurf; Pbo=placebo; Surv=Survanta; Infa=Infasurf

a RDS=FiO2 ≥30% to maintain PaO2 ≥50; MAP ≥6; confirmatory chest x-ray@ 24 hrs; no other cause of resp distress

b RDS=qualified for second dose; i.e., confirmatory chest x-ray 6-48 hrs; mechanical ventilation; FiO2 ≥40%

c RDS=FiO2 ≥30% @ 24 hrs; confirmatory chest x-ray 16-32 hrs

Medical Officer Review of NDA 21-746, Dr. J. Harry Gunkel, Table 10

Abuse Considerations

There are no concerns for abuse of this drug product.

Data Quality, Integrity, and Financial Disclosure

During review of the studies, no irregularities that would raise concerns regarding data integrity were found. No ethical issues were present. All studies were performed in accordance with accepted clinical standards. There were no financial disclosure concerns raised during the review process.

A DSI audit was requested for the pivotal study, KL4-IRDS-06. The clinical sites recommended for audit were selected based on two criteria: 1) the sites that enrolled the most patients; and 2) the sites where there were numerous deaths and/or where there seemed to be inconsistencies between the causes of death as determined by the Adjudication Committee compared to the investigator or compared to the reviewer's opinion. Sites were also selected to evenly represent the European and Latin American countries. Audit of the adjudication process in this study was also requested using the Applicant's records of the patients who died at the same centers included in the clinical audit.

The inspectors issued 483s at some clinical sites for use of unapproved informed consent forms; absent source documentation for some results; and procedures in violation of protocol. At some sites, no 483s were issued.

Audit of the adjudication records and process found scattered instances of judgments out of compliance with the committee's SOPs; missing source documentation for some judgments; and procedures not compliant with the SOPs. The overall assessment of the auditors, however, was that there were no significant issues and that the data are reliable.

Product Name

The Division of Drug Marketing, Advertising, and Communication (DDMAC) and Division of Medication Errors and Technical Support (DMETS) provided consultations review the proposed trade name of Surfaxin®. DMETS does not recommend the use of

the proprietary name, "Surfaxin." DMETS believes that the sound-alike similarities between the name, Surfaxin, and the word, surfactant, increases the risk of confusion and medication errors involving the product, Surfaxin, and other lung surfactants. I disagree with this assessment. I believe that the name is sufficiently different from what is actually the generic name for this drug class, that safety is not an issue. If a nurse heard surfactant for Surfaxin, the worst possible mistake would be treatment with Surfaxin rather than another surfactant, yielding a competitive advantage for Surfaxin over other surfactants. Surprisingly, DDMAC found the proprietary name acceptable from a promotional perspective. I recommend that the Division allow use of the trade name, Surfaxin. This recommendation differs from that of the primary medical reviewer.

Labeling

Labeling was submitted, reviewed, and compared with the latest package inserts from approved surfactants. Several major areas of concern were identified, most of which are of a promotional nature. Note that promotional and/or potentially unsubstantiated claims appear throughout the text of the PI, and these will need culling. Since this drug product will not receive an approval action in this cycle, none of these concerns were discussed with the applicant. Therefore, all will need to be addressed by the applicant prior to an approval action. Please see Dr. Gunkel's review for a more in-depth review of the labeling issues. DDMAC has also provided some comments regarding the draft labeling. Comments will be formulated for the action letter. Some of the major labeling issues that I have noted are listed below, by section.

- (b) (4)
- (b) (4)
- (b) (4)

- (b) (4)
- (b) (4)
- (b) (4)

Summary and Recommendations

Regarding efficacy, if one accepts the adjudicated mortality results, I believe efficacy is established. If one does not accept the adjudicated results, one can still argue that since all-cause mortality by 14 days is similar for all three drugs, and other pertinent and clinically meaningful endpoints are favorable, efficacy is sufficiently established for this drug product.

Regarding safety, in the pivotal study we are left with a suspicion of two safety issues: 14-day non-RDS related mortality safety (particularly with regard to infection) and peri-administration safety. While there are safety issues, I believe that these can be dealt with in the label. Nevertheless, I would like to see some further post-approval exploration of dose-ranging and safety re infection (and renal issues) within the first two weeks of life.

I realize that CMC issues preclude approval on this cycle. Nevertheless, from a clinical perspective, I recommend taking an Approval action for this drug product, pending substantive labeling changes as noted above.

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/s/

Peter Starke
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	021746
Submission Code	N000
Letter Date	April 13, 2004
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Reviewer Name	John Harry Gunkel, M.D.
Review Completion Date	January 14, 2005
Established Name	Lucinactant
(Proposed) Trade Name	Surfaxin®
Therapeutic Class	Lung surfactant
Applicant	Discovery Laboratories, Inc.
Priority Designation	S
Formulation	Suspension (30 mg phospholipids/mL)
Dosing Regimen	5.8 mL/kg q6h, up to 4 doses
Indication	Respiratory Distress Syndrome
Intended Population	Premature Neonates

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List of Abbreviations

AC	Adjudication Committee
AE	adverse event
ARDS	acute/adult respiratory distress syndrome
BPD	bronchopulmonary dysplasia
CRF	case report form
DPPC	dipalmitoylphosphatidylcholine
ETT	endotracheal tube
FiO_2	fraction of inspired oxygen
IVH	intraventricular hemorrhage
MAP	mean airway pressure
MAS	meconium aspiration syndrome
NEC	necrotizing enterocolitis
NRDS	neonatal respiratory distress syndrome
PCA	post-conceptional age
PDA	patent ductus arteriosus
PEEP	positive end expiratory pressure
PIE	pulmonary interstitial emphysema
PIP	peak inspiratory pressure
PVL	periventricular leukomalacia
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
SaO_2	arterial oxygen saturation
SOC	standard of care
U.S.	United States

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The clinical recommendation for this application is **Approval**. Labeling changes will be required and CMC issues will likely preclude the approval in the first cycle, but clinical efficacy and safety have been adequately demonstrated.

The recommendation is founded in the demonstrated effectiveness of Surfaxin® in preventing neonatal respiratory distress syndrome (RDS) and deaths related to RDS. The incidence of RDS was about 17% less in patients treated with Surfaxin than with the active comparator Exosurf, and RDS-related mortality was approximately half the rate in Surfaxin patients (4.7 vs. 9.6%). Consistent results were found in population subgroups based on birth weight, gender, and race.

The evidence was provided by a single, multicenter, multinational, randomized study that compared Surfaxin to Exosurf in a superiority design. A second active comparator, Survanta, was included for reference. The single study met the standards established by the FDA guidance on providing evidence of effectiveness in a single study, and in addition, two other efficacy studies provided results that were supportive. There were challenges in defining the two co-primary endpoints (incidence of RDS and RDS-related mortality) and substantiating them in the clinical study setting, but the Applicant adhered to the agreed-upon processes for dealing with the challenges and carried them out with due diligence.

There was no difference between the surfactants in mortality from any cause, but there was a numerical advantage for Surfaxin that persisted through a one-year follow-up period. Other secondary endpoints generally supported the primary effects of Surfaxin on RDS; however, (b) (4) (b) (4)

The effects of Surfaxin were accompanied by two safety concerns. The first was the possibility for increased infection, and the second was more frequent negative reactions to dose administration than the other surfactants. Neither risk rose to a level to overrule the beneficial effects of the drug, as long as information about both is included in product labeling.

For the first surfactants approved, the benefit/risk was compellingly positive compared to placebo. In assessing benefit/risk for this application, the ratio is naturally made different by availability of other products, but the essence remains the same. Preventing a serious disease with its associated lethality in the most fragile of all populations is of great clinical benefit. It was a natural consequence that a critical component of this review was to examine whether there was evidence of any "trade-off" in that benefit; i.e., increasing the risk to suffer or die for another reason. In a clinical setting of such high acuity, it is difficult to determine for certain a single cause of death and the adjudication process employed in this program amply demonstrated the difficulties. After exhaustive examination, however, this review concludes that there is no

evidence for the hypothetical trade-off. That is, the benefit is real. The safety findings of concern are also real, to be sure, but do not overrule the appreciable benefit of the product.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Applicant's proposed Risk Management program is acceptable (b) (4)

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments are required.

1.2.3 Other Phase 4 Requests

The Applicant will be encouraged to further explore other doses of Surfaxin. Smaller doses may be equally effective and also reduce the risk of negative reactions to dose administration.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Neonatal RDS develops when birth occurs prematurely before full development of the pulmonary surfactant system. Without surfactant, the lungs collapse at the end of expiration resulting in generalized atelectasis. Respiratory failure ensues and is often accompanied by several related complications, all leading to a syndrome of high morbidity and mortality if left untreated. Over the past decade, exogenous surfactants have been developed to prevent and treat RDS.

Surfaxin (Lucinactant) is a peptide-containing pulmonary surfactant formulated as an opaque off-white suspension for intratracheal instillation. It is composed of phospholipids, a fatty acid, and sinapultide. Surfaxin is a new molecular entity by virtue of the constituent sinapultide, a unique synthetic peptide developed for this product. No other product contains sinapultide. Sinapultide is a peptide of 21 lysine and leucine residues developed to specifically mimic the structural and behavioral properties of SP-B, the naturally occurring surfactant-associated protein most associated with reducing alveolar surface tension.

The proposed indication for Surfaxin is the prevention of RDS in premature infants. The incidence of RDS decreases with increasing gestational age. For a preventive approach, the appropriate patient population is those neonates born prematurely enough to have at least a 50% risk of RDS; i.e., those with the best chance to benefit from prevention. The proposed population group for Surfaxin is neonates of birth weights 600-1250 grams (approximately 24-32 weeks gestational age), a population at appropriately high risk for RDS. As with any preventive strategy, some patients will inevitably be treated with Surfaxin who would never have developed RDS at all.

Up to four doses of Surfaxin are proposed. Because RDS begins in the first hours after birth, the first dose would be given as soon as possible after birth, preferably within 30 minutes. Up to three additional doses would be given at minimum 6-hour intervals if RDS develops. Surfaxin is instilled intratracheally through the patient's endotracheal tube. Each of the doses is divided into four quarter-doses for administration. Portioning the total dose reduces the volume instilled into the lungs at any one time and also facilitates distribution of Surfaxin throughout all lung areas.

Four studies were conducted in premature neonates. Three of them investigated the prevention of RDS and were the focus of the efficacy review. The fourth study investigated the treatment of RDS once it had occurred and was not considered to be contributory to the prevention indication. Of the three prevention efficacy studies, KL4-IRDS-06 was the single "pivotal" study. It had 1294 patients. The other two studies were KL4-IRDS-02, with 252 patients, and KL4-IRDS-05, with 11 patients.

Summary results were included in the application for another five studies in different disease conditions, adult respiratory distress syndrome (67 patients exposed) and meconium aspiration syndrome (53 patients exposed). Those studies were reviewed for safety only.

1.3.2 Efficacy

The co-primary endpoints in study KL4-IRDS-06 upon which demonstration of the efficacy of Surfaxin relied were incidence of RDS at 24 hours and RDS-related mortality at 14 days. Both endpoints were agreeable to the Division and both have been used for the other approved surfactant products. Using an all-cause mortality endpoint would have been a more objective endpoint than the cause-specific RDS-related mortality endpoint. However, the fragile health and multi-system immaturity of premature neonates make them vulnerable to several lethal conditions or complications. In those clinical circumstances, the Applicant questioned the feasibility of establishing a survival advantage for a treatment aimed at only one of many concurrent disease processes. Eventually agreement was reached to focus on RDS-related deaths with all causes of death as a secondary endpoint. Having determined that the mortality efficacy endpoint would be cause-specific, it became imperative to try to objectively establish whether a death was related to or associated with RDS. To that end, the Applicant established an Adjudication Committee to review all patient deaths and designate them as RDS-related or not. And because the diagnosis of RDS could also conceivably be affected by investigator judgment, the Adjudication Committee was further charged with determining the presence of RDS. The committee was used only for the major efficacy study, KL4-IRDS-06, and not for the other

studies. The work of the Adjudication Committee was critical to proof of efficacy for this application. Ultimately, this review concluded that the Applicant's compliance with both the spirit and the letter of the adjudication process was acceptable.

In KL4-IRDS-06, the pivotal study, premature neonates between 600 and 1250 grams birth weight were randomized immediately after birth to receive one of three surfactants: Surfaxin, Exosurf, or Survanta. Patients were stratified for randomization into three birth weight strata. The first dose of surfactant was given between 15 and 30 minutes after birth and up to three subsequent doses could be given at 6 hour intervals if respiratory distress continued. The study had two evaluation phases. The first was through 36 weeks post-conceptional age, hospital discharge, or death, whichever occurred later. The second phase consisted of follow-up evaluations at 6 and 12 months corrected age.

As noted, the co-primary efficacy endpoints were incidence of RDS at 24 hours and RDS-related death at 14 days as adjudicated by committee. Secondary endpoints included all-cause mortality; occurrence of air leaks; severity of RDS; number of surfactant doses; BPD; duration of oxygen, ventilation and hospitalization; and the occurrence of concurrent diagnoses. (b) (4)

(b) (4)

The study was of superiority design with Exosurf as the primary comparator. Survanta was a reference product, therefore randomization occurred in a 2:2:1 ratio for the three surfactants. An event driven design was used to estimate sample size based on published incidences of RDS and death for Exosurf-treated patients.

Results for the co-primary efficacy endpoints in KL4-IRDS-06 were statistically persuasive. The incidence of RDS was about 17% less in patients treated with Surfaxin, and RDS-related mortality was approximately half the rate in Surfaxin patients compared to Exosurf patients (4.7 vs. 9.6%). The criteria for efficacy were fairly met, and moreover, the results were consistent across population subgroups based on birth weight, gender, and race. Results for the secondary endpoints showed them to generally support the primary effects of Surfaxin on RDS and RDS-mortality and there were no results that contradicted those effects.

Among the secondary efficacy endpoints was all-cause mortality, and the results for this outcome were not at all straightforward. Despite the difference in RDS-related mortality, there was no difference in all-cause mortality at any time point in the study, and in fact the incidence of non-RDS-related mortality (all the deaths besides those RDS-related) was significantly higher in Surfaxin patients that Exosurf patients. Finding more non-RDS-related deaths in Surfaxin patients made it the most important focus of the safety evaluation of the application, summarized in the next section.

The results from studies KL4-IRDS-02 and KL4-IRDS-05 generally provided evidence of *consistency* with the major efficacy study. They did not show significant differences in incidence of RDS or RDS-related deaths, but they were not designed or powered to detect them,

and the rates of the primary and secondary outcomes were similar to those in the major efficacy study.

Overall, this review finds evidence to conclude that Surfaxin prevents RDS (reduces its incidence) and reduces mortality due to RDS though 14 days of age.

1.3.3 Safety

Safety was assessed in the clinical studies with reports of adverse events, negative reactions to dose administration, vital signs, and concomitant medication use. The last two factors were not considered germane in this review. The most relevant and significant safety issue for this review, however, was not considered by the Applicant; i.e., the deaths that were not due to RDS, as noted in the previous section.

The safety review of this application focused on those deaths in KL4-IRDS-06. In the end, it was found that the non-RDS deaths spanned all causes. Two findings were concluded to reflect idiosyncracies in the adjudication process that was used to determine cause of death: more renal deaths in Surfaxin patients (the difference diminished at later study time points), and deaths in Surfaxin patients from two causes physiologically related to RDS (intraventricular hemorrhage and pulmonary hemorrhage) that were adjudicated as not related. Despite the issues associated with adjudication and cause-specific mortality, the overall results indicate that mortality in Surfaxin patients actually showed a *numerical advantage* that persisted over time with no substantiated evidence to the contrary.

This review identified two safety issues of concern. The Applicant concluded that there were none. First, suggestions of higher rates of infection-related events in Surfaxin patients were found in: a slightly higher number of deaths caused by sepsis in one neonatal RDS study; more serious adverse events of sepsis and pneumonia in RDS studies pooled; and more infection adverse events in one meconium aspiration study. Other data indicated no increased risk of infection, so while causality between Surfaxin and increased risk of infection is inconclusive, there is enough signal to warrant including the information in product labeling. The other area of concern is in negative reactions to administration of Surfaxin. Most likely because the volume of Surfaxin was relatively larger than other surfactants, its administration was reproducibly associated with more negative reactions. The reactions included obstruction of the endotracheal tube and interruption or discontinuation of dosing, events with important clinical implications. These findings also need to be included in product labeling.

1.3.4 Dosing Regimen and Administration

The doses and dosing regimens for the lung surfactant products have mostly been derived empirically. This Applicant selected an initial clinical dose of 133 mg/kg phospholipids based on results in primate studies. Later primate studies showed that a higher dose of 200 mg/kg produced more consistent and longer-lasting effects. A clinical dosing study then compared those two doses, but the study was in the rescue strategy and only eight patients received the

lower dose. Then, the dose selected for Phase 3 development was 175 mg/kg with no obvious rationale.

Administering additional doses of surfactant after the first dose depends on the patient's continuing respiratory status, so patients may receive from 1 to 4 doses. This strategy makes dose-response determinations quite difficult, especially for safety outcomes, because only relatively sicker patients receive more doses. Despite the reality that clinical dose-ranging in the clinical circumstances of NRDS is extremely challenging, additional information about doses and dose regimens is warranted. In particular, as noted above, additional information could help to determine whether any of the associated safety concerns might be modified by using other doses.

1.3.5 Drug-Drug Interactions

Not surprisingly for a critically ill population, concomitant medications were given to most patients in the studies and usually simultaneously with the surfactant dosing period. With such high use of concomitant medications in so many patients, drug-drug interactions were unavoidably difficult to evaluate and no conclusions can be drawn.

1.3.6 Special Populations

The entire intended population for Surfaxin is a special population. There is no basis for establishing special dosing or other considerations for population subgroups.

[Referential Notation: References to source material are provided in this review. Within text, the references are bracketed [] and follow a standard format: the module number within the NDA according to CTD format; the volume number; the section within the volume; and the page number(s) where the source material is located; for example, [M5, v 1.2, sec 5.3.5.1, p 499]. Unless otherwise noted, references refer to the original NDA submission. When referring to source material submitted after the date of the NDA submission, the stamp date is also noted. References within an electronically submitted document show the file name and letter date.]

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

2.1.1 Product Name and Description

The established name of the subject product of this application is Lucinactant and the proposed trade name is Surfaxin®. The proposed trade name will hereinafter be used in this review to refer to the product. Surfaxin is a peptide-containing pulmonary surfactant formulated as an opaque off-white suspension for intratracheal instillation. It is composed of phospholipids, a fatty acid, and the synthetic peptide sinapultide. The specific composition per mL is 30 mg phospholipids (22.5 mg dipalmitoylphosphatidylcholine (DPPC), 7.5 mg palmitoyloleoyl-phosphatidylglycerol); 4.05 mg palmitic acid; and 0.801 mg sinapultide. The proposed packaging is in glass vials containing (b) (4) of product. It is stored refrigerated and warmed to room temperature before use.

2.1.2 Chemical Class

Surfaxin is a new molecular entity by virtue of the constituent sinapultide, a unique synthetic peptide developed for this product. No other product contains sinapultide.

Natural mammalian lung surfactant contains at least four proteins that have been identified so far: surfactant-associated proteins A, B, C, and D (abbreviated SP-A, SP-B, etc). Each of the proteins has distinct functions; of the four, SP-B appears to play the major role in reducing alveolar surface tension. The surface activity of SP-B appears to be highly related to its amphipathic properties, which result from stretches of hydrophobic amino acids interspersed with hydrophilic ones. Sinapultide is a peptide of 21 lysine and leucine residues developed to specifically mimic the structural and behavioral properties of native SP-B. The phospholipid components of Surfaxin are also intended to mimic the in vivo characteristics where SP-B activity depends to large degree on the presence of surface active phospholipids.

2.1.3 Pharmacological Class

Surfaxin is a lung surfactant. The effects of lung surfactants result from their ability to reproducibly lower surface tension at the alveolar-air interface. Refer to section 5 below.

2.1.4 Proposed Indication, Dosing Regimen, Age Groups

The proposed indication for Surfaxin is the prevention of respiratory distress syndrome (RDS) in premature infants. Because it is intended to prevent RDS, a disease that begins in the first hours after birth, the first Surfaxin dose would be given as soon as possible after birth, preferably within 30 minutes. Up to three additional doses would be given at minimum 6-hour intervals if RDS develops. Dosing is intended to be confined to the first 48 hours of life.

Surfaxin is instilled intratracheally through the patient's endotracheal tube (ETT). The volume of a single dose (5.8 mL/kg) represents more than 50% of a premature neonate's tidal volume (8-10 mL/kg), so the total volume of a dose is divided into four quarter-doses or aliquots. Each quarter-dose is administered with the patient placed in a different body position to facilitate distribution of Surfaxin throughout all lung areas. Pauses between the administrations of the quarter-doses are recommended to allow the patient to recover from instillation of the suspension.

The incidence of RDS increases as gestational age decreases. For a preventive approach, the appropriate patient population is those neonates born prematurely enough to have at least a 50% risk of RDS; i.e., those with the best chance to benefit from prevention. The proposed population group for Surfaxin is neonates of birth weights 600-1250 grams (approximately 24-32 weeks gestational age), a population at appropriately high risk for RDS. As with any prophylactic strategy, some patients will inevitably be treated with Surfaxin who would never have developed RDS at all.

2.2 Currently Available Treatment for Indications

Historically, the approach to surfactant therapy in neonatal RDS (NRDS) involved two strategies, which evolved into different indications even though they are both for premature neonates. The first indication is for **prevention of RDS**. In this strategy, surfactant is administered within minutes of birth or as soon as feasible to prevent the development of RDS. Because this is a preventive approach, it has been used only in those neonates whose risk for RDS is greatest; i.e., at least 50%. Generally, these are patients born before about 32 weeks gestational age and less than 1250 grams birth weight. The other strategy is for neonates who did not receive prophylaxis and have developed RDS requiring mechanically assisted ventilation during the first day of life. This is the **treatment or "rescue" indication** and is independent of gestational age or birth weight.

The Applicant is seeking only the prevention indication. Four surfactants have been approved in the United States (U.S.) for NRDS, three of them for the prevention indication. They are shown in Table 1, with Surfaxin included for reference.

Surfaxin is the only one of the surfactants that contains a synthetic peptide. The other surfactants are extracts of mammalian lungs (Survanta, Infasurf, Curosurf) or a combination of non-peptide ingredients (Exosurf). There are two other salient issues for this NDA about the other surfactants:

▪ Exosurf, the first surfactant approved and the primary comparator to Surfaxin in the major efficacy study of this application, is no longer marketed in the U.S. It was at the time the clinical program was developed and studies were started.
▪ Curosurf, the comparator in a supporting study, is not indicated for prevention, the strategy employed in the study and the intended indication for Surfaxin.

Table 1: Surfactant Products

Product	NDA: Date of U.S. Approval	Product Information	Indication
Exosurf	NDA 20-044 August, 1990	**Synthetic** Colfosceril palmitate 67.5 mg/mL; tyloxapol; cetyl alcohol	Prevention and treatment
Survanta	NDA 20-032 July, 1991	**Bovine** 25 mg PL/mL; < 1 mg SP-B/mL	Prevention and treatment
Infasurf	NDA 20-521 July, 1998	**Bovine** 35 mg PL/mL; 0.26 mg SP-B/mL	Prevention and treatment
Curosurf	NDA 20-744 November, 1999	**Porcine** 80 mg PL/mL; 0.3 mg SP-B/mL	Treatment
Surfaxin	NDA 21-746 Pending	**Synthetic** 30 mg PL/mL 0.8 mg sinapultide/mL	Prevention

PL=phospholipids

2.3 Availability of Proposed Active Ingredient in the United States

All surfactants contain at least one phospholipid, but it is difficult to designate a single active moiety in the products because the effects depend on the interaction of the phospholipids and the other components. The unique active moiety in Surfaxin is sinapultide. It has been designated by the Applicant in proposed labeling as the main active ingredient *[M1, v 1.1, sec 1.7, p 2]*. No marketed product contains sinapultide.

2.4 Important Issues With Pharmacologically Related Products

Four major issues have surrounded the reviews and approvals of the other surfactants for NRDS.

1. The criterion for demonstration of clinical efficacy has been the effect on survival. Prematurity is a multi-system phenomenon, however, so death during the neonatal period can occur from any of several causes. As a result, clinical studies for surfactants have included some method to distinguish *respiratory deaths* from others. (The method(s) used for this determination has itself been an important review issue.) The underlying question has been whether a beneficial effect of lung surfactant on RDS-survival can or should favorably affect overall survival. As evidence for efficacy, labeling for the approved surfactants has generally cited a favorable effect on respiratory deaths without a contradictory effect on other causes of death, and these results supported by positive effects on related secondary endpoints; e.g., FiO_2.

2. Part of the safety evaluation of surfactants has included monitoring the occurrence of several *concurrent diagnoses* common in premature neonates; for example, patent ductus arteriosus (PDA) and pulmonary air leaks. Package inserts of approved surfactants have generally provided more information about these events than about conventional adverse events (AE). In a preverbal population, certain kinds of AEs are undetectable, and in a critically ill population they are often difficult to discriminate from underlying pathology and therefore of uncertain significance. In addition, some events considered AEs in older patients are physiologic in premature neonates; for example, hyperbilirubinemia and anemia.
3. Similarly, another important parameter of safety has been those events associated with administration of the products. Not only because of the relatively large dose volumes of surfactants, but also because of the rapid effects on lung function, *reactions to dose administration* have been carefully monitored and reported in clinical studies and in product labeling. Some examples of such events are bradycardia, oxygen desaturation, or ETT obstruction.
4. The ultimate efficacy and safety of a therapy applied early in life is not just seen in survival, but also in normal childhood development. Although normal development is a complex, multifactorial process that occurs over years, some indication of patient status beyond the neonatal period has been required of lung surfactant therapies. Generally, evaluations have included *follow-up assessments* of overall, respiratory, and neurodevelopmental health at 6 and 12 months corrected or adjusted age. (Corrected age refers to correcting the patient's chronological age by the degree of prematurity. So, for example, an infant born 6 weeks prematurely would not reach 12 months "corrected age" until 12 months + 6 weeks chronological age.)

Each of these issues as it pertains to Surfaxin is covered in depth in Sections 6 and 7 below.

2.5 Presubmission Regulatory Activity

IND 40,287 was filed for Surfaxin, known then as "KL-4 Surfactant," for NRDS in August, 1992, by Dr. Charles Cochrane of the Scripps Research Institute. (b) (4) This section focuses on the regulatory history of the neonatal drug development, the subject of this application.

Clinical study plans proceeded for NRDS and an End-of-Phase 2 meeting was held in September, 1995. At that time, the Division communicated concerns about the clinical development plans that had been pursued. The Sponsor proposed to compare Surfaxin to the approved surfactant, Survanta, with a single equivalency trial. (b) (4) (b) (4) . The Division suggested a superiority trial to Exosurf, a non-peptide-containing synthetic surfactant that was marketed in the U.S. at the time.

During the course of this discussion, sponsorship of the IND changed hands in December, 1996, when Acute Therapeutics, Inc., acquired it. (Acute Therapeutics, Inc. subsequently became

known as Discovery Laboratories, Inc.). Discussions about the design of pivotal studies for NRDS continued with the new Sponsor over the next several years with proposals and counter-proposals between the Sponsor and the Division. The issues centered around the appropriate comparator and the appropriate and approvable endpoint(s). In general, the Sponsor wished to study endpoints other than survival because statistical comparisons involving survival against a treated control group would require large studies. The endpoints favored by the Sponsor were air leak events, BPD, and/or incidence of RDS.

(b) (4)

Agreement between the Sponsor and the Division about the design of a pivotal study for NRDS was reached in March-April, 2001. That agreement was for a single superiority study in the prevention strategy with three treatment groups: Surfaxin, Exosurf as the primary comparator, and a natural surfactant as a reference. Co-primary endpoints were agreed upon: incidence of RDS at 24 hours and the composite endpoint, RDS-related deaths and/or air leak at 14 days. Subsequently, the Division acquiesced to a change in the primary endpoints at the urging of the Sponsor. The Division stated that they would accept one of the following alternatives: removing the air leak component from the composite co-primary endpoint, or making the composite endpoint RDS-related deaths "or" air leaks instead of "and/or." The Sponsor chose the former option, and the co-primary endpoints finally agreed upon were incidence of RDS at 24 hours and RDS-related deaths at 14 days. It is important to note that this final agreement was not reached until the major efficacy study had begun, indeed not until after all patients had been enrolled, but before any results or treatments were revealed.

There was agreement that the application would contain a single major efficacy study, but the Applicant planned a second study for support. That study would compare Surfaxin to Curosurf, the leading surfactant in Europe. The Sponsor proposed a non-inferiority design based on the endpoint of survival without BPD at 28 days, with the margin for non-inferiority derived from results of a published study involving Curosurf.[1] The Division disagreed with the approach because the cited study was performed in the rescue strategy, was performed 10 years prior, and did not have the endpoint of survival without BPD as a prospectively planned outcome. The Sponsor proceeded with the study as it originally intended despite the Division's reservations (See Appendix 10.2 below for the complete study review).

On numerous occasions during the presubmission process, the Division stated its position that long-term follow-up data would be necessary for complete evaluation of the drug. The major efficacy study was to include assessments of patients at 6 and 12 months corrected age. The Division stated that the 6-month data should be included in the NDA, with 12-month data to follow as they became available. At the pre-NDA meeting of June 13, 2003, the Division stated, "Your NDA submission must contain complete data for the 36 week PCA [post-conceptional age] and the 6 month corrected age time points. If your NDA contains complete data for these two time points, submission of one year follow-up data as periodic amendments is acceptable to the Division." *[M1, v 1.1, sec 1.5, p 25]* Later, in a facsimile correspondence dated October 14,

2003, the Division wrote, "We reiterate our position that complete 6-month data will be necessary in order for the Division to make a determination of safety and efficacy. Therefore, we recommend that you not submit the application until the 6-month data have been analyzed. Although the Agency may file the application with less than complete 6-month data, it is most likely that the incomplete database would not be sufficient to allow a confident determination of safety and efficacy." *[M1, v 1.1, sec 1.5, p 10]* Ultimately, the application did not contain the 6- or 12-month follow-up data, which were submitted in the 4-month safety update to the application.

2.6 Other Relevant Background Information

There is no other relevant background information. Surfaxin is not marketed in any other country. A Marketing Authorization Application to the European Medicines Authority was filed by the Applicant on October 1, 2004. No other marketing applications have yet been filed.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Dr. Eugenia Nashed has performed the comprehensive CMC review. Her review details the significant issues and problems that will preclude approval of the application in the first review cycle. The following briefly summarizes those findings.

- Three of four DMFs (Drug Master File) supporting the drug substance are inadequate.
- Only 6 months of stability data have been submitted to date.
- The proposed method for biological activity testing is inadequate.
- There are inadequate methods and specifications for an impurity profile.
- Basic microbiology information, especially media fill, for this sterile fill drug product was only submitted to the appropriate DMF in December, 2004. A microbiological consultation is pending.

The major area of concern, however, is in the GMP compliance of the manufacturing and testing sites and processes. Manufacture was transferred from a previous site because of repeated instances of GMP noncompliance there. The current site has also been cited for numerous GMP violations and a repeat inspection is in progress as of the date of this review. Final testing of the product is in the hands of the Applicant and numerous issues have been identified there including out-of-specification results, lack of written SOPs, lack of adequately validated methods, and lack of appropriate documentation.

In summary, the CMC review has identified numerous issues that result in inadequate assurance that drug product can be manufactured reliably and consistently with the quality necessary for marketing.

3.2 Animal Pharmacology/Toxicology

Dr. Huiqing Hao performed the Pharmacology and Toxicology review of the NDA and has recommended approval. According to her review, preclinical pharmacology studies demonstrated reduced surface tension in ex vivo systems; and increased lung compliance and expansion, improved gas exchange, and reduced ventilatory pressures in premature animal models. Toxicology studies were performed in neonatal rabbits, neonatal dogs, and neonatal cats. All studies were characterized by early deaths due to respiratory distress. Histopathology in all repeat dose studies showed evidence of lung inflammation with lung histiocytosis and inflammatory cell infiltrates, especially macrophages. NOAELs could not be established because the findings of lung inflammation were universal. Clinical studies have proceeded and approval is recommended because of the intended clinical benefit.

Dr. Hao has recommended some modifications to the proposed package insert in describing mechanism of action and results of mutagenicity testing.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of clinical data for this review was the studies conducted by the Applicant and included in this application. Additional clinical information that could not be located in the NDA, or data clarifications, were obtained from the Applicant in response to Information Requests made during the review process. Those requests are briefly described in the next Table. In all cases, the Applicant provided the requested information in usable format and the information was incorporated into the review.

Table 2: Clinical Information Requests During NDA Review

Date of Request	Information Requested
June 26, 2004	Filing Letter. Requested submission of 6-month follow-up data as previously requested in pre-NDA meeting
July 15, 2004	Certain clinical study outcomes by batch of drug product. The information was requested to evaluate possible differences in drug batches.
November 2, 2004	Explanation about early termination of 1 ARDS study and 1 MAS study
November 22, 2004	Results of Adjudication Committee results for each committee member
December 14, 2004	Clarification of some of the information provided in the response to the November 22 request.
December 28, 2004	Updated safety data for MAS study terminated early
January 6, 2005	Clarification of procedures for obtaining cranial ultrasounds. Clarification of results of 12-month follow-up neurological findings

Data developed and submitted under investigator-sponsored INDs using Surfaxin were not used for this review. Two other sources of data were used sparingly for specific purposes: literature reports and data from the INDs and NDAs of the approved surfactants.

Literature reports were used insofar as they were referenced by the Applicant in the designs of their studies,[1,2] or to elucidate or guide the review.[3-12] The reports referenced by the Applicant were reviewed and commented upon as appropriate in the reviews of the studies. Photocopies of some literature reports cited by the Applicant were included in the application.

IND and NDA data, especially the approved labeling, were used as regulatory references. The package inserts for the comparator surfactants used in this program - Exosurf, Survanta, and Curosurf - were used thoroughly and frequently.

4.2 Table of Clinical Studies

Table 3 shows all the clinical studies conducted by the Applicant and reported in this application. The studies are organized by disease: NRDS, MAS, or ARDS. The major efficacy ("pivotal") study for NRDS in this application was ***KL4-IRDS-06***, the first one listed in the Table.

Table 3: Table of All Studies

Study	Centers	Design	Test Products/ Therapies	N	Endpoints	Status
Studies for Neonatal RDS						
KL4-IRDS-06 – Major Efficacy Study	*54 US, Europe, Latin America*	*•Prevention •Neonates 600-1250g •Randomized, double-blind, event-driven, active-controlled*	*Surfaxin 175 mg/kg up to 4x Exosurf 67.5 mg/kg up to 3x (Comparator) Survanta 100 mg/kg up to 4x (Reference)*	*527 509 258*	*•Co-Primary: RDS at 24 hr RDS-deaths at 14 days •Numerous secondary •6- & 12-month corrected age follow-up*	*Complete (12-month follow-up ongoing)*
KL4-IRDS-02	35 US, N America, Europe	•Prevention •Neonates 600-1250g •Randomized, double-blind, active-controlled	Surfaxin 175 mg/kg up to 3x Curosurf 175 mg/kg x 1; 100 mg/kg up to 2x	124 128	•Primary: Alive without BPD at 28 days •Numerous secondary •6- & 12-month corrected age follow-up	Complete
KL4-IRDS-05	1 Ecuador	•Prevention •Neonates 600-1250g •Open-label, uncontrolled •Evaluate two ½-doses vs. four ¼-doses	Surfaxin 175 mg/kg up to 4x: 2 half-doses 4 quarter-doses	 9 2	Numerous - similar to "06" and "02" studies	Complete
KL4-IRDS-01	6 US	•Rescue •Neonates 750-1750 g •Open-label, uncontrolled	Surfaxin 133 mg/kg or 200 mg/kg up to 2x	8 39	Efficacy endpoints not defined. Info collected about ventilation requirements, RDS, BPD, death	Complete
Studies for Meconium Aspiration Syndrome						
KL4-MAS-	15 US	•Neonates ≥ 35	Surfaxin 16	15	Numerous including	Complete

Study	Centers	Design	Test Products/ Therapies	N	Endpoints	Status
01		wks •Multicenter, randomized, controlled	mL/kg by lavage over 1-2 hrs Standard of care	 7	Treatment failure, MAS-related death, oxygenation, ventilation	
KL4-MAS-03	55 US	•Neonates ≥ 37 wks •Multicenter, randomized, open-label, controlled	Surfaxin 16 mL/kg by lavage over 1-2 hrs Standard of care	38 31	Numerous including days on ventilator, death, ECMO, chronic lung disease	Terminated early (10/04) for slow enrollment
Studies for Adult RDS						
KL4-ARDS-01	7 US	•Adults with ARDS •Open-label, uncontrolled, Phase 1/2	Surfaxin by ETT instillation in 3 doses Standard of care	1 1	Recovery rate from ARDS, several parameters of lung function	Terminated early when ownership of IND transferred
KL4-ARDS-02	7 US	•Adults with ARDS •Open-label, uncontrolled, Phase 1b	Surfaxin in various doses by lavage	12	Safety and tolerability	Complete
KL4-ARDS-03	34 US	•Adults with ARDS •Multicenter, randomized, open-label, controlled, Phase 3	Surfaxin in 2 lavage regimens Standard of care	9 5	▪ Days alive and off ventilator ▪ Mortality	Terminated early for business decision to devote efforts to MAS and NRDS (b) (4)
KL4-ARDS-04	16 US	•Adults with ARDS •Multicenter, open-label, uncontrolled, two-part, Phase 2	Surfaxin in various dosage lavage regimens Standard of care	45 11	Numerous including days alive and off ventilator and mortality	Ongoing
Source: M5, v 1.88, sec 5.3.5.3, p 20ff						

4.3 Review Strategy

All nine studies represented in Table 3 were reviewed, but emphases on the studies varied. The efficacy review was confined to the three of the four studies in NRDS that used the prevention strategy. The fourth NRDS study, KL4-IRDS-01, was not reviewed for efficacy - even as supportive - because it employed the rescue strategy. Although they both involve premature neonates, prevention and rescue studies cannot be considered comparable for efficacy. Neonates in rescue studies already have RDS and are mechanically ventilated at the time of first treatment. Their outcomes will usually be quite different from patients in prevention studies, some of whom would never have developed the disease at all and in any case are treated before its onset. KL4-IRDS-01, however, is the only NRDS study conducted by the Sponsor that administered different doses of Surfaxin, so it is briefly considered in the context of dose-response.

Of the three prevention efficacy studies, the overwhelming emphasis was placed on study KL4-IRDS-06, which was designated by the Applicant as the major efficacy study. KL4-IRDS-02 was considered supportive. The detailed reviews for both studies are located in Appendix 10. The third NRDS study, KL4-IRDS-05, was considered primarily to determine whether any results contradictory or inconsistent with the two major studies were obtained.

The safety review included all nine studies; however, the NRDS studies were emphasized for safety just as they were for efficacy. The patient populations and dosing regimens used in the ARDS and MAS studies were so different from those for NRDS that their comparability is quite limited, even in evaluating safety. Essentially, the review of the ARDS and MAS studies was performed to detect whether any safety signals that occurred might be applicable to the neonatal population. Detailed written reviews of the ARDS and MAS studies were not performed; the studies are summarily described as needed in the Integrated Review of Safety, section 7.

Reviews of the studies began with and were based on the Applicant's final study reports. Each report was checked against the study protocol and statistical and analytical plan to assure that any changes from the original design and plan were reported and explained. The Applicant's summary data tables were reviewed in detail. Appendix tables and data listings were also reviewed, in varying amounts of detail, depending upon the endpoint and review issue. Case report forms (CRF) of patients who died were all briefly reviewed, except in some cases where particular patients or causes of death needed more intensive examination. In those cases, the CRFs, data listings, and patient narratives provided by the Applicant were thoroughly examined.

The Applicant provided bibliographies within the study reports and included reprints of many articles in the application. Those were reviewed to the extent they were relevant to the review. A few selected other sources from the literature were also reviewed to supplement the Applicant's bibliography for particular issues of interest.

4.4 Data Quality and Integrity

An audit by the Division of Scientific Investigations was requested for this NDA. The clinical sites recommended for audit were selected based on two criteria: 1) the sites that enrolled the most patients; and 2) the sites where there were numerous deaths and/or where there seemed to be inconsistencies between the causes of death as determined by the Adjudication Committee compared to the investigator or compared to the reviewer's opinion. Sites were also selected to evenly represent the European and Latin American countries. Audit of the adjudication process in study KL4-IRDS-06 was also requested using the Applicant's records of the patients who died at the same centers included in the clinical audit.

The inspectors issued 483s at some clinical sites for use of unapproved informed consent forms; absent source documentation for some results; and procedures in violation of protocol. At some sites, no 483s were issued.

Audit of the adjudication records and process found scattered instances of final adjudications not made according to the committee's SOPs; missing source documentation for some judgments;

and procedures not compliant with the SOPs. The overall assessment of the auditors, however, was that there were no significant issues and that the data are reliable.

4.5 Compliance with Good Clinical Practices

The studies were conducted in accordance with acceptable ethical standards. Study reports indicate that informed consents were obtained from parents or guardians and IRB approvals were obtained for all study centers. There were relatively few protocol violations and they did not appear to favor any treatment. In general, they were compatible with the designs of the studies. For example, several neonates were randomized before all eligibility criteria were met, which is an understandable occurrence when the entire process must occur within minutes in a delivery room setting.

4.6 Financial Disclosures

Appropriate financial disclosures were provided for clinical investigators and for members of the Adjudication Committee. None of the disclosures raise questions about financial conflict of interest.

5 CLINICAL PHARMACOLOGY

There were no clinical pharmacology studies for this application, which is appropriate to the nature of the product and the intended patient population. Surfactant acts locally at the alveolar-air interface to reduce surface tension on the alveolar surface and prevent the lungs from collapse at the end of expiration. Nonclinical studies in animals using radiolabelled sinapultide and DPPC demonstrated that most of the delivered amounts of these constituents remains in the lungs, with little entering the systemic circulation. This is consistent with studies showing recycling of the components of native surfactant; that is, surfactant-associated proteins and phospholipids are reabsorbed from the alveolar surface to re-enter type II pneumocytes where they are repackaged and then released once more to the alveolar surface. Consequently, typical pharmacokinetic studies would be inappropriate to the product. In addition, studies using radiolabel techniques and frequent blood sampling would be hazardous for premature neonates.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: Prevention of Neonatal RDS

The Applicant's proposed indication, as stated in the proposed package insert, is ***"Surfaxin is indicated for the prevention of RDS in premature infants."*** *[M1, v 1.1, sec 1.7, p 7]*

The approach to surfactant therapy in NRDS has involved two strategies, which evolved into different indications even though they are both for premature neonates. The indication proposed for Surfaxin in this application is for **prevention of RDS**. In this strategy, surfactant is

administered within minutes of birth or as soon as feasible to prevent the development of RDS. As already noted (section 2.1.4 above), because this is a preventive approach, it has been used only in those neonates whose risk for RDS is greatest; i.e., at least 50%. Generally, these are patients born before about 32 weeks gestational age and less than 1250 grams birth weight. The other strategy, not proposed for Surfaxin, is the treatment or "rescue" indication for neonates who did not receive prophylaxis and develop RDS requiring mechanically assisted ventilation during the first day of life.

6.1.1 Methods

The efficacy review was confined to the three of the four studies in NRDS that used the prevention strategy (see Table 3). The fourth NRDS study, KL4-IRDS-01, was not considered for efficacy because it employed the rescue strategy. Although they both involve premature neonates, prevention and rescue studies cannot be considered equivalent for the demonstration of efficacy. Neonates in rescue studies already have RDS and have endured some oxygen and ventilator therapy at the time of first treatment. Their outcomes will be different from patients in prevention studies, some of whom would never have developed the disease at all and in any case are treated before its onset. Nevertheless, KL4-IRDS-01 is considered briefly in the context of dose-response because it is the only NRDS study conducted by the Applicant that administered different doses of Surfaxin.

Of the three prevention efficacy studies, the overwhelming emphasis was placed on study KL4-IRDS-06, which was designated by the Applicant as the major efficacy study. KL4-IRDS-02 was considered by the Applicant to be supportive; however, its usefulness in supporting the results of KL4-IRDS-06 is severely restricted by significant flaws in study design. Those are discussed in section 6.1.3 below and in the individual study report. The detailed reviews for both studies are located in Appendix 10. The third NRDS study, KL4-IRDS-05, was considered primarily to determine whether any results contradictory or inconsistent with the two major studies were obtained. A detailed written review is not provided, but its design is summarized in section 6.1.3.

Considering the factors just described, therefore, for all practical purposes the demonstration of efficacy for this indication depends on study KL4-IRDS-06 alone.

6.1.2 General Discussion of Endpoints

The co-primary endpoints in study KL4-IRDS-06 upon which demonstration of the efficacy of Surfaxin relies are

- incidence of RDS at 24 hours, and
- RDS-related mortality at 14 days.

Incidence of RDS and mortality endpoints were both advocated by the Division in presubmission communications with the Applicant, and both have been used for the other approved surfactant products. The only other endpoints that the Division considered acceptable during the presubmission discussions with the Applicant were pulmonary air leak (as long as it was

combined with another endpoint) or BPD. But although the Division considered BPD a valid clinical endpoint, it was considered a difficult one because of its multifactorial etiology. The Applicant also favored using the incidence of RDS endpoint, but was initially reluctant to employ a mortality endpoint. The fragile health and multi-system immaturity of premature neonates make them vulnerable to several lethal conditions or complications. In those clinical circumstances, the Applicant questioned the feasibility of establishing a survival advantage for a treatment aimed at only one of many concurrent disease processes. Eventually agreement was reached to focus on RDS-related deaths with all causes of death as a secondary endpoint.

Having determined that the mortality efficacy endpoint would be cause-specific, it became imperative to try to objectively establish whether a death was related to or associated with RDS. To that end, the Applicant established an **Adjudication Committee** (AC) to review all patient deaths and designate them as RDS-related or not. And because the diagnosis of RDS could also conceivably be affected by investigator judgment, the Adjudication Committee was further charged with determining the presence of RDS. The committee was used only for the major efficacy study, KL4-IRDS-06, and not for the other studies.

The work of the Adjudication Committee was critical to proof of efficacy for this application and is discussed in more detail in the next section. The following sections then provide more specific and detailed discussions about the individual endpoints.

6.1.2.1 Adjudication Committee

The AC was established by the Applicant to obtain independent evaluation of key study endpoints and to standardize the quality and consistency of endpoint classifications. A similar approach using an independent body to determine cause of death was employed for Survanta. In studies with Infasurf, the investigator made the primary determination of cause of death, but cases were reviewed and arbitrated in cases of disagreement.

A Standard Operating Procedures Manual for the Committee was issued in April, 2002. The Manual stated that the committee would be comprised of seven members who were neonatologists or pediatric radiologists. They could not be investigators or sub-investigators in the study and had to declare in writing that there was no conflict of interest with the Sponsor. The members were reimbursed for their expenses in performance of their duties and received "reasonable" remuneration for the time.

All AC members were voting members. They appointed a Chair. The AC met throughout the course of the study, generally on a monthly basis. More frequent meetings could occur at the instigation of the members or the Sponsor. Endpoint data were reviewed on an ongoing basis. AC members were blind to study treatments. Adjudication data packages (ADP) were prepared by the Sponsor for AC members, with treatment-revealing information removed. The information that was provided included copies of CRFs containing the relevant endpoint data, digital copies of x-rays stored on CD-R media, serious AE reports, and autopsy reports if available. The packages also included a ballot by which AC members reported their assessments.

Procedures for the AC pertaining to specific endpoints will be discussed with each endpoint below. General procedures were as follows. Two members reviewed each ADP and independently cast their votes on the endpoint under consideration by completing and signing the ballot. The endpoint would be considered adjudicated if both members agreed. If there was disagreement on the RDS or air leak endpoints, the pediatric radiologist adjudicated independently as a tie-breaker. If there was disagreement on the mortality endpoints, the endpoint was adjudicated by "peer consultation." At the beginning of the process, committee members reviewed a series of chest x-rays to agree on rules of interpretation that would be used throughout the process.

6.1.2.2 Incidence of RDS at 24 hours

For a drug product intended to prevent RDS, this is an obvious endpoint, and it was used with all other surfactant products for the prevention indication. RDS is a well-established clinical syndrome and the diagnostic criteria are relatively straightforward. They are based on pulmonary atelectasis severe enough to cause radiographic changes and require supplemental oxygen. Therefore, in clinical practice RDS is considered present if the patient requires supplemental oxygen and has a chest x-ray showing the characteristic diffuse reticulogranular appearance of generalized atelectasis.

In the context of demonstrating efficacy of Surfaxin, however, there were two aspects of the diagnosis that had to be specifically defined for the purpose: 1) interpretation of the x-ray, and 2) the time when the diagnosis was made. These were incorporated by the Applicant into the diagnostic schema used in KL4-IRDS-06:

Diagnosis	Chest x-ray at 24±4 hrs	FiO_2 at 24±4 hrs
RDS	Positive changes	≥ 30% at 24±4 hrs
No RDS	Positive or indeterminate	< 30%
	If no chest x-ray at 24±4 hrs	FiO_2 < 30% prior to or after 24±4 hours

Patients with a chest x-ray positive for RDS between 16 and 20 hours and a repeat positive chest x-ray between 28 and 32 hours and an FiO_2 > 30% at the time of these x-rays were to be counted as having RDS. All other patients outside the time windows in the table were to be counted as not having RDS.

The Applicant addressed x-ray interpretation satisfactorily by including a pediatric radiologist on the AC for expert and unbiased x-ray interpretation. The second element of the diagnosis was problematic in KL4-IRDS-06, however. The time window itself, 24±4 hours, was appropriate and consistent with other surfactant studies. (The time of diagnosis is important so that RDS is not mistaken for other disease entities. Too early diagnosis might confuse RDS with retained amniotic fluid or asphyxia and also not allow sufficient time for the effect of surfactant to manifest. Too late diagnosis might confuse RDS with pneumonia.) The problem is that no limitations or rules were established for assessing the FiO_2 during that time window. In other words, the diagnostic criteria state that FiO_2 must be at least 30% during that time, but do not state whether that must be the lowest or highest value, whether it must be persistent or repeated, whether a value < 30% *at any time* rules out RDS, etc. Without those caveats on the criterion, a

patient might have a single, transient FiO_2 value of 35%, for example, and all other values be <30% and the patient would meet the diagnostic criterion. The reverse could of course also be true. This is a flaw in the design of KL4-IRDS-06, agreed to by the Division, which somewhat weakens the ability to demonstrate this particular effect of Surfaxin.

To adjudicate the incidence of RDS at 24 hours, AC members first reviewed the appropriate time-specific chest x-ray obtained according to the rules above. Then members reviewed the CRF page that contained the appropriate FiO_2 data to establish the definition of RDS.

6.1.2.3 RDS-related mortality at 14 days

The rate of neonatal mortality is highest in the first few days of life. Fourteen days of age is a suitable and reliable time point to determine whether an intervention has had a meaningful effect on survival.

Although improved survival is the sine qua non of a clinically important effect, determining whether a single intervention improved survival is not always perfectly straightforward. Besides RDS, neonates may succumb to other manifestations of immaturity (e.g., intraventricular hemorrhage (IVH), sepsis) or to complications of care (e.g., air leaks). It is difficult to sort out all the events that occur during this critical time because they are frequently temporally or physiologically correlated. For example, air leaks result from mechanical ventilation which is used because of RDS. IVH results from instability in the cerebral vascular bed which cannot be separated from the cardiovascular instability of RDS and mechanical ventilation. To attempt to discriminate all these processes by attributing death to RDS or not is difficult at best. On the other hand, surfactant therapy cannot reasonably be expected to affect the occurrence of sepsis or a lethal cardiac malformation, so an attempt to distinguish respiratory deaths from others was warranted.

The approach adopted for previously approved surfactants was to establish a method for objective review of patient deaths to come to a clinically expert, unbiased judgment about whether a death was related to or associated with RDS. The same approach was used for this application with formation of the AC.

The additional challenge in evaluating a cause-specific mortality endpoint is in determining the relative importance of RDS-related deaths and all causes of death. In other words, what has been gained for the patient if he/she survives RDS only to die for another reason? The underlying question is whether a beneficial effect of lung surfactant on RDS-survival can or should favorably affect overall survival. The precedent of the approved surfactants indicates that a standard of efficacy is fairly met if the surfactant demonstrates a favorable effect on respiratory deaths without a contradictory effect on other causes of death, and these results are supported by positive effects on related secondary endpoints; e.g., FiO_2.

Procedurally for this endpoint, AC members reviewed all chest x-rays and CRF ventilator setting data for all patients who died through day 14. Serious AE reports and available autopsy reports were also reviewed.

6.1.2.4 Other endpoints

The secondary endpoints in KL4-IRDS-06 and the endpoints in the other efficacy studies (KL4-IRDS-02 and KL4-IRDS-05) tend to fall into two broad categories: those reflecting the effects of Surfaxin on acute lung function and those reflecting more general health status. Endpoints in the latter group were assessed several days or weeks after the study treatment period and are inextricably related to prematurity and RDS. For the most part, these other endpoints are universally medically accepted within the specialty and have been used for all the other surfactant products.

The endpoints used to indicate acute lung effects included:

- air leaks (pneumothorax, pneumomediastinum, pneumopericardium, pulmonary interstitial emphysema (PIE)). Air leak phenomena reflect lung compliance and the degree of ventilatory support.
- severity of RDS, as manifested by FiO_2 and mean airway pressure (MAP)
- the number of surfactant doses

The endpoints that reflect more general health status included:

- BPD
- durations of supplemental oxygen, ventilation, and hospitalization
- status at 6 and 12 months corrected age

There is a unique category of endpoints used in this program and in all the other surfactant programs that straddles efficacy and safety and reflects acute lung function as well as general status. These are the *concurrent diagnoses* commonly recognized in premature neonates:

- IVH
- necrotizing enterocolitis (NEC)
- periventricular leukomalacia (PVL)
- apnea
- PDA
- retinopathy of prematurity (ROP)
- pulmonary hemorrhage

Having these many endpoints in common enhanced across-study perspectives on efficacy, but that benefit was countered somewhat by the caveats about differences in study design pointed out in the next section.

6.1.3 Study Design

Detailed reviews of the major efficacy study (KL4-IRDS-06) and the supporting study (KL4-IRDS-02) are found in the Appendix, section 10. The third study reviewed for efficacy was a single-center, open-label study in Ecuador (KL4-IRDS-05). A detailed written review of KL4-IRDS-05 was not performed because its primary purpose was to evaluate the feasibility of the study logistics and procedures that would be required in later Phase 3 studies, and only 11

patients were enrolled. Consequently, it contributes little to the demonstration of efficacy of Surfaxin and was reviewed to ascertain whether any unique events occurred.
The Table below shows some of the characteristics of the efficacy studies. Following the Table, each of the three studies' designs is briefly summarized in narrative. The next sections then discuss the individual elements of study design that attest to whether the studies were adequate and well-controlled and whether their results are generalizable; i.e., choice of control, patient populations, minimization of bias, and efficacy endpoints. In this program one of the elements of study design that needs particular attention is the geographic locale of centers – the major efficacy study was not performed in any U.S. centers. This issue is specifically considered in section 6.1.3.3.1 below.

Table 4: Surfaxin Efficacy Study Designs

Study	Design	Test Products/ Therapies	N	Endpoints
KL4-IRDS-06 – Major Efficacy Study	•Multicenter Prevention •Neonates 600-1250g •Randomized, double-blind, event-driven, active-controlled ▪ Adjudication Committee	Surfaxin 175 mg/kg up to 4x Exosurf 67.5 mg/kg up to 3x (Comparator) Survanta 100 mg/kg upto 4x (Reference)	527 509 258	•Co-Primary: RDS at 24 hr RDS-deaths at 14 days •Secondary RDS severity Air leaks No. of surfactant doses BPD Duration of oxygen, ventilation, hospitalization Concurrent diagnoses
KL4-IRDS-02	•Multicenter Prevention •Neonates 600-1250g •Randomized, double-blind, active-controlled ▪No Adjudication Committee	Surfaxin 175 mg/kg up to 3x Curosurf 175 mg/kg x 1; 100 mg/kg up to 2x	124 128	•Primary: Alive without BPD at 28 days •Secondary All-cause mortality RDS severity Air leaks No. of surfactant doses Duration of oxygen, ventilation, hospitalization Concurrent diagnoses
KL4-IRDS-05	•Single-center Prevention •Neonates 600-1250g •Open-label, uncontrolled •Evaluate two ½-doses vs. four ¼-doses ▪ No Adjudication Committee	Surfaxin 175 mg/kg up to 4x: 2 half-doses 4 quarter-doses	 9 2	All-cause mortality RDS severity Air leaks No. of surfactant doses BPD Duration of oxygen, ventilation, hospitalization Concurrent diagnoses

6.1.3.1 Descriptions of efficacy study designs

As the major efficacy study, KL4-IRDS-06 is considered the "standard" among the efficacy studies. Differences in the other studies compared to it are noted in these summaries.

6.1.3.1.1 KL4-IRDS-06

Premature neonates between 600 and 1250 grams birth weight were randomized immediately after birth to receive one of three surfactants: Surfaxin, Exosurf, or Survanta. Patients were stratified for randomization into three birth weight strata. The first dose of surfactant was given between 15 and 30 minutes after birth and up to three subsequent doses could be given at 6 hour intervals if the following criteria for respiratory distress were met: the patient continued to require mechanical ventilation with MAP $\geq$ 6 cm H_2O and $FiO_2 \geq 0.30$ to maintain PaO_2 between 50 and 80 mm Hg or an oxygen saturation between 88 and 95% and a chest radiograph consistent with RDS. Procedures described in section 6.1.3.4 below were used to mask the treatments to caregivers.

The study had two evaluation phases. The first was through 36 weeks post-conceptional age (PCA), hospital discharge, or death, whichever occurred later. The second phase consisted of follow-up evaluations at 6 and 12 months corrected age.

There were co-primary efficacy endpoints: incidence of RDS at 24 hours and RDS-related death at 14 days. Both endpoints were adjudicated by the 7-member AC who reviewed all relevant study material. Their decisions were used in the primary analyses. Secondary endpoints included all-cause mortality; occurrence of air leaks; severity of RDS; number of surfactant doses; BPD; duration of oxygen, ventilation and hospitalization; and the occurrence of concurrent diagnoses. Safety was assessed through AE reports, negative reactions to dose administration, concomitant medications, and physical examination and vital signs.

The study was of superiority design with Exosurf as the primary comparator. Survanta was a reference product, therefore randomization occurred in a 2:2:1 ratio for the three surfactants. An event driven design was used to estimate sample size based on published incidences of RDS and death for Exosurf-treated patients. With this scheme, 400 RDS events and 66 RDS-death events would be needed and this was anticipated to require 600 patients in the Surfaxin and Exosurf groups.

6.1.3.1.2 KL4-IRDS-02

Premature neonates between 600 and 1250 grams birth weight were randomized immediately after birth to receive Surfaxin or Curosurf. Patients were stratified for randomization into two birth weight strata (*vs. three groups in "-06")*. The first dose of surfactant was given between 15 and 30 minutes after birth, and up to two subsequent doses (*vs. three in "-06". The difference was to be consistent with product labeling for Curosurf)* could be given at 6 hour intervals if criteria for respiratory distress were met *(retreatment criteria were slightly different from "-06". There was no MAP criterion, P_aO_2 and oxygen saturation criteria were different).* Procedures described in section 6.1.3.4 below were used to mask the treatments to caregivers.

The study had two evaluation phases. The first was through 36 weeks PCA, hospital discharge, or death, whichever occurred later. The second phase consisted of follow-up evaluations at 6 and 12 months corrected age.

The primary efficacy endpoint was the incidence of being alive without BPD at 28 days of age. Investigators determined whether BPD was present according to protocol criteria: requirement for mechanical ventilation, or requirement for supplemental oxygen to maintain oxygen saturation ≥90% (except if needed only during feeding). Secondary endpoints included incidence of RDS at 24 hours; RDS-related mortality at 14 days; all-cause mortality; occurrence of air leaks; severity of RDS; number of surfactant doses; BPD; duration of oxygen, ventilation and hospitalization; and the occurrence of concurrent diagnoses. *(RDS was defined in the same manner as in "-06." Cause of death was determined by investigators. No adjudication committee was used in this study).* Safety was assessed through AE reports, negative reactions to dose administration, concomitant medications, and physical examination and vital signs.

The study was of non-inferiority design. A non-inferiority margin of -14.5% was set and a sample size of 248 patients/group was determined to be needed for the study. However, the non-inferiority margin was set based upon results of a rescue study comparing Curosurf to placebo in which the endpoint of being alive without BPD was not used.[1] These factors make the calculation of the non-inferiority margin invalid, and render the study of very limited utility. As it turned out, the study was terminated prematurely for business reasons, which weakens its support even more.

6.1.3.1.3 KL4-IRDS-05

This was an open-label study to demonstrate safety and efficacy of Surfaxin, and examine the logistics and feasibility of procedures for Phase 3 studies. Although the study was open-label and uncontrolled, to accomplish the objective of testing procedures mock randomization and masking procedures were attempted.

Premature neonates between 600 and 1250 grams birth weight were eligible. All patients were treated with 175 mg/kg Surfaxin, but half of the patients were to receive the doses in two half-dose aliquots and half were to receive the doses in four quarter-dose aliquots. Patients were "assigned" to the two groups, presumably by randomization but it is unstated. The first dose of surfactant was given between 15 and 30 minutes after birth, and up to three subsequent doses could be given at 6 hour intervals if criteria for respiratory distress were met *(retreatment criteria were slightly different from "-06." The MAP criterion was different (7 vs. 6), P_aO_2 and oxygen saturation criteria were different).* The procedures for masking described in section 6.1.3.4 below were tested in this study.

Patients in the study were followed through 28 days of age; there were no long-term assessments. The co-primary efficacy endpoints were the incidence of RDS at 24±2 hours and the incidence of RDS-related mortality through 14 days and/or air leak through 7 days of age. Presence of RDS was determined by protocol criteria and cause of death was assigned by the investigator. Secondary endpoints included all-cause mortality; occurrence of air leaks; severity of RDS; number of surfactant doses; BPD; duration of oxygen, ventilation and hospitalization; and the occurrence of concurrent diagnoses. Safety was assessed through AE reports, negative reactions to dose administration, concomitant medications, and physical examination and vital signs.

A sample size of 10 patients, 5 in each dosing group, was selected based on non-statistical considerations. Descriptive statistics were used to summarize the results.

6.1.3.2 Choice of control

As Table 4 shows, the two controlled studies used different comparators, which eliminates the ability to pool results to enlarge the efficacy database. KL4-IRDS-05 was designed as a feasibility study, so lack of a control group was appropriate to its purpose but the absence weakens the study's contribution to demonstration of efficacy.

It was not possible to include a placebo control group in the Surfaxin studies because the approved surfactants beneficially affect survival or other clinically important outcomes and withholding them would be unethical. Given this reality, the Applicant selected Exosurf as the active control for the major efficacy study because it was the only other non-natural surfactant available. When Exosurf was subsequently voluntarily withdrawn from the U.S. market for business reasons after the Surfaxin studies had begun, an unfortunate situation was left for U.S. prescribers. They would have to consider the effects of Surfaxin vs. an unavailable, unfamiliar product. This consequence was beyond the control of the Applicant; the use of Exosurf as the primary comparator for efficacy as originally conceived was an appropriate choice endorsed by the Division.

Choosing Curosurf for the supporting study created the third comparator product in the program, along with Exosurf and the reference Survanta, and ultimately resulted in a complicated set of results. A sounder scientific decision would have been to use Exosurf or Survanta in the supporting study, but the choice of Curosurf was a business decision.

6.1.3.3 Patient populations

A strength of the Surfaxin clinical program was that all three efficacy studies provided "adequate assurance that [patients] have the disease or condition being studied" *[21 CFR 314.126(b)(v)(3)]*, because the studies had identical patient populations: premature neonates of 600-1250 grams birth weight. In addition, the studies all had nearly identical patient eligibility criteria for enrollment and the criteria were appropriate and consistent with other surfactant studies. A single exception was that mothers with chorioamnionitis were excluded from KL4-IRDS-06, but not from KL4-IRDS-02. Otherwise, there were very few excluding criteria other than the birth weight limits. This implies that results of the studies should be broadly generalizable.

On the other hand, the studies were widely dispersed geographically, which could have important implications. KL4-IRDS-06 was carried out in eastern Europe and Latin America. KL4-IRDS-02 centers were in the U.S., Canada, and Europe, but the only European countries in common with KL4-IRDS-06 were Poland and Hungary. There were regional racial and practice differences that make a broad view of results across studies somewhat problematic (the specific baseline differences are discussed in section 6.1.4.3 below). The same factors could also affect the specific study outcomes and limit the extent to which results can be generalized to a U.S. population. That issue is discussed in the next section.

6.1.3.3.1 International perspective

Whether there are differences in the care of neonates abroad is a significant factor in evaluating this application. Although there were protocol "recommendations" for ventilatory management, there were no requirements per se. Moreover, there is no evidence in the application or in the known history of the program that any other standardization of care practices among the study centers was attempted; nor is there any indication that the baseline outcomes at the centers were surveyed before the studies began. Although it would be mistaken to believe that there is great homogeneity of practice and results among U.S. centers;[3] it was, nevertheless, important to contrast the rates of the key outcomes in KL4-IRDS-06 to those in the U.S. To that end, two literature reports of North American outcomes were reviewed. The first report was in fact a study that served as a model for the design of KL4-IRDS-06, so the populations are quite similar;[2] and the second report gave outcomes for neonates 501-1500 grams birth weight from 1991-1999 in 39 North American centers.[4] The second report is included because it represents such a large group of centers over a long period of recent time; however, the incidences reported are for all neonates and only about 55% of them received surfactant. Consequently, they are not directly comparable to the other two data sets. They are included for the important perspective they provide.

Keeping in mind the caveats of different clinical experiences and differently defined outcomes, the incidences in the Table below generally indicate that the experience in KL4-IRDS-06 for death, pneumothorax, and NEC was not much different from the North American reports. The striking difference is in the much higher incidences of severe IVH in patients in KL4-IRDS-06. That will be dealt with further in the Integrated Review of Safety.

Table 5: Outcomes in KL4-IRDS-06 vs. North American Centers

Outcome (%)	KL4-IRDS-06			Hudak et al[2]		Horbar et al[4]
	Surfaxin	Exosurf	Survanta	Infasurf	Exosurf	
RDS-Death	4.7	9.6	10.5	1.7	5.4	N.D.
All Death	19.0	21.4	23.6	17.7	19.4	17.7, 15.1[a]
RDS[b]	39.1	47.2	33.3	16	42	68.9, 70.7
Pneumothorax	4.4	5.7	3.9	4	6	8.6, 7.3
NEC > stage 1	6.4	8.3	13.6	5.4	7.6	6.5, 7.4
Severe IVH	19.2	18.0	20.6	11.8	8.3	9.7, 8.2

[a]The two incidences for Horbar et al represent the incidences in 1991 and 1999, respectively
[b]The definition of RDS in Hudak et al is the same as KL4-IRDS-06. The definition is not specified for Horbar et al

The population differences and international composition of the studies in this program should be noted in product labeling. Overall, they do not necessarily overrule the strength of the common study entry criteria that the studies shared.

6.1.3.4 Minimization of bias

The two controlled studies were randomized appropriately. Using birth weight strata was also appropriate because the severity of RDS and frequency of complications are highly correlated with degree of prematurity, which manifests in birth weight. Other surfactant studies have used other strata as well: exposure to antenatal steroids, gestational age, and postnatal age. All of these factors are also appropriate, but none is essential and the Applicant cannot be faulted for not using them.

Blinding has been a challenge in all surfactant studies for several reasons:

- The clinical situation is frequently emergent with many personnel involved.
- Different surfactants have different appearances.
- Surfactant is administered into the ETT and may require several minutes to completely enter the airway, leaving it visible to the eye.

The Applicant demonstrated proper diligence in attempting to blind the studies. The same procedures were used in the two controlled studies. Upon determining eligibility and enrolling a patient in the study, the investigator notified a ***Dosing Preparer***. This was an individual who was not involved in determining the patient's eligibility nor would be otherwise involved in the patient's care. The Dosing Preparer determined the assigned treatment by opening the next sequential opaque envelope for the patient's birth weight stratum. The Dosing Preparer then prepared the assigned treatment according to specific directions in a protocol appendix. The preparation instructions for the comparator products conformed to the package inserts. The surfactant was prepared in a location not visible to the patient's caregivers, preferably the pharmacy. The surfactant was drawn into a syringe that was wrapped in an opaque label to mask the surfactant's appearance. The label had gradations to permit accurate dosing.

The prepared dosing syringe was delivered to a ***Dosing Administrator*** who would give the surfactant to the patient. The Dosing Administrator was also an individual not involved in determining the patient's eligibility or involved in the care. The Dosing Administrator could be the same person as the Dosing Preparer. Surfactant administration had to be performed in a location or in a manner not visible to the patient's caregivers.

6.1.3.5 Efficacy endpoints

The study endpoints, their advantages and disadvantages, their use in the studies, and the role of an Adjudication Committee in KL4-IRDS-06 were discussed in section 6.1.2 above. Although the commonality of endpoints in all the studies should enhance across-study perspectives on efficacy, two other elements of study design weakened that perpsective:

- Determination of RDS and cause of death by AC in KL4-IRDS-06 vs. by investigators in the other studies
- Different retreatment criteria affected the number of surfactant doses given

6.1.3.6 Dose-ranging

No true dose-ranging was done for Surfaxin. A fourth NRDS study, KL4-IRDS-01, (b) (4) [redacted] not the prevention strategy for which the indication is sought. The study is briefly mentioned here, however, because it was the only study in the program that used more than one dosage.

KL4-IRDS-01 was an open-label, uncontrolled study designed to examine the effectiveness of two doses of Surfaxin. Neonates between 750 and 1750 grams birth weight with RDS (arterial/alveolar oxygen ratio (a/APO_2) <0.22) within 4 hours of birth were treated with either 133 mg/kg or 200 mg/kg Surfaxin. A second dose could be given 6-12 hours later if there had been an initial increase of a/APO_2 >30% with a subsequent fall back to <0.22. Efficacy endpoints included indicators of pulmonary function (FiO_2, MAP, P_aO_2, a/APO_2, and oxygenation index), radiographic score for RDS, clinical+radiographic score for BPD, time on ventilation, mortality, and 1-year follow-up. As it turned out, only 8 of the 47 patients in the study received the lower dose of Surfaxin. The effects of the two doses are summarized in the next section, but this study's main contribution to the program is in enlarging the safety data base.

6.1.4 Efficacy Findings

6.1.4.1 Basis for efficacy

As noted, there are three studies in this application that provide the evidence supporting efficacy, but only one of them, KL4-IRDS-06, was a major efficacy study. The Division accepted that approach and acknowledged the supporting study, KL4-IRDS-02. The perspective of this review, however, is that the support from KL4-IRDS-02 is extremely impaired by the critical differences in the key efficacy outcomes and by its near-fatal design flaw described in detail in the individual study report. As a consequence, KL4-IRDS-06 stands nearly alone for conclusions about efficacy of Surfaxin with KL4-IRDS-02 providing what might be termed affirmation without evidence of contradiction.

The Applicant's Integrated Summary of Efficacy was an important source of the data reviewed and discussed in this section, particularly for summary tables of data.

6.1.4.2 Patient populations and disposition

Table 6 shows the enrollments and patient dispositions in each of the three efficacy studies.

Table 6: Patient Disposition: Integrated Efficacy

	KL4-IRDS-06			KL4-IRDS-02		KL4-IRDS-05
	Surfaxin	**Exosurf**	**Survanta**	**Surfaxin**	**Curosurf**	**Surfaxin**
Randomized	527	509	258	124	128	11
Treated	524	506	258	119	124	11
Completed	522 (99.1%)	505 (99.2%)	258 (100%)	124 (100%)	128 (100%)	11 (100%)

Source: M5, v 56, sec 5.3.5.3., pp 30, 32

Four of the five non-completing Surfaxin patients in KL4-IRDS-06 withdrew consent and the fifth did not have a final evaluation. All four non-completers in the Exosurf group withdrew consent.

The six patients who were randomized but not treated in KL4-IRDS-06, and the reasons, were:

- Surfaxin
  - Patient 052001 had a 5-minute APGAR of 3, which was recognized after randomization as an exclusion criterion, so the patient was not treated.
  - Patient 081007 was not treated when it was discovered that the study drug refrigerator temperature had not been properly maintained.
  - Patient 312001 was not intubated, which was required for study drug delivery.
- Exosurf
  - Patient 023008 was mistakenly randomized despite an exclusion criterion.
  - Patient 732005 experienced problems with intubation and could not be treated.
  - Patient 781002 developed a pulmonary hemorrhage at 28 minutes after birth and died shortly thereafter.

6.1.4.3 Baseline Characteristics

To be able to examine results across studies, the similarities or differences in the patients at baseline must be considered. The next two Tables display important baseline maternal and neonatal characteristics, respectively, in the three studies. There are some notable differences in maternal characteristics:

- Within a study, the only difference is in KL4-IRDS-02 where significantly more neonates in the Curosurf group were born to mothers with gestational diabetes
- Between studies, large differences are noted between KL4-IRDS-06 and KL4-IRDS-02:
  - lower incidence of maternal chorioamnionitis in KL4-IRDS-06 where it was an exclusion criterion
  - higher incidence of pregnancy-induced hypertension, higher incidence of artificial rupture of membranes, and less use of tocolytic therapy in KL4-IRDS-06

It is possible that these latter factors are inter-related; i.e., more maternal hypertension may lead to more urgency in delivering the baby, so membranes are artificially ruptured and tocolysis is not initiated. On the other hand, the differences might only reflect regional differences in perinatal diagnosis and management.

The neonatal characteristics are notable in the following ways:

▪ The higher rate of multiple births in KL4-IRDS-02. This could represent genetic differences between the different population groups in the studies.
▪ Higher rate of emergency C-section in KL4-IRDS-06, again most likely reflecting regional practice differences
▪ The most remarkable differences are noted in racial distributions. First, there are practically no black patients in the entire clinical program. Second, there is a marked difference in the proportions of Hispanic patients. It must be noted, however, that the Hispanic patients in KL4-IRDS-06 (the study was conducted in several Latin American countries) were designated for some unexplained reason as "Other" rather than Hispanic. Nevertheless, there are still far fewer Hispanic patients in KL4-IRDS-02.

Differences occurred between KL4-IRDS-05 and the other studies, as well, but with only 11 patients, the rates of events in that study cannot be said to reliably represent a generalized population.

Table 7: Baseline Maternal Characteristics: Integrated Efficacy

	KL4-IRDS-06				KL4-IRDS-02			KL4-IRDS-05
	Surfaxin	**Exosurf**	**Survanta**	**p-value[a]**	**Surfaxin**	**Curosurf**	**p-value**	**Surfaxin**
Mother's Age								
N	527	509	258	0.229	117	123	0.774	11
Mean (SD)	28.4 (6.8)	27.9 (6.4)	28.2 (6.5)		29.7 (5.7)	29.9 (5.9)		26.3 (9.7)
Gravidity								
N	527	509	258	0.709	119	124	0.510	11
Mean (SD)	2.5 (2.1)	2.6 (1.9)	2.5 (1.6)		2.8 (1.9)	2.6 (1.7)		3.6 (3.3)
Parity								
N	527	509	258	0.847	119	124	0.777	11
Mean (SD)	2.0 (1.4)	2.0 (1.4)	1.9 (1.2)		2.0 (1.3)	1.9 (1.2)		2.7 (2.5)
			N (%)					
Chorioamnionitis								
No	504 (95.6)	487 (96.2)	245 (95.0)	0.613	96 (80.7)	98 (79.0)	0.544	11 (100)
Yes	23 (4.4)	19 (3.8)	13 (5.0)		23 (19.3)	26 (21.0)		
Gestational Diabetes								
No	508 (96.8)	495 (98.0)	250 (98.0)	0.243	115(99.1)	115(94.3)	0.036	11 (100)
Yes	17 (3.2)	10 (2.0)	5 (2.0)		1 (0.9)	7 (5.7)		
Insulin-dependent Diabetes								
No	519 (98.5)	505 (99.4)	254 (98.4)	0.162	117(98.3)	121(97.6)	0.705	11 (100)
Yes	8 (1.5)	3 (0.6)	4 (1.6)		2 (1.7)	3 (2.4)		
Pregnancy-induced Hypertension								
No	384 (73.0)	362 (71.3)	196 (76.0)	0.612	102(87.2)	111(89.5)	0.468	9 (81.8)
Yes	142 (27.0)	146 (28.7)	62 (24.0)		15 (12.8)	13 (10.5)		2 (18.2)

	KL4-IRDS-06				KL4-IRDS-02			KL4-IRDS-05
Labor History								
Spontaneous	255 (80.4)	233 (81.5)	133 (83.6)	0.939	72 (82.8)	84 (86.6)	0.288	6 (85.7)
Induced	62 (19.6)	53 (18.5)	26 (16.4)		15 (17.2)	13 (13.4)		1 (14.3)
Oligohydramnios >21 days								
No	520 (98.7)	502 (43.8)	257 (99.6)	0.873	114(95.8)	118(96.7)	0.650	11 (100)
Yes	7 (1.3)	6 (1.2)	1 (0.4)		5 (4.2)	4 (3.3)		
Rupture of membranes								
Spontaneous	228 (43.4)	220 (43.8)	131 (51.0)	0.734	61 (51.3)	72 (59.5)	0.188	6 (60.0)
Artificial	297 (56.6)	297 (56.6)	126 (49.0)		58 (48.7)	49 (40.5)		4 (40.0)
Steroid Treatment								
No	109 (20.8)	108 (21.5)	66 (25.7)	0.734	14 (11.8)	19 (15.3)	0.344	6 (54.6)
Yes	415 (79.2)	394 (78.5)	191 (74.3)		105(88.2)	105(84.7)		5 (45.4)
Tocolytic Therapy								
No	327 (62.0)	307 (60.8)	129 (50.0)	0.571	47 (39.8)	45 (36.3)	0.637	8 (80.0)
Yes	200 (38.0)	198 (39.2)	129 (50.0)		71 (60.2)	79 (63.7)		2 (20.0)

[a]Surfaxin vs. Exosurf
Source: M5, v 56, sec 5.3.5.3, pp 112-115

Table 8: Baseline Neonatal Characteristics: Integrated Efficacy

	KL4-IRDS-06				KL4-IRDS-02			KL4-IRDS-05
	Surfaxin	**Exosurf**	**Survanta**	**p-value [a]**	**Surfaxin**	**Curosurf**	**p-value**	**Surfaxin**
Birth Weight								
N	527	509	258	0.685	119	124	0.772	11
Mean (SD)	974 (183.4)	970 (185.8)	967 (187.0)		929 (189.0)	937 (195.5)		1052 (215.2)
Median	980	990	980		945	938		1150
Range	600-1250	600-1250	600-1390		570-1330	586-1650		700-1320
Gestational Age								
N	522	507	256	0.976	118	122	0.669	11
Mean (SD)	28.2 (2.0)	28.2 (2.0)	28.1 (2.1)		27.0 (1.2)	27.1 (1.4)		32.0 (0.8)
Median	28	28	28		27	27		32.0
Range	23.0-32.0	23.0-33.0	22.0-34.0		24.0-29.0	24.0-32.0		31.0-34.0
1-min APGAR								
N	527	509	258	0.909	119	124	0.774	11
Mean (SD)	5.3 (2.2)	5.3 (2.15)	5.3 (2.1)		5.8 (2.1)	5.8 (2.2)		3.3 (2.5)
5-min APGAR								
N	526	508	257	0.971	118	124	0.590	11
Mean (SD)	7.1 (1.4)	7.2 (1.4)	7.1 (1.4)		7.9 (1.5)	7.9 (1.4)		6.5 (1.4)
			N (%)					
Birth Status								

	KL4-IRDS-06				KL4-IRDS-02			KL4-IRDS-05
Single	426 (80.8)	412 (80.9)	206 (79.8)	0.940	86 (72.3)	89 (71.8)	0.820	8 (72.7)
Multiple	101 (19.2)	97 (19.1)	52 (20.2)		33 (27.7)	35 (28.2)		3 (27.3)
Congenital Anomaly								
No	522 (99.2)	500 (98.2)	254 (98.4)	0.144	117(98.3)	120(96.8)	0.382	11 (100)
Yes	4 (0.8)	9 (1.8)	4 (1.6)		2 (1.7)	4 (3.2)		
Mode of Delivery								
Vaginal spontaneous	132 (25.0)	122 (24.0)	69 (26.7)	0.600	43 (36.1)	37 (29.8)	0.634	4 (36.4)
Vaginal assisted	9 (1.7)	4 (0.8)	1 (0.4)		4 (3.4)	5 (4.0)		1 (9.1)
Elective C-section	2 (0.4)	2 (0.4)	0		3 (2.5)	2 (1.6)		0
Emer C-section	384 (72.9)	381 (74.9)	188 (72.9)		69 (58.0)	80 (64.5)		6 (54.5)
Race								
White	409 (77.6)	397 (78.0)	204 (79.1)	0.339	101(84.9)	100(80.6)	0.500	0
Black	3 (0.6)	4 (0.8)	3 (1.2)		3 (2.5)	7 (5.6)		0
Hispanic	0	0	0		9 (7.6)	7 (5.6)		0
Other	115 (21.8)	108 (21.2)	51 (19.8)		6 (5.0)	10 (8.1)		11 (100)
Gender								
Male	263 (49.9)	254 (49.9)	129 (50.0)	0.892	59 (49.6)	64 (51.6)	0.769	6 (54.5)
Female	264 (50.1)	255 (50.1)	129 (50.0)		60 (50.4)	60 (48.4)		5 (45.5)

[a]Surfaxin vs. Exosurf
Source: M5, v 56, sec 5.3.5.3, pp 36-38

In sum, there were baseline differences observed between the two major studies so that the patients were not truly equivalent at baseline in some prognostic categories. This limits the ability to draw inferences across the two studies. On the other hand, there is nothing in the baseline characteristics that suggests that relevant obstetric practices are remarkably different from those in the U.S. The rates of Caesarean section are consistent with the range found among U.S. centers. The use of antenatal steroids was slightly higher than the 60-70% reported for the U.S. In terms of extrapolating the results of these studies to the U.S., the latter factor ought to improve the outcomes related to lung maturity, if there is any effect at all.

6.1.4.4 Primary efficacy findings

In this integrated summary, the hierarchy of efficacy endpoints will align with that in the single major efficacy study, KL4-IRDS-06. Using that approach, the primary efficacy endpoints in KL4-IRDS-02 and KL4-IRDS-05, which were secondary endpoints in KL4-IRDS-06, will be considered secondary in this integrated summary, and vice versa.

The co-primary efficacy endpoints in KL4-IRDS-06 each had to be demonstrated superior in the Surfaxin patients at the 5% level of significance. The Applicant dealt with them independently, and the results of each are presented in that manner in the following sections. It is clinically relevant, however, to also consider the inter-relatedness of RDS and RDS-deaths, so this reviewer examined the data from that perspective also.

6.1.4.4.1 Incidence of RDS at 24 hours

In study KL4-IRDS-06, Surfaxin fairly met the standard of efficacy for this endpoint. Table 9 below shows the results from all three studies. The results for KL4-IRDS-06 are those derived from the AC determinations, but the results were also significant when the investigators' diagnoses were used (Table 57); i.e., the results of this outcome are robust. Included in Table 9 are the results of the Applicant's comparison of Surfaxin to Survanta performed in "exploratory" analyses in KL4-IRDS-06.

There was no difference between the treatments in KL4-IRDS-02, although incidence of RDS was a secondary endpoint in that study. The most apparent difference between results in the two studies, however, is the much lower incidence of RDS in KL4-IRDS-02, which most likely reflects the different diagnostic approaches used: by the AC in one study vs. by the clinical investigators in the other.

The diagnostic criteria that investigators in KL4-IRDS-02 were to use in diagnosing RDS were very nearly the same as those in KL4-IRDS-06, but the subtle differences could explain the different results. In KL4-IRDS-06, the diagnosis only specified an FiO_2 requirement >30%, while it also included mechanical ventilation in KL4-IRDS-02. The FiO_2 requirement had to be within an 8-hour window bracketing 24 hours in KL4-IRDS-06, while it was to be "at 24 hours" in KL4-IRDS-02. Finally, x-rays were interpreted by a pediatric radiologist adjudicator in KL4-IRDS-06, while they were interpreted by the clinical investigator in KL4-IRDS-02. It is notable that the incidences of RDS in KL4-IRDS-02 are nearly the same as those recorded by the investigators, not the AC, in KL4-IRDS-06 (see Table 57), which indicates that across the studies, clinicians were consistent in their diagnosis of RDS.

Further insight is gained by examining the data listings for KL4-IRDS-06. Investigators were to record their interpretations of the chest x-rays at 24 hours (consistent with RDS or not). Some data points are missing from the listings, but the data that are available reveal that only 96 24-hour x-rays in Surfaxin patients were considered by investigators to be consistent with RDS and only 112 in Exosurf patients. These numbers are quite consistent with the numbers of patients with RDS according to investigators that are shown in Table 57 (83 and 102, respectively). Contrasting these numbers with the numbers of patients with RDS in KL4-IRDS-06 shown in Table 9 below, then, it appears that the major difference between the adjudications and the investigators in determining the presence of RDS was interpretation of the chest x-rays.

Table 9: Incidence of RDS at 24 Hours: Applicant's Analyses (Integrated Efficacy)

	KL4-IRDS-06					KL4-IRDS-02			KL4-IRDS-05
	Surfaxin N=527	**Exosurf N=509**	**Survanta N=258**	**Surfaxin vs. Exosurf**	**Surfaxin vs. Survanta**	**Surfaxin N=119**	**Curosurf N=124**	**p-value**	**Surfaxin**
Incidence N (%)	206 (39.1)	240 (47.2)	86 (33.3)	OR=0.679 (0.519-0.888) P=0.005	OR=1.319 (0.941-1.849) P=0.108	22 (18.5)	19 (15.3)	0.508	4 (36.4)

Source: M5, v 56, sec 5.3.5.3, p 42

The Applicant also performed several "exploratory" analyses in KL4-IRDS-06 including gender, race, and weight group results. Those results are displayed in Table 58. The results of these additional analyses were quite consistent with the overall results in KL4-IRDS-06 and offer no evidence of contradictory or aberrant results in the groups.

To provide another context to interpret the results of the Surfaxin studies, information about incidence of RDS was collated from the Exosurf and Survanta package inserts for this review, with full recognition of the differences in those clinical programs. In addition, results from a published study comparing Exosurf to Infasurf were reviewed because that study was closest in design to the Surfaxin studies; indeed, was a model for the Surfaxin studies.[2] The information is summarized in the next Table. Despite the different clinical circumstances and different definitions of RDS, there does appear to be some consistency in the rates of RDS in Exosurf- and Survanta-treated patients in Table 9 and Table 10. The other observation that can be made from the studies in Table 10 is that although there was a range of RDS incidences in the placebo groups, the rate is generally about 50% or greater, which confirms the basic assumption of the prevention strategy and provides a perspective for results in the Surfaxin program where there were no placebo-treated patients.

Table 10: Incidence of RDS in Exosurf and Survanta Package Inserts

	Exosurf Study A[a] (700-1350 g)		Exosurf Study B[a] (700-1100 g)		Survanta Study A[b] (600-1250 g)		Survanta Study B[b] (600-1250 g)		Published Study[2] (<29 wks gestation)[c]	
	Exo	Pbo	Exo	Pbo	Surv	Pbo	Surv	Pbo	Exo	Infa
Incidence of RDS (%)	42	46	55	55	27.6	63.5	28.6	48.3	42	16

Exo=Exosurf; Pbo=placebo; Surv=Survanta; Infa=Infasurf
[a]RDS=FiO_2 ≥30% to maintain PaO_2 ≥50; MAP ≥6; confirmatory chest x-ray@ 24 hrs; no other cause of resp distress
[b]RDS=qualified for second dose; i.e., confirmatory chest x-ray 6-48 hrs; mechanical ventilation; FiO_2 ≥40%
[c]RDS=FiO_2 ≥30% @ 24 hrs; confirmatory chest x-ray 16-32 hrs

6.1.4.4.2 Mortality

The evolution of a mortality endpoint, with ultimate selection of RDS-related mortality at 14 days as the co-primary efficacy endpoint, was described in section 6.1.2 above. The next Table shows that Surfaxin was significantly superior to both comparators for that endpoint, as adjudicated by the AC, in the major efficacy study. The results shown in the Table include those from the Applicant's primary analyses of Surfaxin vs. Exosurf, as well as their Surfaxin-to-Survanta comparison performed in "exploratory" analyses.

Table 11: RDS-Related Mortality at 14 Days (Integrated Efficacy)

	KL4-IRDS-06				
	Surfaxin N=527	Exosurf N=509	Survanta N=258	Surfaxin vs. Exosurf	Surfaxin vs. Survanta
RDS-related Mortality by AC	*25 (4.7)*	*49 (9.6)*	*27 (10.5)*	*OR=0.417 (0.246-0.707) p=0.001*	*OR=0.347 (0.183-0.658) p=0.001*

Source: M5, v 56, sec 5.3.5.3, p 46

The efficacy of Surfaxin in preventing RDS deaths was demonstrated in the study, but while acknowledging the key place of RDS-related mortality in the demonstration of efficacy, any possible effects of Surfaxin on other deaths cannot be put aside. Table 12 below places the results of RDS-related mortality at 14 days in context with results of all-cause mortality and non-RDS-related mortality at the same time point. The Table distinguishes the analyses of RDS-related mortality based on AC results in KL4-IRDS-06 from those based on investigator judgments recorded on CRFs in the other studies. The results shown in the Table for RDS-related and all-cause mortality include those from the Applicant's primary analyses, as well as their Surfaxin-to-Survanta comparison performed in "exploratory" analyses. Non-RDS-related mortality represents all patients who died whose death was not judged RDS-related by the AC in KL4-IRDS-06 or by the investigator in the other two studies; i.e., all-cause mortality *minus* RDS-related mortality. The subset of patients whose deaths were not RDS-related was not addressed by the Applicant. The analyses shown in the Table for that group were not performed by the Applicant; they were performed for this review by the FDA biostatistical reviewer.

The Applicant also performed exploratory analyses in demographic subgroups (see Table 60 for results in KL4-IRDS-06), whose results were consistent with the overall results shown below.

Table 12: Mortality at 14 Days (Integrated Efficacy)

	KL4-IRDS-06					KL4-IRDS-02			KL4-IRDS-05
	Surfaxin N=527	**Exosurf N=509**	**Survanta N=258**	**Surfaxin vs. Exosurf**	**Surfaxin vs. Survanta**	**Surfaxin N=119**	**Curosurf N=124**	**p-value**	**Surfaxin**
RDS-related Mortality by AC[a]	*25 (4.7)*	*49 (9.6)*	*27 (10.5)*	*OR=0.417 (0.246-0.707) p=0.001*	*OR=0.347 (0.183-0.658) p=0.001*	*NA*	*NA*	*NA*	*NA*
RDS-related Mortality by CRF	1 (0.2)	3 (0.6)	0	p=0.309	ND	1 (0.8)	0	0.779	0
All-cause Mortality[b]	84 (15.9)	86 (16.0)	48 (18.6)	OR=0.869 (0.603-1.251) p=0.450	OR=0.782 (0.500-1.225) p=0.284	13 (10.9)	17 (13.7)	0.498	3 (27.3)
Non-RDS-related Mortality[c]	59 (11.2)	37 (7.3)	21 (8.1)	p=0.022	N.D.	12 (10.1)	17 (13.7)	N.D.	3 (27.3)

[a]Co-primary efficacy endpoint for KL4-IRDS-06. Applicant's primary analysis based on AC results. Source: M5, v 56, sec 5.3.5.3, p 46
[b]Secondary endpoint. Applicant's primary analyses. Source: M5, v 56, sec 5.3.5.3, p 92
[c]FDA analysis

Table 12 illustrates the issues that were critical in reviewing the mortality endpoint and in reaching a conclusion about its place in the overall evaluation of Surfaxin:

- ***RDS-related mortality*** at 14 days was significantly reduced by Surfaxin treatment in KL4-IRDS-06, and this effect was consistent within race, gender, and birth weight subgroups.
- RDS-related mortality in KL4-IRDS-06 according to the AC was much higher than RDS-related mortality according to investigators.
- There was no effect on ***all-cause mortality*** in any study.
- Moreover, the incidence of ***non-RDS-related mortality*** was significantly increased in Surfaxin patients in KL4-IRDS-06.

These points capture the basic conundrum involving the three highlighted mortality endpoints in the results of the Surfaxin clinical program. Is the apparent improved survival from RDS simply a result of an arbitrary adjudication process full of subjectivity? Or is the improved survival real, but accompanied by a disadvantage in another pathophysiologic process that would increase the risk for another kind of death? Or is the difference in non-RDS-related deaths a natural residual effect of improved early survival of RDS? That is, does Surfaxin allow neonates to survive the early course of RDS to succumb later to another disease process unrelated to surfactant deficiency?

Those questions focused the remainder of the review of mortality results, which proceeded by first examining the AC results more closely; then further examining causes of death; and lastly, examining the occurrence of deaths over time. The last point was considered important in exploring whether Surfaxin prevented early RDS deaths and opened the door for later mortal events.

The mortality endpoint in this program straddles efficacy and safety. The RDS-related mortality results establish the product's efficacy in achieving the stated objective, but the possibility raised by the data shown in Table 12 that other types of deaths might be *adversely affected* by the product shifts the focus to safety. Although there is a degree of artificiality in separating the two types of considerations, ultimately the product's *benefit* and *risk* must be assessed and those are separate realms. To maintain that perspective, the other elements that formed the review of mortality results are found in the Integrated Review of Safety in section 7.1.1 below.

Before moving to consider the secondary efficacy endpoints, another component to the evaluation of the effectiveness of Surfaxin on mortality is reviewed in the next section.

6.1.4.4.3 RDS and mortality

The Applicant considered the two endpoints incidence of RDS and RDS-related mortality separately and independently. It makes clinical sense, however, to explore how they might have interacted. The patients in KL4-IRDS-06 who were adjudicated to have RDS and who died by 14 days were examined further.

The next Table summarizes some findings about these patients. The approach used in generating the results shown in the Table was exploratory. The outcome of patients with RDS vs. no RDS was not a stipulated analysis and results should not, and have not, been used to make conclusions about Surfaxin. However, that does not obviate the clinical perspective the results may bring to

consideration of the benefit and risk of Surfaxin. The results in the Table indicate that patients treated with Surfaxin, even if they get RDS – an outcome that could be considered a treatment failure – die of RDS much less commonly than those treated with the other surfactants. And if they die, it is not likely to be from an RDS-related cause. In fact, it is most likely to be from sepsis, which occurs about equally in Surfaxin and Exosurf patients. On the other hand, if a patient does not have RDS and dies, the causes appear to be different for different surfactants. A difference in sepsis is noted, as it was in previous analyses of causes of death; but it also appears that deaths due to IVH and pulmonary hemorrhage were more likely in the patients who did not have RDS. As noted, IVH and pulmonary hemorrhage are generally associated with RDS pathophysiology, so the finding here could reflect one of several processes. First, the results reflect an adjudication process more than physiology. Second, the cases of IVH and pulmonary hemorrhage reflected here were somehow physiologically different, which is a reasonable possibility. Or third, RDS was prevented but not completely eliminated by treatment, leaving enough lung pathology to still induce the IVH and pulmonary hemorrhage events. The information is not available to sort through those different explanations of the findings. What can be most confidently obtained from these data explorations is additional evidence for a beneficial influence of Surfaxin on the occurrence and course of RDS. When RDS causes fewer deaths, the relative proportions of other deaths may increase. As long as causality in the other deaths is not demonstrable, this is not of itself a negative effect. In fact, clinical focus is then freed up to shift to other disease conditions.

Table 13: Relation of RDS and Death in KL4-IRDS-06 (Integrated Safety)

	Surfaxin	Exosurf	Survanta
No. of patients with RDS (Table 9)	206	240	86
No. with RDS and Any Cause Death by 14 Days	42	62	29
% of RDS Who Died	42/206=20.4%	62/240=25.8%	29/86=33.7%
No. with RDS and RDS-Related Death by 14 Days	22	45	22
% of RDS Who Died of RDS-Related Cause	22/206=10.7%	45/240=18.8%	22/86=25.6%
% of All Deaths that were RDS-Related in RDS Patients	22/42=52.4%	45/62=72.6%	22/29=75.8%
Causes of Death if RDS but Death not RDS-Related			
Sepsis	10	11	1
Renal failure	5	1	0
NEC	1	1	3
Pulmonary hypoplasia	1	1	0
Surgical complications	1	0	0
IVH	1	2	0
Pulmonary hemorrhage	1	0	0
Congenital heart disease	0	1	0
Other	0	0	0
Causes of Death When No RDS			
Sepsis	12	7	3
Renal failure	1	1	0
NEC	3	1	1
Pulmonary hemorrhage	8	2	5
Congenital heart disease	1	1	0
IVH	9	6	8
Air leak	2	2	0
Other	6	3	2

6.1.4.5 Secondary efficacy findings

The three efficacy studies all used essentially the same endpoints, described in section 6.1.2.4 above. The comparative effects of Surfaxin on the secondary endpoints are described in detail for KL4-IRDS-06 and KL4-IRDS-02 in the individual study reports (refer to sections 10.1.3.5.2 below and 10.2.3.4.2 below). Those results show no treatment differences between Surfaxin and any of the comparators for number of surfactant doses; severity of RDS; or durations of supplemental oxygen, mechanical ventilation, or hospitalization. There is no evidence of either advantage or disadvantage of Surfaxin for those endpoints.

Two of the other endpoints deserve further attention in this integrated summary:
▪ RDS-related mortality at 14 days and/or air leak at 7 days because it was the original co-primary endpoint for KL4-IRDS-06, and
▪ alive without BPD because it was the primary endpoint in KL4-IRDS-02, (b) (4) (b) (4) and BPD was considered by the Division as a clinically meaningful endpoint (section 6.1.2).

Results of the Applicant's primary analyses of these two endpoints are shown in Table 14. Because both endpoints are composites, the Table includes results for the components, air leak at 7 days and BPD, to shed more light on the composite results. BPD at both 28 days and 36 weeks PCA is shown. The former was the primary endpoint in KL4-IRDS-02, but the latter is more clinically meaningful – many very premature neonates require oxygen at 28 days by virtue of their prematurity, not because of lung injury. The later time point more accurately reflects lung injury.

Table 14: Results of Secondary Endpoint Analyses (Integrated Efficacy)

	KL4-IRDS-06					KL4-IRDS-02			KL4-IRDS-05
	Surfaxin N=527	Exosurf N=509	Survanta N=258	Surfaxin vs. Exosurf	Surfaxin vs. Survanta	Surfaxin N=119	Curosurf N=124	p-value	Surfaxin
RDS-related Mortality at 14 days and/or air leak at 7 days	92 (17.5)	110 (21.6)	49 (19.0)	OR=0.716 (0.517-0.992) p=0.045	OR=0.901 (0.591-1.371) p=0.625	18 (15.1)	18 (14.5)	OR=1.086 (0.508-2.321) p=0.880	5 (45.5)
Air Leak at 7 Days[a]	80 (15.2)	89 (17.5)	35 (13.6)	OR=0.803 (0.565-1.141) p=0.221	OR=1.166 (0.728-1.868) p=0.523	11 (9.2)	9 (7.3)	OR=1.351 (0.518-3.521) p=0.538	2 (18.2)
Alive, No BPD at 28 days[a]	221 (41.9)	190 (37.3)	106 (41.1)	OR=1.345 (1.008-1.796) p=0.044	OR=1.068 (0.747-1.526) p=0.719	45 (37.8)	41 (33.1)	OR=1.465 (0.763-2.813) p=0.251	6 (54.5)
BPD at 28	306	319	152	OR=0.743	OR=0.936	74	83	OR=0.683	5

	KL4-IRDS-06					KL4-IRDS-02			KL4-IRDS-05
days[a]	(58.1)	(62.7)	(58.9)	(0.557-0.993) p=0.044	(0.655-1.338) p=0.719	(62.2)	(66.9)	(0.355-1.311) p=0.251	(45.5)
Alive, No BPD at 36 wks PCA[a]	313 (59.4)	274 (53.8)	144 (55.8)	P=0.021 (OR ND)	NA	77 (64.7)	84 (67.7)	0.753	ND
BPD at 36 wks[a]	214 (40.6)	235 (46.2)	114 (44.2)	OR=0.717 (0.539-0.953) p=0.022	OR=0.817 (0.575-1.159) p=0.257	42 (35.3)	40 (32.3)	OR=1.114 (0.593-2.092) p=0.251	ND

[a]Not imputed for death. The Applicant features results imputed for death in the proposed package insert.
Source: M5, v 56, sec 5.3.5.3, Tables 2.2.2.1E, 2.2.2.3A, 2.2.2.3E

The results of these secondary efficacy analyses provide support for the primary endpoints, but the support is tempered somewhat by two factors. First, the difference in RDS-related mortality and/or air leak is driven by the difference in RDS-related mortality because there is no difference in air leaks; and the difference in alive-without-BPD is driven by BPD. This is important because the presence of BPD was determined by the need for oxygen, with no radiographic criterion, and there were no requirements or standards for oxygen use in the studies. Because of the great variability in these parameters among clinicians, the differences observed in KL4-IRDS-06 cannot be considered to have great robustness.

6.1.4.6 Other efficacy findings

6.1.4.6.1 Demographic subgroup results

For all of the efficacy endpoints, the Applicant performed analyses in seven subgroups: male, female, white, non-white, 600-800 grams, 801-1000 grams, and 1001-1250 grams. Within each subgroup, results were generally consistent with overall results. There were no alarming or unexpected findings. In logistic regression analyses of treatment effects, there were consistent effects of birth weight strata and gender. This is expected: RDS is more common and severe with decreasing birth weight and with male gender and these are the effects noted.
In this program, black patients were under-represented relative to the anticipated U.S. population. Only 20 patients in the entire program were black, and they were not analyzed separately. Only a "nonwhite" subgroup was analyzed, which was presumably nearly entirely Hispanic and/or Native American because about half the study centers were in Latin America. Race is a well-known prognostic factor in prematurity and RDS; i.e., prematurity is more common in black women than in Caucasians or Hispanics, and black neonates with RDS fare worse. The demographic composition of this program should be noted in product labeling.

6.1.4.6.2 Dose-response

The only clinical glimpse into effects of different doses of Surfaxin in NRDS comes from study KL4-IRDS-01, but it provides little information because it was a rescue study, not prevention.

The study was open-label and had two phases. In the first phase patients received 133 mg/kg Surfaxin, and in the second phase they received 200 mg/kg. Study patients were neonates of 750-1750 grams birth weight who had RDS. Thirty-nine of the 47 patients enrolled in the study were evaluated for efficacy, eight in the lower dose group and 31 in the higher (eight patients were not included in the efficacy analyses because of protocol violations or receiving another surfactant). The endpoints were acute measures of lung function for six hours following the dose, and BPD.

The results are summarized in the next Table. The study contributes little to this application because it was not the intended prevention use, only eight patients received the lower dose, and neither dose was used for Phase 3 or is intended for marketing.

Table 15: Surfaxin Dose-Response (Integrated Efficacy)

Endpoint	Low Dose (133 mg/kg) N=8	High Dose (200 mg/kg) N=31
a/APO_2 at 6 hrs (mean±SE)	0.42±0.10	0.37±0.03
FiO_2 at 6 hrs (mean±SE)	0.31±0.03	0.35±0.02
MAP at 6 hrs (mean±SE)	6.71±0.57	7.03±0.31
RDS radiographic severity score: pre-/post-treatment	3.53/2.33	3.68/1.93
BPD at 37 wks PCA	0/7	3/28
Source: KL4-IRDS-01 study report: M5, v 1.133, sec 5.3.5.3, p 1		

6.1.4.6.3 Applicant's other findings

In its Integrated Summary of Efficacy, the Applicant also performed analyses of all-cause mortality comparing Surfaxin to "the animal-derived, protein-containing surfactants [Survanta+Curosurf]…as a class." *[M5, v 56, sec 5.3.5.3, p 93ff]* These analyses were not considered in this review because 1) they were "unplanned" and not discussed with the Division; 2) there is no evidentiary basis for combining Survanta and Curosurf effects or considering them together as a drug class; 3) the pooling of efficacy results from the two studies is invalid; and 4) the Applicant presents no scientific rationale or basis for the approach.

6.1.5 Clinical Microbiology

This section does not apply to this application because Surfaxin does not have antimicrobial properties.

6.1.6 Efficacy Conclusions

The application included three clinical studies to support efficacy in the prevention strategy, but one of the studies constituted essentially the entire basis of evidence. Depending on the results of one study for the application was discussed and agreed upon with the Division beforehand. Of the other two efficacy studies, one was uncontrolled and included only 11 patients; and the other was of flawed design, used a different comparator and different endpoints, and used a non-recommended dose of the comparator. The fourth clinical study submitted in the application was a rescue study and was not considered in the efficacy review.

The major efficacy study was well-designed and was intended to demonstrate superiority in the co-primary endpoints to the active control, Exosurf. A second active comparator, Survanta, was used as reference. The Applicant concluded that *"...Surfaxin is superior (with overwhelming statistical significance) to Exosurf in preventing and ameliorating RDS, and clinically important complications associated with prematurity, mechanical ventilation and RDS, in premature neonates who weigh between 600 and 1250 grams at birth and who are 24 to 32 weeks in gestational age"* [M1, v 1.1, cover letter]. (b) (4)

With the evidence of effectiveness coming from the single study KL4-IRDS-06, it was reviewed and evaluated according to the guidance for "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products." The study met the standards set forth in that guidance, as follows.

a) KL4-IRDS-06 was a large, adequately designed multicenter study. It was randomized and appropriately stratified for birth weight within each of the many international centers. Because of the route of administration of surfactant, blinding is difficult, but appropriate and diligent efforts were made to accomplish and maintain blinding in the study. The comparator products were appropriate and consistent with the Division's recommendations. Similarly, the primary efficacy endpoints and the superiority design of the study were compliant with the Division's recommendations, even though the definition of the co-primary endpoints underwent changes by protocol amendments after initiation of the study. By the time of analysis, the endpoints were those agreed upon with the Division. The challenges in defining the two co-primary endpoints, incidence of RDS and RDS-related mortality, and substantiating them in the clinical study setting were previously discussed. Given those challenges, adjudication of the endpoints via the mechanism of an independent committee was appropriate, and the Applicant adhered to the agreed-upon process and carried it out with due diligence.

b) There were multiple secondary efficacy endpoints involving different events, satisfying another criterion of the guidance. In addition, the secondary endpoints were generally similar to those used for other surfactant products.

In considering all studies, results for the secondary endpoints showed them to generally support the primary effects of Surfaxin on RDS and RDS-mortality, and there were no results that contradicted those effects. (b) (4)

Evaluation of the results for BPD is more complicated. BPD was an endpoint discussed with the Division, indeed, was supported as a primary endpoint by the Division, but the Applicant's definition of the condition was not sufficiently refined. In a correspondence dated September 26, 2001, the Division stated that "…BPD should be defined by peripheral oxygen saturation parameters that specify when an infant requires supplemental oxygen… (b) (4)

(b) (4)

Among the secondary efficacy endpoints was all-cause mortality, and the results for this outcome were not at all straightforward. Despite the difference in RDS-related mortality, there was no difference in all-cause mortality at any time point in the study, and in fact the incidence of non-RDS-related mortality (all the deaths besides those RDS-related) was significantly higher in Surfaxin patients than Exosurf patients. The Applicant did not report this finding, so the conclusions about it were based on FDA analyses and interpretation. Finding more non-RDS-related deaths in Surfaxin patients obligated consideration of the mortality endpoint in a safety context and that review and its conclusions are found in the Integrated Review of Safety.

c) Results for the co-primary efficacy endpoints were statistically persuasive, another necessary criterion for reliance on a single study suggested by the guidance. The incidence of RDS was about 17% less in patients treated with Surfaxin, and RDS-related mortality was approximately half the rate in Surfaxin patients compared to Exosurf patients (4.7 vs. 9.6%). The criteria for efficacy were fairly met, and moreover, the results were consistent across population subgroups based on birth weight, gender, and race.

This review considered two other elements in the review of efficacy. The first was whether the conclusions about efficacy from this international program could be applied to patients in the U.S. There were too few black patients in the program to specifically evaluate the effects of Surfaxin in them, but in the absence of evidence of deleterious effect, and with proper labeling about the demographic composition of the clinical studies, there is no reason to prohibit use of Surfaxin in black patients despite the lack of specific evidence of effect. Regarding the European and Latin American study sites, there was no evidence that the efficacy outcomes from those sites were inherently any worse than would be expected in the U.S.; consequently, the reported effects of Surfaxin should not be different in neonates in the U.S.

Another element considered was selection of the proposed dosage of Surfaxin. The Applicant selected an initial clinical dose of 133 mg/kg phospholipids based on results in primate studies. Later primate studies showed that a higher dose of 200 mg/kg produced more consistent and longer-lasting effects. A clinical dosing study then compared those two doses, but the study was in the rescue strategy and only eight patients received the lower dose. Then, the dose selected for Phase 3 development was 175 mg/kg with no obvious rationale for its selection instead of a 200 mg/kg dose. Administering additional doses of surfactant after the first dose depends on the patient's continuing respiratory status, so patients may receive from 1 to 4 doses. This strategy makes dose-response determinations quite difficult, especially for safety outcomes, because only

relatively sicker patients receive more doses. Despite the reality that clinical dose-ranging in the circumstances of NRDS is extremely challenging, additional information about doses and dose regimens is warranted. In particular, additional information could help to determine whether any of the associated safety concerns discussed in the next section might be modified by using other doses.

Finally, the results from the other two efficacy studies generally provided evidence of *consistency* with KL4-IRDS-06. Although there were no significant differences in incidence of RDS or RDS-related deaths, the studies were not designed or powered to detect them, and the rates of the events as well as secondary outcomes were similar to those in the major efficacy study.

In conclusion, returning to the Applicant's proposed indication and effects, this review finds evidence to support:

- the proposed indication: prevention of RDS (b) (4)

(b) (4)

(b) (4)

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The lung surfactant drug class and the intended population, premature newborns, prompt some adaptations in the Integrated Review of Safety. Evaluating the safety of a therapy in this population is complicated. The patients are not only pre-verbal but they are also not under the care of their parents, so that many possible symptomatologies (pain, distress, nausea, etc.) are undetectable and unreported. In addition, by virtue of prematurity, many events that would be considered "abnormal" or "adverse" in other patients are considered "physiologic" or at least expected in these patients (e.g., hyperbilirubinemia, apnea). The occurrence of truly adverse events (e.g., IVH) can be somewhat common because of the underlying disease itself, and differentiating whether the event is due to the underlying disease or therapy requires a high level of discrimination.

Some "adverse events" are common enough in premature neonates with RDS that they have been designated in previous surfactants' development programs as a separate category of ***"concurrent diagnoses"*** for prospective monitoring. The same approach was used in this application. Although this assures a high degree of certainty about the rates of those particular events, it also leads to double-reporting by investigators as AEs as well.

Surfactants are liquid products that are instilled into the lungs via the ETT and this creates yet another special set of events. These events, known as ***"negative reactions to dose administration"*** in this application, have also been separately monitored and analyzed, and like concurrent diagnoses, frequently double-reported.

These unique circumstances are reflected in the approved surfactants' package inserts, as well as in this Applicant's proposed package insert. The "Adverse Reactions" sections of the package inserts convey the information about (b) (4) negative reactions to dose administration, not the more typical adverse reactions (headache, nausea, etc.).

Finally, in this program the only clinical laboratory testing used to monitor patients was blood gases, which were measures of efficacy. There was no requirement to check hematological, chemical, etc. parameters. Abnormalities that occurred in those laboratory tests were only reported as AEs.

This Integrated Review of Safety will adhere to the precedence of the other surfactants and conform to the Applicant's safety monitoring program. Because they do represent AEs, but in a non-conventional way, *concurrent diagnoses* and *negative reactions to dose administration* will be reviewed as "Other significant adverse events" in section 7.1.3.3 below. The other AEs are reported and evaluated, but warrant less attention and emphasis for the reasons described.

7.1.1 Deaths

In the discussion of mortality as an efficacy endpoint in section 6.1.4.4.2 above, considering other aspects of the mortality results in a safety context was discussed. Those results are in this section. The review proceeded by first examining the AC results more closely; then further examining causes of death; and lastly, examining the occurrence of deaths over time. The last point was considered important in exploring whether Surfaxin prevented early RDS deaths and opened the door for later mortal events.

7.1.1.1 Adjudication Committee results

A critical factor in working out the effect of Surfaxin on mortality was to understand more about the work of the AC. The process of determining the RDS-relatedness of a death by the AC was described in section 6.1.2.1 above, however, results from each member of the committee were not included in the NDA. They were requested during the review period.

From the information provided by the Applicant in response to the request, the vote of each member of the committee for each patient who died in KL4-IRDS-06 was examined for this review. Two issues were of particular interest in the review. First, noting the similarities or differences between AC and investigator causes of death. The AC was primarily charged with determining the RDS-relatedness of deaths, but also assigned a cause of death for each patient. It is important to realize that deciding a death was RDS-related did not necessarily mean the death was caused by RDS. The critical distinction here is *relatedness* vs. the actual ultimate *cause* of

death. The second issue in the review was whether there was any evidence of bias within the AC.

Of the 218 patients who died through day 14, the RDS-relatedness of the deaths was agreed upon by two committee members on initial review in 141 cases (64.7%). The remaining deaths had to be adjudicated by a third member or by committee vote to make the determination. The number of deaths that were said to be RDS-related by each AC member for each treatment is shown in the next Table. With the overall results showing significantly less RDS-related deaths in the Surfaxin group, similar trends would be expected among the AC members. The purpose of viewing members' results individually was to determine whether there might be evidence of bias or radically different results from a single member, for example, that might have influenced the overall results. No such effect is apparent in the Table.

Table 16: RDS-related Mortality: AC Member Results

	Surfaxin	Exosurf	Survanta
		N (%)	
Study Overall[a]	25/84 (29.8)	49/86 (56.9)	27/48 (56.3)
Adjudicator 1	10/26 (38.5)	17/34 (50.0)	8/21 (38.1)
Adjudicator 2	1/4 (25.0)	0/2	0/1
Adjudicator 3	15/30 (50.0)	12/23 (52.2)	13/18 (72.2)
Adjudicator 4	15/49 (30.6)	16/46 (34.8)	16/27 (59.3)
Adjudicator 5	9/22 (40.9)	9/17 (52.9)	4/5 (80.0)
Adjudicator 7[b]	15/40 (37.5)	23/48 (47.9)	10/20 (50.0)
Committee Votes	9/28 (32.1)	13/20 (65.0)	9/15 (60.0)

[a]RDS-related deaths/total deaths
[b]Adjudicator 6 was a pediatric radiologist who did not adjudicate deaths
Source: "Adjudication_RDS_Death.xpt", December 1, 2004

Regarding the causes of death assigned by the AC, the deaths in the study were reviewed for the similarities between the AC- and investigator-assigned causes. The reasoning used for the approach was that if the causes from the two sources were found to be similar, the observed discrepancy between RDS-related and all-cause mortality could be explained by a straightforward difference of clinical opinion about whether a death was related to RDS or not. Judgment about the clinical effect of the drug would then not be clouded by uncertainty about the cause of death.

Of the 84 Surfaxin patients who died through day 14, the AC and investigator causes of death were the same in 59. Of the 86 Exosurf patients, the causes were the same in 59 patients. There was agreement in 30 of the 48 Survanta deaths. Table 17 lists the patients for whom different causes of death were assigned. Patients whose deaths were judged RDS-related are shown in **bold font**. The Table shows that when using the literal causes assigned by the AC and investigators, the rates of concurrence about cause of death were similar in the three treatment groups at about 60-70%. A closer examination, however, indicates that they are probably higher than that. There are several investigator-assigned causes that are nonspecific descriptions of the

terminal occurrences rather than true causes of death (e.g., bradycardia, cardiopulmonary failure). Similarly, there are some causes that are literally different, but probably the same functionally; for example, IVH and birth trauma.

Table 17: AC and Investigator Differences in Cause of Death in KL4-IRDS-06 (Integrated Safety)

Surfaxin			Exosurf			Survanta		
Pt #	**AC Cause**	**Inv. Cause**	**Pt #**	**AC Cause**	**Inv. Cause**	**Pt #**	**AC Cause**	**Inv. Cause**
21012	RDS	IVH	**22002**	RDS	Septic shock	**21005**	PH	NEC
22011	NEC	IVH	**51005**	Cardio-pulmonary failure	Septic shock	**21006**	Unknown	Sepsis
302018	RDS	Cardio-respiratory arrest	**301002**	IVH	Neonatal asphyxia	**72001**	IVH	Cardiac failure
311003	IVH	Metabolic acidosis	**303027**	PH	Septic shock	173014	NEC	Septic shock
312005	PTX	Septic shock	**303041**	PIE	IVH	**302016**	IVH	Hypovolemic shock
313011	Unknown	Septic shock	**511003**	PH	Sepsis	**303020**	IVH	PIE
321009	NEC	Renal failure	513014	Sepsis	Esophageal atresia	322006	Sepsis	Renal failure
322012	Air leak	Circulatory failure	**611002**	PH	Cardiac arrest	**322013**	PH	Multi-organ failure
513002	Sepsis	IVH	**631007**	RDS	Circulatory failure	**323013**	PH	Hypo-volemic shock
513008	Sepsis	IVH	**631008**	IVH	Maternal condition	511002	NEC	PH
542006	PH	Sepsis	701002	IVH	Cardio-pulmonary failure	**631006**	PH	IVH
631004	IVH	Circulatory failure	**702010**	PTX	Hype-rkalemia	702005	IVH	PH
632006	IVH	Renal failure	722014	PTX	PH	**711013**	PH	PDA
661002	Broncho-pneumonia	PIE	**722020**	PH	Cardiac failure	**721013**	IVH	Cardiac failure
671002	PH	Sepsis	**731013**	IVH	Cardiac failure	**762002**	IVH	Multi-organ failure
702009	IVH	TOGV	**732005**	Pulm hyper-tension	RDS	801003	NEC	Sepsis
732023	IVH	Cardiac failure	**733010**	PTX	Pneumonia	**802011**	PTX	Pulm hypertension
751012	PIE	IVH	751020	Hyper-kalemia	Renal failure	**861003**	Unknown	Respiratory failure
751019	RDS	Hyper-kalemia	752007	IVH	Sepsis			
751032	PH	IVH	752011	Hyper-kalemia	Renal failure			
752015	Pneumonia	IVH	**752036**	PH	IVH			
752018	IVH	Birth trauma	**761001**	PH	Cardiopulmonary failure			

Surfaxin			Exosurf			Survanta		
Pt #	**AC Cause**	**Inv. Cause**	**Pt #**	**AC Cause**	**Inv. Cause**	**Pt #**	**AC Cause**	**Inv. Cause**
753025	Surgical complications	IVH	**762004**	IVH	Cardiopulmonary failure			
762003	Sepsis	Cardiac failure	**782002**	Air leak	RDS			
783010	Sepsis	Bradycardia	791002	Cerebral hemorrhage	Adrenal hemorrhage			
791004	Renal failure	IVH	851002	Renal failure	Sepsis			
822001	PH	Sepsis	**863005**	IVH	Cardiac failure			
861008	Hyper-kalemia	Cardiac failure						
DOD=day of death; PTX=pneumothorax; PH=pulmonary hemorrhage; TOGV=transposition of the great vessels								

Discriminating the single cause of death is difficult when several morbid conditions are present simultaneously. Patient 751012 presented a clinical course that was not unusual in these studies. The patient was born on (b) (6) and developed RDS. She had a cardiac arrest on (b) (6), PIE was diagnosed on (b) (6), sepsis was diagnosed on (b) (6), and IVH also occurred on (b) (6). She died on (b) (6). She had several lethal events within a short time span. Each one presumably contributed something to her demise and perhaps even initiated a process that led to the next event. Which one "caused" her death?

Taking those circumstances into consideration, there appears to have been high agreement about causes of death in KL4-IRDS-06. Differences were primarily in determining whether the causes were RDS-related; indeed, the most noticeable finding in Table 17 is the different proportions of deaths that were determined to be RDS-related, as identified in bold font. In the Surfaxin group in Table 17, 7/28 (25%) deaths were RDS-related vs. 19/27 (70.4%) in Exosurf patients and 13/18 (72.2%) in Survanta patients. The odds ratio confidence intervals for the overall results (Table 12) would only allow up to 70.1% and 65.8%, respectively.

The observation that there were larger-than-expected differences in RDS-relatedness among a sub-group of the study population prompted an examination of the relationship, if any, between cause of death, RDS-relatedness, and the effect of Surfaxin among all the deaths. The question in the examination was whether surfactant affects those events related to RDS, but not others. The next section considers causes of death and their RDS-relatedness.

7.1.1.2 Causes of death

The most common causes of death in the studies through 14 days are shown in the next Table. For KL4-IRDS-06, the causes are those assigned by the AC; for the other studies, the causes were assigned by the investigators. It needs to be borne in mind that the deaths in KL4-IRDS-06 represented in Table 18 are not the same as non-RDS-related deaths. The Table is derived from all patients who died in the study; some of them were designated RDS-related by the AC and some were not.

Table 18: Causes of Death Through 14 Days (Integrated Safety)

Cause of Death	KL4-IRDS-06			KL4-IRDS-02		KL4-IRDS-05
	Surfaxin N=527	Exosurf N=509	Survanta N=258	Surfaxin N=119	Curosurf N=124	Surfaxin N=11
	N (%)					
Air Leak	8 (1.5)	10 (2.0)	4 (1.6)	2 (1.6)	2 (1.6)	0
IVH	17 (3.2)	28 (5.5)	18 (7.0)	5 (4.0)	6 (4.8)	0
NEC	4 (0.8)	2 (0.4)	4 (1.6)	0	0	0
Pulmonary Hemorrhage	15 (2.8)	12 (2.4)	11 (4.3)	0	0	0
Renal Failure	7 (1.3)	1 (0.2)	0	0	0	0
Sepsis	23 (4.4)	18 (3.5)	4 (1.6)	2 (1.7)	4 (3.2)	2 (67)

Source: M5, v 1.1, sec 5.3.5.1, p 75; M5, v 1.41, sec 5.3.5.1, p67; M5 , v 1.114, sec 5.3.5.3., p 57

Based on the observations noted in the previous section, the results for study KL4-IRDS-06 in Table 18 were reconsidered for whether they were RDS-related or not, as determined by the AC. The next Table summarizes the results of that inquiry. The most common causes of death are listed in the Table, with the numbers that were adjudged RDS-related and non-RDS-related. An "Other" category is included to be sure there are not results in that group that might skew the overall results. The results in the Table illustrate three obvious groupings of the causes of death:

- Highly RDS-related: air leaks
- Highly non-RDS-related: NEC, renal failure, sepsis
- Intermediate: IVH, pulmonary hemorrhage.

Table 19: RDS-Relatedness by Cause of Death in KL4-IRDS-06 (Integrated Safety)

Cause of Death	Surfaxin			Exosurf			Survanta		
	No. of deaths	RDS-Related N (%[a])	Non-RDS-Related N (%)	No. of Deaths	RDS-Related N (%)	Non-RDS-Related N (%)	No. of Deaths	RDS-Related N (%)	Non-RDS-Related N (%)
Air leak	8	6 (75.0)	2 (25.0)	10	9 (90.0)	1 (10.0)	4	4 (100)	0
IVH	17	8 (47.1)	9 (52.9)	28	21 (75.0)	7 (25.0)	18	13 (72.2)	5 (27.8)
NEC	4	0	4 (100)	2	1 (50.0)	1 (50.0)	4	0	4 (100)
Pulmonary Hemorrhage	15	6 (40.0)	9 (60.0)	12	11 (91.7)	1 (8.3)	11	7 (63.6)	4 (36.4)
Renal failure	7	1 (14.3)	6 (85.7)	1	0	1 (100)	0	0	0
Sepsis	23	0	23 (100)	18	0	18 (100)	4	0	4 (100)
Other	10	4 (40.0)	6 (60.0)	15	6 (40.0)	9 (60.0)	7	3 (42.9)	4 (57.1)

[a]**% is per cent of deaths for that cause**

The findings in Table 19 are supported by biologic plausibility. Air leak is a commonly recognized and accepted consequence of RDS and mechanical ventilation, and indeed was originally a component of the primary endpoints for KL4-IRDS-06. Conversely, on a biologic

basis, there should be no causal relationship between RDS and NEC, sepsis, or renal failure. IVH and pulmonary hemorrhage have generally been associated with RDS, and in some reports with surfactant treatment.[5,6] In this evaluation, they will be considered RDS-related. The results by treatment for these two events are discordant in Table 19; further insight might be found by examining timing of the events, which is discussed in section 7.1.1.3.

Using the relatedness perspective to reconstruct the causes of death shown in Table 18 is informative. The next Table shows the same data as Table 18, but with results grouped by RDS-relatedness of the causes, according to the rationale just discussed. Only results for KL4-IRDS-06 are shown.

Table 20: Causes of Death by RDS-Relatedness in KL4-IRDS-06 (Integrated Safety)

Cause of Death	Surfaxin	Exosurf	Survanta
		N (%)	
RDS-Related: Air Leak, IVH, pulmonary hemorrhage	40 (7.5)	50 (9.9)	33 (12.9)
Non-RDS-Related: NEC, Renal Failure, Sepsis	34 (6.5)	21 (4.1)	8 (3.2)

The results in Table 20 support to some extent the beneficial effect of Surfaxin on RDS-related causes of death, although the difference from Exosurf is clearly not as profound as that in the Applicant's primary analysis. But the more significant result is that there is a higher proportion of deaths in the Surfaxin group for the causes that are not related to RDS. These results illuminate the results of the FDA analyses of "non-RDS-related" deaths, shown in Table 12, by indicating that the higher mortality in the non-RDS group in fact occurs from the causes that would not be expected to be benefited by surfactant.

That observation begs exploration of two other critical aspects of the mortality results: 1) are the observed differences in non-related events due to any deleterious effect of the surfactant; or 2) are the differences due to an indirect effect of allowing non-related events to emerge as patients survive longer? The latter phenomenon will be explored more in section 7.1.1.3 below. Regarding the former effect, two non-related causes of death occurred somewhat more commonly in the Surfaxin-treated patients in KL4-IRDS-06 through the first 14 days: renal failure and sepsis (Table 18). The patients who died of those causes were examined more closely to try to determine what causative role Surfaxin played, if any.

7.1.1.2.1 Renal deaths

Table 21 summarizes some information about the eight patients who died of renal failure through the first 14 days of life. Several summary observations can be made.

- All deaths occurred after the first week of life
- Investigators agreed with the AC about cause of death for all but two of the patients
- None of the deaths but one were considered RDS-related
- In most cases, the renal failure came after concurrent diagnoses associated with hypotension and poor perfusion; e.g., IVH, sepsis, air leak, and was probably a terminal event.

In two of the Surfaxin cases, 312006 and 791004, the oliguria was noted early within the first two days. In 791004, this could be a result of perinatal asphyxia reflected in low APGAR scores, but that was not the case for 312006. The single Exosurf patient's narrative does not even mention renal failure. The investigator attributed the death to sepsis. The basis for the AC determination of renal death is not apparent.

Table 21: Deaths Due To Renal Failure Through 14 Days (Integrated Safety)

Patient ID	Day of Death	Cause of Death by Investigator	Death RDS-related?	Notes
		Surfaxin		
312006	14	Renal failure	No	Female 820 g. "Acute renal failure" day 2
321003	14	Renal failure	Yes	Female 600 g. IVH, hypotension. Anuric 48 hrs prior to death
322008	13	Renal failure	No	Female 900 g. Multiple pneumothoraces, IVH, cardiac arrest. Dx of renal failure day12
631010	12	Renal failure	No	Male 700 g. Pulmonary hemorrhage. Dx renal failure day 8
752001	10	Renal failure	No	Female 1000 g. Persistent hypotension, IVH, seizures. Dx renal failure day 4
791004	9	IVH	No	Female 700 g. Asphyxia. Oliguria day 2. Thrombocytopenia, IVH
812007	8	Renal failure	No	Male 930 g. Asphyxia (5-min APGAR 1). Pneumothorax
		Exosurf		
851002	8	Sepsis	No	Female 610 g. Sepsis, "malformation left bronchial tree". Renal failure not mentioned in patient narrative.

The death of an additional Exosurf-treated patient, #752011, at 10 days was attributed by the AC to hyperkalemia. Review of the patient narrative reveals the hyperkalemia to be secondary to renal failure, which was the cause assigned by the investigator. In five of the Surfaxin deaths, the renal failure could reasonably be considered a terminal event after previous catastrophic insults. There is no apparent reason, however, why the same phenomenon did not occur, according to AC review, in Exosurf patients who presumably suffered the same types of events.

As discussed in section 7.1.1.3 below, there were additional deaths due to renal failure after 14 days and more of those occurred in the Exosurf group, leading to less discrepancy in this cause of death overall. Nevertheless, the discrepancy in the first 14 days remains.

Given the clinical pattern of renal failure deaths as terminal events and the absence of any other evidence of nephrotoxicity in preclinical studies (section 3.2) or in clinical or laboratory adverse renal event reports (section 7.1.5.6.1), the difference in renal failure deaths most likely reflects the subjectivity of the adjudication process and not an event related to the drug.

7.1.1.2.2 Sepsis

Establishing the presence of sepsis, by either the AC or investigator did not require the presence of positive cultures; it could be based on "substantial clinical evidence of infection." In fact, organisms were not required to be reported on CRFs. In clinical practice, neonatal sepsis is a

clinical syndrome. There are two main reasons. First, causative organisms can rarely be isolated when blood cultures are limited to the very small volumes that safe practice dictates in premature neonates. Second, in the absence of an organism, diagnosis of sepsis must be based in clinical signs. Because of their multi-system immaturity, premature neonates have a very limited repertoire for responding to clinical insults. By clinical signs, sepsis may be indistinguishable from IVH, acidosis, or hypothermia, for example.

As a result of these factors, further exploration of the deaths due to sepsis was limited. Specific organisms were recorded by happenstance in AEs for only 12 of the Surfaxin patients and six of the Exosurf patients. In both groups, the commonest organisms reported were gram negative rods and group B streptococcus. These are the expected organisms.

There generally was good agreement between the AC determination of cause of death and the investigators for patients in this subgroup. Investigators assigned causes of death other than sepsis for four Surfaxin patients (two IVH, 1 cardiac failure, 1 bradycardia) and one Exosurf patient (esophageal atresia).

Cases tended to be slightly more clustered by center for Surfaxin patients than Exosurf patients. Twelve Surfaxin patients came from five centers, while only two patients in the Exosurf group came from a single center; i.e., all other individual cases were from separate centers. In the Surfaxin group, there were four study centers that had at least three deaths due to sepsis.

The absence of rigorous, objective diagnostic criteria for sepsis makes it difficult to conclusively attribute cause to the drug. On the other hand, the presence of some other signals from AE reports (section 7.1.5.6.2) suggests a consistency about the possibility of increased risk of infection.

7.1.1.3 Time of deaths

Table 22 displays the incidences of death in the studies through the later study time points. RDS-related deaths are not shown because no deaths were judged by the AC to be RDS-related after 14 days. The Table includes results from the 6- and 12-month follow-up evaluations. Those evaluations were a separate phase of the studies. The results were submitted in the 4-month safety update, and are reviewed in section 7.2.9.2 below, but the mortality results are included in the Table for completeness. The 12-month evaluations are still in progress, so the results shown for that time are incomplete. Treatment comparisons were not performed for the 6- and 12-month results because they were rightfully considered as safety evaluations.

The data in Table 22 are also displayed graphically in Figure 1 following the Table. As Table 22 and Figure 1 show, there were no significant differences between Surfaxin and Exosurf at any time point, but the relative differences stay nearly constant throughout; i.e., there is no evidence of a changing pattern beyond the period of acute illness and dosing. Surfaxin compared to Survanta, on the other hand, showed a widening gap in mortality favoring Surfaxin with the difference at 36 weeks PCA essentially achieving statistical significance. The lower margin of

the confidence interval at that time point allows as much as half the mortality rate in Surfaxin patients.

Table 22: Incidences of Death at All Time Points (Integrated Safety)

	KL4-IRDS-06					KL4-IRDS-02			KL4-IRDS-05
	Surfaxin N=527	**Exosurf N=509**	**Survanta N=258**	**Surfaxin vs. Exosurf**	**Surfaxin vs. Survanta**	**Surfaxin N=119**	**Curosurf N=124**	**p-value**	**Surfaxin**
Day 14	84 (15.0)	86 (16.9)	48 (18.6)	OR=0.869 (0.603-1.251) p=0.450	OR=0.782 (0.500-1.225) p=0.284	13 (10.9)	17 (13.7)	OR=0.752 (0.330-1.714) p=0.498	3 (27.3)
Day 28	100 (19.0)	109 (21.4)	61 (23.6)	OR=0.799 (0.569-1.121) p=0.193	OR=0.687 (0.451-1.047) p=0.081	14 (11.8)	20 (16.1)	OR=0.636 (0.287-1.411) p=0.266	5 (45.5)
36 Weeks PCA	111 (21.1)	121 (23.8)	68 (26.4)	OR=0.800 (0.576-1.110) p=0.182	OR=0.668 (0.445-1.002) p=0.051	19 (16.0)	23 (18.5)	OR=0.767 (0.368-1.597) p=0.478	5 (45.5)
6 mos[a]	133 (25.2)	146 (28.7)	72 (27.9)	N.D.	N.D.	21 (16.9)	26 (20.3)	N.D.	N.A.
12 mos[a]	138 (26.2)	148 (29.1)	72 (27.9)	N.D.	N.D.	21 (16.9)	26 (20.3)	N.D.	N.A.

[a]The figures in this Table differ slightly from those in Table 38 and Table 40. The latter reflect per-protocol populations. The figures above reflect ITT populations to correspond with the other time points.
Source: M5, v 56, sec 5.3.5.3, pp 92-93 ; M5 (9/30/2004), v 2.1, sec 5.3.5.3, p 45 ; M5 (9/30/2004), v 2.16, sec 5.3.5.1, p 40

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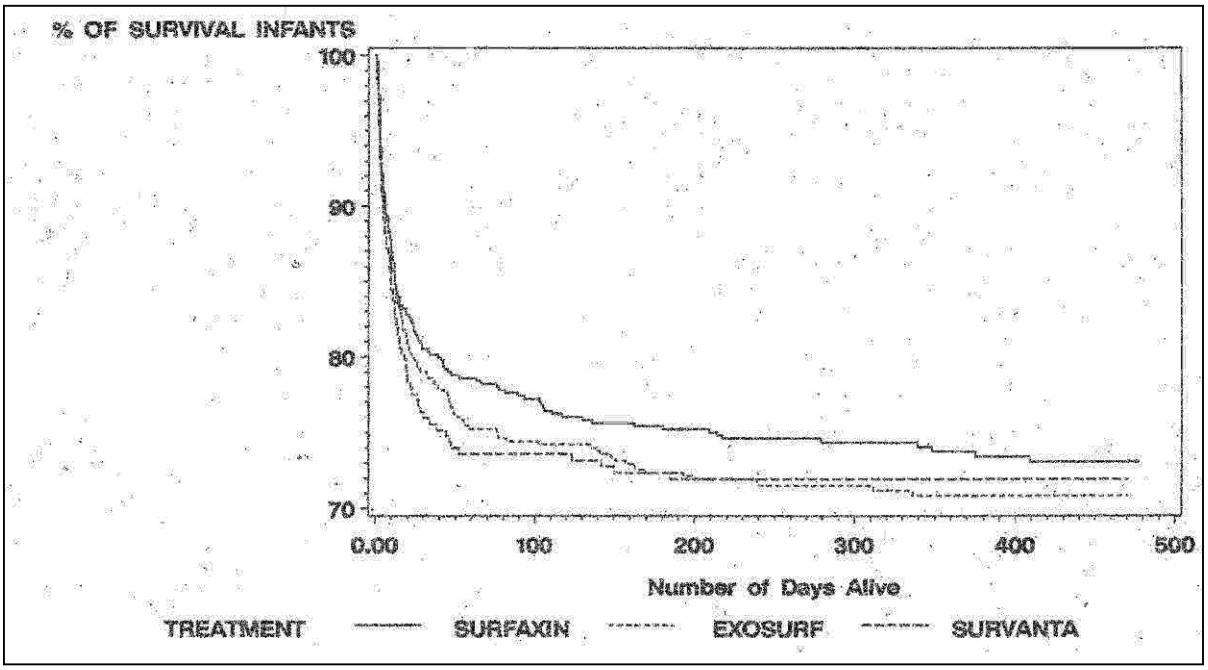
Figure 1: Survival Analysis in KL4-IRDS-06



Source: M5 (9/30/04), v 2.15, sec 5.3.5.1, p 124

Table 23 shows the deaths broken down by causes for the same time points. The following observations can be made about the data in the Table:

- The RDS-related causes (air leak, IVH, pulmonary hemorrhage) generally do not show much change after 14 days. This would be expected for causes related to RDS as time passes beyond the acute RDS period. The single possible exception is that there tended to be more later deaths from IVH in Exosurf and Survanta patients than Surfaxin (4 and 5 vs. 2).
- The non-RDS-related causes (NEC, sepsis, renal failure) tended to increase with time, again as expected. Of note is that the early gap in renal deaths between Surfaxin and Exosurf narrows by 36 weeks PCA, although it remains about twice as common in Surfaxin patients.

Table 23: Causes of Death at All Time Points (Integrated Safety)

	KL4-IRDS-06			KL4-IRDS-02		KL4-IRDS-05
	Surfaxin N=527	Exosurf N=509	Survanta N=258	Surfaxin N=119	Curosurf N=124	Surfaxin N=11
Cause of Death	N (%)					
	Through 14 Days					
Air Leak	8 (1.5)	10 (2.0)	4 (1.6)	2 (1.6)	2 (1.6)	0
IVH	17 (3.2)	28 (5.5)	18 (7.0)	5 (4.0)	6 (4.8)	0
NEC	4 (0.8)	2 (0.4)	4 (1.6)	0	0	-
Pulmonary Hemorrhage	15 (2.8)	12 (2.4)	11 (4.3)	0	0	0
Renal Failure	7 (1.3)	1 (0.2)	0	0	0	0
Sepsis	23 (4.4)	18 (3.5)	4 (1.6)	2 (1.7)	4 (3.2)	2 (18)
	Through 28 Days					

	KL4-IRDS-06			KL4-IRDS-02		KL4-IRDS-05
	Surfaxin N=527	Exosurf N=509	Survanta N=258	Surfaxin N=119	Curosurf N=124	Surfaxin N=11
Cause of Death	N (%)					
Air Leak	8 (1.5)	13 (2.6)	4 (1.6)	2 (1.6)	2 (1.6)	0
IVH	19 (3.6)	32 (6.3)	23 (8.9)	5 (4.0)	6 (4.8)	0
NEC	5 (0.9)	6 (1.2)	7 (2.7)	1 (0.8)	0	0
Pulmonary Hemorrhage	16 (3.0)	13 (2.6)	12 (4.7)	0	0	0
Renal Failure	9 (1.7)	3 (0.6)	1 (0.4)	0	0	1 (9)
Sepsis	30 (5.7)	24 (4.7)	6 (2.3)	2 (1.7)	6 (4.8)	3 (27)
Through 36 Weeks PCA						
Air Leak	8 (1.5)	13 (2.6)	4 (1.6)	2 (1.6)	2 (1.6)	0
IVH	19 (3.6)	32 (6.3)	23 (8.9)	5 (4.0)	6 (4.8)	0
NEC	8 (1.5)	8 (1.6)	9 (3.5)	3 (2.5)	0	0
Pulmonary Hemorrhage	16 (3.0)	14 (2.8)	12 (4.7)	0	0	0
Renal Failure	9 (1.7)	4 (0.8)	1 (0.4)	0	0	1 (9)
Sepsis	35 (6.6)	28 (5.5)	7 (2.7)	3 (2.5)	6 (4.8)	3 (27)

Source: M5, v 1.1, sec 5.3.5.1, p 75; M5, v 1.41, sec 5.3.5.1, p67; M5 , v 1.114, sec 5.3.5.3., p 57

The data in Table 23 generally support a pattern of RDS-related deaths occurring earlier than non-RDS deaths. To further examine the relationship of time and cause, all the patient deaths in KL4-IRDS-06 were reviewed for their causes and RDS-relatedness to see how they distributed by time. The time points used were Day 1, Day 2, Day 3, Days 4-7, Days 8-14, and >14 Days. The first three days were considered individually because they represented the most acute phase of RDS and also the period of dosing. Between 4 and 14 days, a single separation was arbitrarily made at 7 days. The results of this review are shown in Table 24, and then are presented again in Table 25 in different iterations of combined data in order to view overall patterns.

Table 24: Deaths in KL4-IRDS-06 by Cause and Time (Integrated Safety)

Cause	RDS-Related?	Day 1	Day 2	Day 3	Days 4-7	Days 8-14	>14 Days
Surfaxin (N=84 deaths)							
Air Leak	Yes		2	1	1	2	
	No						
IVH	Yes		2	1	4	1	
	No		2	1	2	4	
NEC	Yes						
	No				1	3	
PH	Yes		1	2	3		27
	No			6	2	1	
Renal Failure	Yes					1	
	No					6	
Sepsis	Yes						
	No	1	4	2	8	6	
Other	Yes	1	1	2			
	No			3	3	2	
Exosurf (N=86 deaths)							
Air Leak	Yes	1	2	2	3	3	36
	No				2		

Cause	RDS-Related?	Day 1	Day 2	Day 3	Days 4-7	Days 8-14	>14 Days
IVH	Yes	2	3	8	5	5	
	No		1	1	2	4	
NEC	Yes					1	
	No					1	
PH	Yes	1	2	4	6		
	No					1	
Renal Failure	Yes						
	No					1	
Sepsis	Yes						
	No		4	1	1	14	
Other	Yes	2	3			1	
	No		2	4	1	2	
Survanta (N=48 deaths)							
Air Leak	Yes	1		1		2	20
	No						
IVH	Yes	1	3	1	5	3	
	No				3	2	
NEC	Yes						
	No				2	2	
PH	Yes		1	2	3	1	
	No		1	2	1		
Renal Failure	Yes						
	No						
Sepsis	Yes						
	No		1			3	
Other	Yes	1	2				
	No	1		1		2	

Table 25: Combined Deaths in KL4-IRDS-06 by Cause and Time (Integrated Safety)

Cause	RDS-Related?	Day 1	Day 2	Day 3	Days 4-7	Days 8-14	>14 Days
Surfaxin (N=84 deaths)							
RDS-related: Air Leak, IVH, Pulmonary Hemorrhage	Yes		5	4	8	3	27
	No		2	7	5	6	
Non-RDS-related: NEC, Renal Failure, Sepsis	Yes					1	
	No	1	4	2	9	15	
Exosurf (N=86 deaths)							
RDS-related: Air Leak, IVH, Pulmonary Hemorrhage	Yes	4	6	12	13	6	36
	No		1	1	2	5	
Non-RDS-related: NEC, Renal Failure, Sepsis	Yes					1	
	No		3	1	1	15	

Cause	RDS-Related?	Day 1	Day 2	Day 3	Days 4-7	Days 8-14	>14 Days
Survanta (N=48 deaths)							
RDS-related: Air Leak, IVH, Pulmonary Hemorrhage	Yes	2	4	4	8	6	20
	No		1	2	4	2	
Non-RDS-related: NEC, Renal Failure, Sepsis	Yes						
	No		1		2	5	
Surfaxin (N=84 Deaths)							
		Days 1-3			**Days 4-14**		**>14 Days**
RDS-Related	Yes	9			11		27
	No	9			11		
Non-RDS-Related	Yes	0			1		
	No	7			24		
Exosurf (N=86 Deaths)							
RDS-Related	Yes	22			19		36
	No	2			7		
Non-RDS-Related	Yes	0			1		
	No	4			16		
Survanta (N=48 Deaths)							
RDS-Related	Yes	10			14		20
	No	3			6		
Non-RDS-Related	Yes	0			0		
	No	1			7		
Surfaxin (N=84 Deaths)[a]							
RDS-Related		22 (26.2)			22 (26.2)		27 (32.1)
Non-RDS-Related		10 (11.9)			30 (35.7)		
Total		32 (38.1)			52 (61.9)		
Exosurf (N=86 Deaths)[a]							
RDS-Related		29 (33.7)			27 (31.4)		36 (41.9)
Non-RDS-Related		10 (11.6)			20 (23.3)		
Total		39 (45.3)			47 (54.7)		
Survanta (N=48 Deaths)[a]							
RDS-Related		16 (33.3)			20 (41.7)		20 (41.7)
Non-RDS-Related		3 (6.3)			9 (18.8)		
Total		19 (39.6)			29 (60.5)		
[a]Includes the deaths from the "Other" category							

The data in the last segment of Table 25 are displayed using another method in Table 26. The grid in Table 26 allows easy viewing of treatment results side-by-side and easy calculation of proportions in the various groupings; i.e., related or non-related, early or late.

Table 26: Summary of Deaths in KL4-IRDS-06 (Integrated Safety)

	Early (1-3 days)				Late (4-14 days)				Total
	Surfaxin	Exosurf	Survanta	Subtotal	Surfaxin	Exosurf	Survanta	Subtotal	
Related	22	29	16	67	22	27	20	69	136
Non-									

	Early (1-3 days)				Late (4-14 days)				Total
	Surfaxin	Exosurf	Survanta	Subtotal	Surfaxin	Exosurf	Survanta	Subtotal	
Related	10	10	3	23	30	20	9	59	82
Total	32	39	19	90	52	47	29	128	218

The two preceding Tables show that there are proportionately fewer early (<4 days) deaths in the Surfaxin group than Exosurf group. The proportions in each time period, however, are different for the type of death. In the Surfaxin group, 22/32 (68.8%) early deaths are RDS-related compared to 29/39 (74.4%) in the Exosurf and 16/19 (84.2%) in the Survanta groups. Of the late deaths, the balance shifts more: 22/52 (42.3%) of Surfaxin deaths are RDS-related vs. 27/47 (57.4%) of Exosurf and 20/29 (69%) of Survanta deaths. For Exosurf and Survanta patients, more deaths are RDS-related whether in the early or late group, while the preponderance of RDS-related deaths in Surfaxin patients in the early period (22 vs. 10) reverses in the later period when more deaths are non-RDS-related (22 vs. 30).

7.1.2 Other Serious Adverse Events

Because of the characteristics of the drug, disease, and population described in section 7.1 above, and the overlap of some AEs and outcome measures, virtually every patient (99.7%) in this clinical program had at least one AE reported. Serious AEs were also frequently reported (≈70%). The Applicant summarized serious AEs that occurred in ≥10% of patients. This cut-off level was considered too high for this review, so as was done in the individual study reviews, the Applicant's summary was expanded by including serious events that occurred in ≥1% of patients and more commonly in Surfaxin patients. The Applicant combined Surfaxin patients from all studies in the Integrated Safety Summary, which is appropriate, and also combined all control groups, which is not. Each control group received a different drug and they cannot all be considered equivalent in their associated AEs. They are separated in the Table below. For completeness, each organ class is shown in the Table, even if it did not meet the frequency criterion for display.

The rates of most serious AEs in Surfaxin patients were within the range of the comparators; that is, higher than some and lower than some. However, the rates were higher in Surfaxin patients than in all comparators for six events: bradycardia NOS, oxygen saturation decreased, acidosis, pneumothorax, septic shock, and convulsions. The first three represent negative reactions to dose administration and are considered further in that section. Pneumothorax represents double-reporting, because it was also monitored as an efficacy measure. There was no significant increase in pneumothorax in the efficacy analyses, which is more reliable than spontaneous AE reporting. Sepsis was considered separately in depth in section 7.1.5.6.2 below. The unexpected finding in these results is the higher rate of neonatal convulsions. Standing alone, this result is difficult to interpret because there were no other findings that might explain or reflect that finding. There was no difference in the metabolic abnormalities that can cause convulsions, for example hypoglycemia; no detectable difference in perinatal asphyxia; and although infection was different, there was no evidence of a difference in nervous system infection. The

importance of the observation can best be determined from the long-term follow-up evaluations where neurologic sequelae would be detected.

Besides those increased events in Surfaxin patients, there are some pertinent negatives in Table 27. The rate of serious renal and urinary AEs in Surfaxin patients is similar to those in Exosurf and Survanta patients, and the rates of renal failure are similar in Surfaxin and Exosurf patients. In addition, the rates of all infection events are similar among the three surfactants, as are the rates of neonatal sepsis.

Table 27: Serious Adverse Events (Integrated Safety)

MedDRA Organ Class/ MedDRA Preferred Term	Surfaxin (N=701)	Exosurf (N=506)	Survanta (N=258)	Curosurf (N=124)
	N (%)			
ANY EVENT	483 (68.9)	395 (78.1)	194 (75.2)	79 (63.7)
Blood and lymphatic system	23 (3.3)	21 (4.2)	10 (3.9)	0
Cardiac disorders	41 (5.8)	31 (6.1)	10 (3.9)	2 (1.6)
Bradycardia NOS	13 (1.9)	8 (1.6)	2 (0.8)	0
Congenital, familial, genetic disorders	93 (13.3)	76 (15.0)	38 (14.7)	12 (9.7)
Patent ductus arteriosus	84 (12.0)	68 (13.4)	37 (14.3)	11 (8.9)
Endocrine disorders	2 (0.3)	1 (0.2)	0	0
Eye disorders	33 (4.7)	34 (6.7)	14 (5.4)	8 (6.5)
Gastrointestinal disorders	60 (8.6)	46 (9.1)	26 (10.1)	10 (8.1)
Necrotizing enterocolitis	37 (5.3)	32 (6.3)	23 (8.9)	6 (4.8)
General disorders	6 (0.9)	6 (1.2)	8 (3.1)	0
Hepato-biliary disorders	5 (0.7)	5 (1.0)	3 (1.2)	0
Infections and infestations	175 (25.0)	126 (24.9)	73 (28.3)	29 (23.4)
Pneumonia NOS	48 (6.8)	31 (6.1)	24 (9.3)	5 (4.0)
Sepsis neonatal	99 (14.1)	80 (15.8)	37 (14.3)	13 (10.5)
Septic shock	24 (3.4)	10 (2.0)	7 (2.7)	4 (3.2)
Injury and poisoning	4 (0.6)	0	1 (0.4)	0
Investigations	22 (3.1)	11 (2.2)	5 (1.9)	0
Oxygen saturation decreased	22 (3.1)	11 (2.2)	5 (1.9)	0
Metabolism and nutrition disorders	16 (2.3)	13 (2.6)	4 (1.6)	3 (2.4)
Acidosis NOS	7 (1.0)	2 (0.4)	1 (0.4)	0
Musculoskeletal, connective tissue, bone	1 (0.1)	0	1 (0.4)	0
Nervous system disorders	38 (5.4)	32 (6.3)	13 (5.0)	7 (5.6)
Convulsion neonatal	14 (2.0)	6 (1.2)	2 (0.8)	0
Hydrocephalus NOS	13 (1.9)	13 (2.6)	5 (1.9)	2 (1.6)
Pregnancy and perinatal	2 (0.3)	0	1 (0.4)	0
Renal and urinary	21 (3.0)	16 (3.2)	7 (2.7)	1 (0.8)
Renal failure neonatal	15 (2.1)	11 (2.2)	2 (0.8)	0
Respiratory, thoracic, mediastinal disorders	392 (55.9)	326 (64.4)	156 (60.5)	53 (42.7)
BPD	113 (16.1)	101 (20.0)	47 (18.2)	8 (6.5)
Neonatal hypoxia	9 (1.3)	12 (2.4)	3 (1.2)	2 (1.6)
Neonatal RDS	275 (39.2)	243 (48.0)	100 (38.8)	32 (25.8)
Pneumothorax NOS	47 (6.7)	32 (6.3)	13 (5.0)	2 (1.6)
Pulmonary hemorrhage	48 (6.8)	39 (7.7)	24 (9.3)	6 (4.8)
Pulmonary interstitial emphysema	31 (4.4)	33 (6.5)	10 (3.9)	4 (3.2)
Surgical and medical	1 (0.1)	2 (0.4)	0	1 (0.8)
Vascular disorders	117 (16.7)	97 (19.2)	51 (19.8)	14 (11.3)
IVH neonatal	102 (14.6)	82 (16.2)	44 (17.1)	9 (7.3)
Source: M5, v 1.89, sec 5.3.5.3, p 172ff				

7.1.3 Dropouts and Other Significant Adverse Events

There were no dropouts from any NRDS study because of AEs. There were discontinuations of some treatments because of negative reactions to dose administration and those are discussed in section 7.1.3.3 below.

7.1.3.1 Overall profile of dropouts

This section is not applicable because there were no dropouts.

7.1.3.2 Adverse events associated with dropouts

This section is not applicable because there were no dropouts.

7.1.3.3 Other significant adverse events

7.1.3.3.1 Concurrent diagnoses

This section discusses the rates of concurrent diagnoses, as they were prospectively monitored in the three studies KL4-IRDS-06, KL4-IRDS-02, and KL4-IRDS-05. In KL4-IRDS-01, they were collected only as spontaneously reported AEs and are consequently included in Table 27 above.

The Applicant considered these events to be measures of efficacy, so results of the analyses are presented in the Integrated Summary of Efficacy of the NDA. At the same time, a tabular summary of the events is located in the "Adverse Reactions" section of the proposed package insert where the events are referred to as "common complications of RDS and prematurity." Because they were considered as measures of efficacy, the Applicant did not pool results from Surfaxin patients across studies. This reviewer pooled the Surfaxin patients to provide a safety perspective and the results are shown in the Table below.

The incidences of the events in Table 28 are generally similar for Surfaxin, Exosurf, and Survanta. The rates in the patients who received Curosurf are frequently different, sometimes favorably so and sometimes not. It is possible that some of that variation could be due to the relatively smaller number of patients who received Curosurf. It is also possible it is due to expected clinical variation between different studies. A third possibility is that the different rates reflect different standards of care or diagnostic standards among the participating centers. Curosurf was used in KL4-IRDS-02, which included the U.S. and Canada and fewer Latin American and European centers than the other studies. Such differences were mentioned in section 6.1.3.3.1 above. Table 5 illustrated the differences in severe IVH in particular between studies in different locales. That difference is seen again in the Table below. It is not possible to prove beyond doubt that the differences reflect geographical differences, but the issue for IVH has been raised before.[5] In any event, it can reasonably be concluded that the observed differences are not related to Surfaxin specifically because the pattern of differences, when present, is between Curosurf and all others rather than between Surfaxin and others.

It is noteworthy that the rates of acquired sepsis are not different among Surfaxin, Exosurf, and Survanta.

Table 28: Concurrent Diagnoses (Integrated Safety)

		Surfaxin (N=657)	Exosurf (N=509)	Survanta (N=258)	Curosurf (N=124)
Diagnosis	**Stage/ Grade**	**N (%)**			
IVH	None	326 (49.8)	222 (43.6)	118 (45.7)	77 (62.1)
	Grade 1	74 (11.3)	86 (16.9)	30 (11.6)	20 (16.1)
	Grade 2	131 (20.0)	109 (21.4)	57 (22.1)	17 (13.7)
	Grade 3	68 (10.4)	44 (8.6)	26 (10.1)	5 (4.0)
	Grade 4	49 (7.5)	48 (9.4)	27 (10.5)	5 (4.0)
	Overall	322 (49.2)	287 (56.4)	140 (54.3)	47 (37.9)
NEC	None	552 (84.4)	424 (83.3)	210 (81.4)	105 (84.7)
	Stage I	62 (9.5)	43 (8.4)	13 (5.0)	8 (6.5)
	Stage IIa	13 (1.99)	15 (2.9)	13 (5.0)	4 (3.2)
	Stage IIb	3 (0.46)	5 (1.0)	6 (2.3)	2 (1.6)
	Stage IIIa	6 (0.91)	4 (0.8)	3 (1.2)	2 (1.6)
	Stage IIIb	21 (3.2)	18 (3.5)	13 (5.0)	3 (2.4)
	Overall	105 (16.1)	85 (16.7)	48 (18.6)	19 (15.3)
PVL	Yes	58 (8.9)	51 (10.0)	32 (12.4)	12 (9.7)
	No	599 (91.1)	458 (90.0)	226 (87.6)	112 (90.3)
Apnea	Yes	357 (54.3)	264 (51.9)	119 (46.1)	93 (75.0)
	No	300 (45.7)	245 (48.1)	139 (53.9)	31 (25.0)
PDA	Yes	246 (37.4)	177 (34.8)	95 (36.8)	54 (43.5)
	No	411 (62.6)	332 (65.2)	163 (63.2)	70 (56.5)
ROP	None	479 (72.9)	375 (73.3)	193 (74.8)	85 (68.5)
	Stage 1	75 (11.4)	55 (10.8)	27 (10.5)	17 (13.7)
	Stage 2	62 (9.4)	44 (8.6)	22 (8.5)	12 (9.7)
	Stage 3	40 (6.1)	32 (6.3)	16 (6.2)	9 (7.3)
	Stage 4	1 (0.15)	3 (0.6)	0	1 (0.8)
	Overall	178 (27.1)	134 (26.3)	65 (25.2)	39 (31.5)
Pulmonary hemorrhage	Yes	62 (9.4)	59 (11.6)	36 (14.0)	10 (8.1)
	No	595 (90.6)	450 (88.4)	222 (86.0)	114 (91.9)
Acquired sepsis	Yes	292 (44.4)	224 (44.0)	113(43.8)	64 (51.6)
	No	365 (55.6)	285 (56.0)	145 (56.2)	60 (48.4)
Source: M5, v 1.57, sec 5.3.5.3, pp 448-451					

7.1.3.3.2 Negative reactions to dose administration

The next Table displays the events associated with administration of the surfactants. The specific events were designated by protocol as the events of interest and were required to be reported on CRFs. The rates shown in the Table should therefore be more reliable than the rates reflected in the spontaneous AE reports. The Table includes the AE report rates for comparison.

Table 29: Negative Reactions to Dose Administration (Integrated Safety)

	Surfaxin	Exosurf	Survanta	Curosurf
	N (%)			
Dose 1	**N=654**	**N=506**	**N=257**	**N=124**
Interruption	44 (6.7)	18 (3.6)	13 (5.1)	1 (0.8)
Pallor	51 (7.8)	15 (3.0)	21 (8.2)	4 (3.2)
ETT reflux	130 (19.9)	111 (21.9)	48 (18.7)	27 (21.8)
ETT obstruction	47 (7.2)	10 (2.0)	8 (3.1)	1 (0.8)
AE	66 (13.0)	39 (9.5)	31 (14.5)	3 (3.8)
Dose 2	**N=260**	**N=209**	**N=86**	**N=32**

	Surfaxin	Exosurf	Survanta	Curosurf
	N (%)			
Interruption	27 (10.4)	4 (1.9)	5 (5.8)	1 (3.1)
Pallor	22 (8.5)	9 (4.3)	8 (9.3)	3 (9.4)
ETT reflux	43 (16.6)	7 (3.3)	10 (11.6)	3 (9.4)
ETT obstruction	20 (7.7)	0	4 (4.7)	0
AE	44 (21.2)	16 (9.9)	16 (21.3)	2 (8.3)
Dose 3	**N=135**	**N=143**	**N=46**	**N=4**
Interruption	15 (11.1)	10 (7.0)	6 (13.0)	0
Pallor	16 (11.9)	11 (7.7)	5 (10.9)	0
ETT reflux	32 (23.9)	18 (12.6)	5 (10.9)	1 (25.0)
ETT obstruction	11 (8.2)	5 (3.5)	6 (13.0)	0
AE	22 (20.8)	12 (11.4)	7 (17.1)	1 (25.0)
Dose 4	**N=70**	**N=101**	**N=27**	
Interruption	6 (8.6)	4 (4.0)	3 (11.1)	NA[a]
Pallor	10 (14.3)	2 (2.0)	3 (11.1)	
ETT reflux	13 (18.6)	7 (7.0)	4 (14.8)	
ETT obstruction	2 (2.9)	1 (1.0)	1 (3.7)	
AE	12 (21.4)	9 (11.5)	5 (20.0)	
Dose 5	**N=66**	**N=79**	**N=28**	
Interruption	4 (6.1)	10 (12.7)	3 (10.7)	NA
Pallor	8 (12.1)	9 (11.4)	1 (3.6)	
ETT reflux	13 (19.7)	18 (22.8)	0	
ETT obstruction	3 (4.5)	5 (6.3)	0	
AE	8 (14.0)	13 (21.0)	2 (8.7)	

[a]Only 3 doses were allowed in KL4-IRDS-02
Source: M5, v 1.88, sec 5.3.5.3, p 69

It is clear from the Table that the rates of negative dosing reactions were higher with Surfaxin than with the other surfactants. Further information provided by the Applicant follows.

Focusing on study KL4-IRDS-06, 358 (68.3%) Surfaxin patients experienced one of the negative reactions compared to 253 (50.0%) Exosurf and 143 (55.4%) Survanta patients. Differences were significant ($p<0.05$) for dose interruption, pallor, and ETT obstruction after doses 1 and 2.

Some patients had ETT obstructions with more than one dose: multiple events occurred in 9 Surfaxin neonates and 2 each Exosurf and Survanta patients. The total number of Surfaxin patients with an obstruction event was 44 (8.4%) vs. 19 (3.8%) Exosurf and 17 (6.6%) Survanta patients. Of the 44 Surfaxin patients with ETT obstruction, 11 (25.0%) were in the 600-800 g weight stratum, 15 (34.1%) in the 801-1000 g stratum, and 18 (40.9%) in the 1001-1250 g stratum. In the Exosurf patients, the distribution was 6/19 (31.6%) in stratum 1, 5/19 (26.3%) in stratum 2, and 8/10 (42.1%) in stratum 3. For Survanta patients: 5/17 (29.4%) in stratum 1, 7/17 (41.2%) in stratum 2, and 5/17 (29.4%) in stratum 3. The mortality rates at 14 days for the patients who had ETT obstruction were 7/44 (16%) Surfaxin, 3/19 (15.8%) Exosurf, and 5/17 (29.4%) Survanta.

ETT obstruction resulted in interruption of the dose in 17 (39%) Surfaxin patients vs. 9 (47%) Exosurf, and 4 (23.5%) Survanta. Considering all ETT obstruction events (not patients), the proportion that resulted in dose interruption was highest with Exosurf (48%), followed by Surfaxin (40%) and Survanta (26%). Outcomes for patients who had to have study drug interrupted were:

Surfaxin: 11/17 IVH, 9/17 BPD, 3/17 air leak, 3/17 deaths
Exosurf: 8/9 IVH, 6/9 BPD, 3/9 air leak, 0/9 deaths
Survanta: 1/4 IVH, 3/4 BPD, 3/4 deaths

The higher frequency of negative reactions to dose administration did not appear to compromise the patients' eventual outcomes. The Applicant did not address possible causes for the higher frequency. The most obvious likelihood is that the larger dose volume per kg of weight of Surfaxin is responsible.

(b) (4)

7.1.4 Other Search Strategies

Discovery Laboratories is conducting clinical programs in MAS and ARDS, as well as in NRDS. The application includes summary safety reports from those other programs in the Integrated Summary of Safety. Review of those reports yielded some notable findings, described in this section, but determining the significance of those findings requires caution.

The patient populations and dosing regimens in the MAS and ARDS studies were very different from the neonatal studies. Although MAS patients are neonates, they are full-term, developmentally more mature, and not liable to some of the conditions that are prominent and have such high morbidity in premature neonates; for example, IVH, NEC, and pulmonary hemorrhage. Moreover, the pathophysiology of MAS is completely unrelated to RDS. The same is true for ARDS where surfactant deficiency arises from a completely different mechanism. Finally, in both MAS and ARDS studies Surfaxin was administered in much larger doses (up to 16 mL/kg) and was delivered using a lavage technique. In ARDS studies, the total dose was also administered via bronchoscope and sometimes divided into as many as 16 different aliquots delivered to each lung segment. All these differences obligate due caution in carrying over results into an NRDS indication. For this review, a standard was applied that sought evidence of consistency, replication, and biologic plausibility in results before they might be considered drug-related and/or applicable to NRDS use of the drug.

Descriptions of the MAS and ARDS studies are included in Table 3. The following points bear importantly upon this safety review:

- The studies are mostly Phase 1 and 2
- The studies are open-label; some are randomized, most are not. Some studies were in two stages with one stage uncontrolled and one stage randomized
- When a control group was used, the control therapy was "Standard of Care" (SOC), essentially allowing whatever clinical approach the investigator chose.

These points are critical to interpreting results of the safety review, because the treated patients were not necessarily equivalent at baseline to control patients.

The safety summaries provided by the Applicant consisted solely of AE reports as of the cut-off date (some studies are still in progress), and listings of deaths in the ARDS studies. There were

no deaths in the MAS studies. Minimal information other than the listings was provided for the ARDS patients who died. Prominence was given in the safety summaries to AE severity according to investigators and relationship to drug as determined by investigators. Serious AEs were not provided in the Integrated Summary of Safety; they had to be collated for this review from each individual study report.

The following findings were notable in the MAS studies. It is notable that the two types of events, infection and renal, were those also of interest for NRDS. Nothing else in the summaries generated any safety concerns for these patients.

Table 30: Selected Safety Outcomes in MAS Studies (Integrated Safety)

	KL4-MAS-01[a]		KL4-MAS-03[b]		Overall	
	Surfaxin N=15	SOC N=7	Surfaxin N=38	SOC N=31	Surfaxin N=53	SOC N=38
	N (%)					
Baseline Factors	No Differences		Mean OI 14.37	Mean OI 16.31	No Differences	
Any AE	13 (86.7)	7 (100)	36 (94.7)	26 (83.9)	49 (92.5)	33 (86.8)
Infection/Infestation	4 (26.7)	1 (14.3)	21 (55.3)	11 (35.5)	25 (47.2)	12 (31.6)
Sepsis	0	0	10 (26.3)	3 (9.7)	10 (18.9)	3 (7.9)
Renal/urinary	2 (13.3)	1 (14.3)	9 (23.7)	3 (9.7)	11 (20.8)	4 (10.5)
Oliguria	0	0	4 (10.5)	2 (6.5)	4 (7.5)	2 (5.3)
Urinary tract infection	2 (13.3)	0	0	0	2 (3.8)	0
Deaths	0	0	0	0	0	0

SOC=Standard of care; OI=oxygenation index [(FiO_2) x MAP]/PaO_2
[a]Randomized 2 Surfaxin: 1 SOC
[b]Randomized 1:1

Interpretation of the safety data from the ARDS studies is more difficult. There were four studies but only two of them were randomized. Several different dosing regimens of Surfaxin were used, so there was no consistency of exposure and the Applicant did not present data according to exposure. ARDS is a disease that often represents a final common pathway from many different causes, and consequently patients with that single diagnosis are quite different in their underlying diseases and conditions. The Applicant did not distinguish among these factors in presenting the data. All these reasons, in addition to a radically different patient population from the NRDS studies, obligate caution in interpreting the data. With that in mind, this safety review focused on the two randomized studies. Among all AEs, there were more in Surfaxin patients for virtually every MedDRA system organ class. Because none of the studies was blinded, more attention was placed on the serious AEs and deaths.

Remaining mindful of the cautionary points in interpreting these results, the differences in serious AEs and deaths in KL4-ARDS-04 stand out. There were several pneumothoraces and more reports of hypoxia in the Surfaxin patients. These are almost certainly related to the lavage surfactant administration procedure. Several AEs were infection-related, and accentuating that difference are the three deaths in the Surfaxin group caused by sepsis or septic shock compared

to none in the control group. This finding is one of those that must be approached cautiously - there were more patients in the Surfaxin group whose etiology of ARDS was sepsis (44.4% vs. 30%), but there were more due to pneumonia in the control group (48.9% vs. 60%). Nevertheless, what makes the finding notable is the higher rate of sepsis-related deaths in Surfaxin patients in the NRDS studies, and the more frequent sepsis-related AEs in the MAS studies; i.e., consistency. The other event noted in the neonatal studies, renal failure, was reported in two ARDS patients – such a small difference is difficult to interpret.

Table 31: Selected Safety Outcomes in ARDS Studies (Integrated Safety)

	KL4-ARDS-03		KL4-ARDS-04	
	Surfaxin N=9	**SOC N=5**	**Surfaxin N=45**	**SOC N=11**
Etiology of ARDS				
Aspiration	3 (33.3)	3 (60.0)	9 (20.0)	3 (30.0)
Pneumonia	7 (77.8)	4 (80.0)	22 (48.9)	6 (60.0)
Toxic inhalation	1 (11.1)	0	0	0
Lung contusion	1 (11.1)	2 (40.0)	3 (6.7)	3 (30.0)
Chest trauma	1 (11.1)	2 (40.0)	4 (8.9)	3 (30.0)
Blood transfusion	0	1 (20.0)	6 (13.3)	0
Major surgery	0	1 (20.0)	9 (20.0)	1 (10.0)
Multiple trauma	0	0	5 (11.1)	2 (20.0)
Pancreatitis	0	0	3 (6.7)	0
Sepsis	0	1 (20.0)	20 (44.4)	3 (30.0)
Other	2 (22.2)	0	6 (13.3)	0
Serious AE's	5: 4 pneumothorax 1 septic shock	0	41: 3 Multi-organ failure 4 Sepsis NOS 1 Septic shock 1 Empyema NOS 1 Lung abscess 1 Necrotizing enterocolitis 12 Pneumothorax 1 Ischemic stroke 1 Metabolic encephalopathy 1 ARDS 2 Pulmonary embolism 6 Hypoxia 1 Pleural effusion 1 Pulmonary edema 1 Respiratory failure 1 Bradycardia NOS 1 Hypotension NOS 2 Renal failure NOS	2 1 Respiratory failure 1 Venous thrombosis
Deaths	0	0	10 2 Hypoxia 1 Lung abscess 3 Multi-organ failure 1 Respiratory failure 3 Sepsis/septic shock	1 1 Respiratory failure

SOC=Standard of Care
Source: M5, v 1.113, sec 5.3.5.3, p 8627ff; M5 v 1.135, sec 5.3.5.4, p62; M5, v 1.122, sec 5.3.5.3, p 49

7.1.5 Common Adverse Events

As noted before, the proposed package insert for Surfaxin, following the precedent of other surfactant products, contains (b) (4) negative reactions to dose administration. As a result, this section of the review is done outside the context of summarizing the findings for product labeling.

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were reported spontaneously by investigators during the course of the studies. The protocol for study KL4-IRDS-06 is typical of the others and gives this instruction: "All treatment emergent adverse experiences are to be assessed in all patients throughout the period from enrollment through study termination and documented as events occur. Each treatment-emergent AE should be reported spontaneously or in response to general, non-directed discussion with the attending nurse or physician." *[M5, v 1.2, sec 5.3.5.1, p 32]*

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The Applicant used the MedDRA dictionary for classifying AEs and applied it throughout the program. Most study centers in the program were in Europe and Latin America. For the most part, investigators recorded AEs on CRFs in English but there were rare entries in the investigator's native language. The Applicant provided no translation or other information about how those entries were translated and classified. They were rare enough, however, that they are unlikely to change the safety profile of the drug in any case.

Preferred terms were examined for this review and spot-checked against CRFs, particularly for patients who died. In general, the Applicant handled the CRF language appropriately for the unique clinical circumstances of the premature neonate. Some difficulties are inevitable because of these circumstances. For example, as previously noted, several "adverse events" are physiologic in this population, the best example probably being hyperbilirubinemia. Another example, the most common reported AE in this program, was neonatal anemia, which is almost universally present in premature neonates and exacerbated by iatrogenic blood monitoring. From review of the CRFs, it appears that the Applicant classified reports equitably among the treatment groups.

The need to collect AEs and also specifically monitor certain types of events (concurrent diagnoses and negative reactions to dose administration) led to frequent double-reporting. For example, the more frequent reports of bradycardia, decreased oxygen saturation, and acidosis noted earlier among Surfaxin patients (section 7.1.2) upon examination are found to reflect negative reactions to dose administration, which were also reported separately in the studies.

7.1.5.3 Incidence of common adverse events

The Applicant's reporting and display of AEs was consistent within each study report and in the Integrated Summary of Safety. The primary presentation of AE results used by the Applicant was events occurring in ≥10% of patients. There were no summary tabulations at rates below that level. To find and compare rates at lower levels, the reviewer was required to examine the data listings. There were also separate tabulations of events by investigator-assigned severity (mild, moderate, severe) and investigator-determined relationship to drug. For the most part, those presentations of events were not reviewed in depth. Finally, serious AEs were presented separately also using the 10% cut-off.

In the Integrated Summary of Safety, the Applicant combined Surfaxin patients from all studies, which is appropriate, and also combined all control groups, which is not. Each control group received a different drug and they cannot all be considered equivalent in their associated AEs. For this review, the AEs in Surfaxin patients were examined against each control comparator drug.

7.1.5.4 Common adverse event tables

(b) (4)

7.1.5.5 Identifying common and drug-related adverse events

Several observations of increased rates of two types of events in Surfaxin-treated neonatal patients raised concern about their being drug-related. The concern was reinforced by the events appearing to also occur more frequently in the MAS and ARDS studies and by possible causative roles in some deaths. The events are those subsumed under the MedDRA system organ classes "Infection and Infestation" and "Renal and Urinary Systems." The observations were noted in other sections of this review and are brought together in the summary Table below. Because the issue is drug-relatedness, only the controlled studies are included in the Table.

The data in the Table reflect *consistency* among all the studies for these events, but not always *reproducibility*. That is, when there is a treatment difference it almost always shows more events in the Surfaxin patients (the notable exceptions occur in KL4-IRDS-02 where Curosurf patients tended to have more infections); but differences do not occur in every study. And differences are sometimes for certain specific events (for example, fungal infection) rather than for all infection events. Nevertheless, there appears to be a pattern of more renal and infection AEs and/or deaths associated with Surfaxin. Additional discussion and interpretation is in the next section.

Table 33: Infection and Renal Events (Integrated Safety)

	NRDS		**MAS**		**ARDS**	
	KL4-IRDS-06	**KL4-IRDS-02**	**KL4-MAS-01**	**KL4-MAS-03**	**KL4-ARDS-03**	**KL4-ARDS-04**
Renal Cause of Death	Surfaxin 7 (1.3) Exosurf 1 (0.2) Survanta 0	Surfaxin 0 Curosurf 0	0	0	0	0
Infection-related Cause of Death	Surfaxin 23 (4.4) Exosurf 18 (3.5) Survanta 4 (1.7)	Surfaxin 2 (1.7) Curosurf 4 (3.2)	0	0	0	Surfaxin 4 (8.9) SOC 0
Acquired Sepsis Concurrent Diagnosis	Surfaxin 232 (44.0) Exosurf 224 (44.0) Survanta 113 (43.8)	Surfaxin 54 (45.4) Curosurf 64 (51.6)	NA	NA	NA	NA
Renal Adverse Event	Surfaxin 75 (14.3) Exosurf 70 (13.8) Survanta (14.7)	Surfaxin 15 (12.6) Curosurf 21 (16.9)	Surfaxin 2 (13.3) SOC 1 (14.3)	Surfaxin 9 (23.7) SOC 3 (9.7)	Surfaxin 2 (22.2) SOC 0	Surfaxin 11 (24.4) SOC 1 (9.1) **Renal failure NOS:** Surfaxin 7 (15.6) SOC 0
Renal Serious Adverse Event	Surfaxin 19 (3.6) Exosurf 16 (3.2)	Surfaxin 0 Curosurf 1 (0.8)	Surfaxin 2 (13.3) SOC 1 (14.3)	N.A.	0	Surfaxin 2 SOC 0

	NRDS		MAS		ARDS	
	7 (2.7)					
Infection Adverse Event	Surfaxin 358 (68.1) Exosurf 346 (68.4) Survanta 181 (70.2)	Surfaxin 87 (73.1) Curosurf 98 (79.0)	Surfaxin 4 (26.7) SOC 1 (14.3)	Surfaxin 21 (55.3) SOC 11 (35.5)	Surfaxin 4 (44.4) SOC 3 (60.0)	Surfaxin 25 (55.6) SOC 3 (27.3)
	Fungal infection NOS: Surfaxin 11 (2.1) Exosurf 3 (0.6) Survanta 2 (0.8)			**Sepsis:** Surfaxin 10 (26.3) SOC 3 (9.7)		**Sepsis:** Surfaxin 7 (15.6) SOC 0
Infection Serious Adverse Event	Surfaxin 151 (28.8) Exosurf 126 (24.9) Survanta 73 (28.3)	Surfaxin 19 (16.0) Curosurf 29 (23.4)	Surfaxin 4 (26.7) SOC 1 (14.3)	N.A.	Surfaxin 1 SOC 0	Surfaxin 7 (15.6) SOC 0
	Septic shock: Surfaxin 18 (3.4) Exosurf 10 (2.0) Survanta 7 (2.7)					

SOC=Standard of Care

7.1.5.6 Additional analyses and explorations

7.1.5.6.1 Renal

The observations of renal events in the preceding section are perplexing. There is no immediately obvious reason why surfactant administered locally to the lungs should affect renal function. Preclinical studies indicate that the components of surfactant mostly stay within the lung and very little is systemically absorbed. An indirect effect would therefore need to be postulated. For example, in the discussion of neonatal deaths due to renal failure, renal failure was noted as a terminal event following insults that compromised cardiac output or renal blood flow (section 7.1.1.2.1). Although no other study had similar results, KL4-ARDS-04, which had a relatively high death rate, is the only study with more renal AEs in treated patients. It is possible that the cases of renal failure reflect populations of very ill patients with high mortality risk, and the study-to-study inconsistencies reflect the vagaries of reporting and attempts to adjudicate cause of death.

Because adverse renal findings are not replicated among studies and because there is no substantiation of the renal-related deaths in KL4-IRDS-06 by AE reports, this review finds no compelling evidence overall for drug-related adverse renal effects.

7.1.5.6.2 Infection

Infection might be a different matter. In the first place, there are at least theoretical bases for drug-relatedness. Endogenous surfactant, especially the constituent proteins, plays a role in local host defense,[7] so different surfactants that differ primarily in protein composition might have different effects. Attempts to demonstrate differences, however, have generated equivocal results.[8] In addition, the possibility of product contamination must be considered.

A second difference from renal events is that the differences in rates of infection-related AEs shown in Table 33 are more prevalent across all studies than renal events were. There are also higher rates of sepsis and septic shock events. There was not the same consistency for renal events. Except for KL4-ARDS-04 among MAS and ARDS studies, there did not appear to be more infection-related deaths in Surfaxin patients; and the higher death rate in that study could be due to more patients with sepsis as the ARDS-precipitating event. More controlled data would be needed to sort that out. It is possible that infections were more severe in Surfaxin patients when they occurred, leading to sepsis and septic shock but falling short of leading directly to death. The reports of septic shock in KL4-IRDS-06 and infection-related deaths in KL4-ARDS-04 were examined more closely.

Of the 35 patients with septic shock in KL4-IRDS-06, 24 of them died. The deaths were almost all ascribed to sepsis, so these patients were already considered in the infection-related death discussion, and this finding can be understood as simply another expression of the infection-related deaths. Interestingly, however, of the 11 patients with septic shock who did not die, 8 were treated with Surfaxin. This suggests another infection-related event more common in Surfaxin patients. In other words, although there is large overlap of the sets of septic shock AE and sepsis-death patients, they are not completely the same. There is a group of Surfaxin patients with more septic shock AEs who were not captured by the other groupings of data.

Four patients had infection-related deaths in KL4-ARDS-04:

- Patient 06022, a 58 year-old female, had pneumonia as the ARDS etiology. Several AEs were reported including hemoptysis, necrotizing enterocolitis, pneumothorax, diarrhea, renal failure, and sepsis. Death was due to sepsis.
- Patient 08021, a 76-year old male, had pneumonia and pancreatitis as ARDS etiologies. Lung abscess was reported 6 days after his first dose of Surfaxin and lung abscess was the cause of death.
- Patient 09024, a 50 year-old female, had ARDS as a result of major surgery and sepsis. Pneumothorax, pleural effusion, increased creatinine, and sepsis were reported and she died of septic shock.
- Patient 10001, a 45 year-old male, had ARDS because of pneumonia and sepsis. He died of sepsis.

All four patients had pneumonia and/or sepsis before they entered the study, so their deaths from sepsis cannot be related to drug without further information. There were also patients in the

control group with precedent sepsis and pneumonia who did not die, but information needed to compare the severity of their illnesses or other factors is not available.

The patients in KL4-IRDS-06 with fungal infections were examined. Some clustering of infection-related deaths was previously noted for KL4-IRDS-06 (section 7.1.1.2.2). The cases of fungal infection appear to be clustered as well with more than half of them coming from centers in Poland, including multiple cases from single centers. Almost all the reports are of skin lesions or oral candidiasis. Based on this information, not much significance can be attached to these reports.

Finally, evaluation of possible drug-related infections must consider product contamination. Only three batches of Surfaxin were used in KL4-IRDS-06. One of the batches was given to only 16 patients. The rates of acquired sepsis in patients who received the other two batches were 46.0% and 42.4%. These clinical batches were produced at a former manufacturing site no longer used and not proposed for commercial manufacturing. The site of origin of these clinical batches was discontinued because of frequent GMP violations (refer to section 3.1).

The absence of rigorous, objective diagnostic criteria for sepsis makes it difficult to conclusively attribute cause to the drug. On the other hand, a slightly higher number of Surfaxin patients who died of sepsis in KL4-IRDS-06 (section 7.1.1.2.2), along with these AE reports suggest a consistency about the possibility of increased risk of infection. The Applicant will be encouraged to incorporate rigorous monitoring into its Risk Management and postmarketing surveillance plan.

7.1.6 Less Common Adverse Events

The proposed package insert contains no information about AEs, uncommon or otherwise.

It has been noted that AEs were reported for nearly every patient in this program. The frequency of uncommon events reflects that same trend. There were 330 AEs reported at ≤1% frequency in the 701 patients in the Surfaxin safety data base and 361 events in the 888 control patients. The vast majority of those uncommon events occurred 1 or 2 times. Such a large number of isolated events cannot be realistically attributed to a therapy or included in product labeling, but an attempt was made to determine if any of those events could be discriminated somehow. Events that occurred at least 0.5% more commonly in Surfaxin patients was considered a reasonable level of discrimination to search for possible treatment differences in uncommon events. Using that criterion, nine events were identified:

Table 34: Uncommon Adverse Events (Integrated Safety)

Event	Surfaxin N (%)	Control N (%)
Pericardial effusion	4 (0.6)	0
Gastrointestinal motility disorder	7 (1.0)	4 (0.5)
Malnutrition NOS	5 (0.7)	2 (0.2)
Jaundice neonatal	7 (1.0)	0
Neonatal anuria	5 (0.7)	2 (0.2)
Hydrocele	6 (0.9)	3 (0.3)

Event	Surfaxin N (%)	Control N (%)
Bronchospasm NOS	6 (0.9)	3 (0.3)
Skin contusion	7 (1.0)	1 (0.1)
Dermatitis exfoliative NOS	4 (0.6)	1 (0.1)
Source: M5, v 1.89, sec 5.3.5.3, p211		

Without additional information, finding a relationship between surfactant and gastrointestinal motility is difficult. The difference in pericardial effusion can reasonably be attributed to reporting differences considering the absence of any signal in the occurrence of pneumopericardium. Malnutrition is an extremely unusual diagnosis in a neonate. Upon examination, all the reports are from the same center and probably reflect an investigator's area of interest. Similarly, all the reports of "jaundice" were from the single-center uncontrolled study and probably reflect the investigator's preferred terminology for hyperbilirubinemia. Any possible true difference in hydrocele would have little clinical significance. It is difficult to interpret the differences in skin contusion and exfoliative dermatitis without more information, but the reports come from one center where there may have been a unique circumstance.
Two of the events have possible clinical significance. More reports of neonatal anuria in Surfaxin patients are consistent with the other renal system findings discussed elsewhere in this review. Bronchospasm could have importance for a drug applied to the lungs. It is of interest that the three control reports were from each of the three different surfactant controls; i.e., single reports for each of the other surfactants vs. the 6 Surfaxin cases. This could represent a true difference and warrants further post-marketing monitoring.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing for safety purposes was not done in any studies in this program. The only laboratory data required were arterial blood gases which were used as efficacy measures. Therefore, the only laboratory data available for safety review were those spontaneously reported as AEs. Contrasting treatment based on those results is difficult, however, because of the spontaneous nature of the reports and because there were no standards for normal or abnormal values. For those reasons, the review was limited to serious AEs in hopes of uncovering any differences that might have clinical importance. The results are shown below. There appears to be no increase in laboratory abnormalities associated with Surfaxin.

Table 35: Laboratory Abnormalities Reported as Adverse Events (Integrated Safety)

Laboratory Test	Surfaxin (N=701)	Exosurf (N=506)	Survanta (N=258)	Curosurf (N=124)
	N (%)			
Anemia	11 (1.6)	11 (2.2)	4 (1.6)	0
Eosinophilia	1 (0.1)	0	0	0
Leukopenia NOS	1 (0.1)	1 (0.2)	0	0
Leukopenia neonatal	1 (0.1)	0	0	0
Pancytopenia	0	1 (0.2)	0	0
Thrombocytopenia	3 (0.4)	2 (0.4)	1 (0.4)	0
Hyperglycemia NOS	1 (0.1)	1 (0.2)	1 (0.4)	0

Laboratory Test	Surfaxin (N=701)	Exosurf (N=506)	Survanta (N=258)	Curosurf (N=124)
	N (%)			
Hyperkalemia	2 (0.3)	5 (1.0)	0	1 (0.8)
Hypoglycemia neonatal	1 (0.1)	0	0	0
Hyponatremia	0	0	0	1 (0.8)
Metabolic acidosis NOS	4 (0.6)	5 (1.0)	1 (0.4)	1 (0.8)
Acidosis NOS	7 (1.0)	2 (0.4)	1 (0.4)	0
Source: M5, v 1.89, sec 5.3.5.3, p 172ff				

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

See section 7.1.7.1 above.

7.1.7.3 Standard analyses and explorations of laboratory data

See section 7.1.7.1 above.

7.1.7.4 Additional analyses and explorations

See section 7.1.7.1 above.

7.1.7.5 Special assessments

See section 7.1.7.1 above.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were recorded at 2, 6, 12, 24, 36, 48, and 72 hours after the first surfactant dose in each of the studies. The vital signs collected were systolic and diastolic blood pressures, mean arterial blood pressure, heart rate, spontaneous respiratory rate, and oxygen saturation by pulse oximetry. These infrequent time point recordings carry little clinical meaning in patients who are critically ill with many on mechanical ventilation. The Applicant presents mean, median, and range values for these vital signs. There are no meaningful differences among the treatments. With the limited data set available, no further investigation or analysis is warranted.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

See section 7.1.8.1 above.

7.1.8.3 Standard analyses and explorations of vital signs data

See section 7.1.8.1 above.

7.1.8.4 Additional analyses and explorations

See section 7.1.8.1 above.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were not performed in this program, which was appropriate to the drug, patient population, and intended indication.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

See section 7.1.9.1 above.

7.1.9.3 Standard analyses and explorations of ECG data

See section 7.1.9.1 above.

7.1.9.4 Additional analyses and explorations

See section 7.1.9.1 above.

7.1.10 Immunogenicity

The active ingredient of Surfaxin is sinapultide, a synthetic 21-amino acid residue peptide. In a letter to Discovery Laboratories dated September 26, 2001, in reference to the protocol for KL4-IRDS-06, the Division wrote, "No assessment of anti-surfactant antibodies is included in this protocol…the potential for Surfaxin immunogenicity should be addressed in a subset of infants." *[M1, v 1.1, sec 1.5, p 46]* This comment was made, however, in the context of a statement in the Investigational Drug Brochure claiming less antigenicity of Surfaxin compared to animal-derived surfactants.

The Applicant performed pre-clinical immunotoxicity studies in guinea pigs, which showed no evidence of immune response. Despite the letter from the Division, no clinical immunogenicity assessments were performed, nor does the Applicant address the issue in the clinical sections of the NDA. The rationale is presumably based in the Applicant's summary of the guinea pig study: "It is unlikely that a totally water-insoluble peptide such as KL4, or fragment of KL4 would induce an immune response since presentation to the T-cell and B-cell normally required (sic) that the peptide be in an aqueous medium. KL4 exists in a lipid environment, in the acyl side chains of a phospholipid layer." *[M2, v 1.1, sec 2.6, p 36]*

Notwithstanding the Division's earlier comment, the Applicant's rationale for not performing clinical assessments has merit. In addition to the reasons given, premature neonates are immunologically immature and mount very poor immune responses; hence the rationale for delaying many immunizations until children reach 6-8 weeks of age. Furthermore, the Applicant has not made any claims for decreased immunogenicity of Surfaxin. The proposed package insert contains the factu (b) (4)

[M1, v 1.1, sec 1.7, p 2]

The lack of immunogenicity assessments is acceptable for the NRDS indication, but the package insert should contain a statement in the clinical section that no immunogenicity assessments were performed. The issue will have to be re-addressed for an adult indication, because the adult immune system is quite different and adult patients will require larger doses.

7.1.11 Human Carcinogenicity

Carcinogenicity studies are not appropriate for this product and were not performed.

7.1.12 Special Safety Studies

No special safety studies were required and none were performed.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

This section is not applicable because there is no abuse potential or possible withdrawal phenomenon.

7.1.14 Human Reproduction and Pregnancy Data

Human reproduction and pregnancy studies are not applicable to the NRDS indication.

7.1.15 Assessment of Effect on Growth

Appropriately, no assessment of the effect on growth per se was performed, but growth was one of the variables examined in the 6- and 12-month follow-up studies, discussed in section 7.2.9 below.

7.1.16 Overdose Experience

The Applicant did not address whether any inadvertent overdoses occurred in the course of the studies. It seems a likely possibility, but a search of the data listings for KL4-IRDS-06 revealed no record of too many doses administered. The volume of surfactant delivered was not recorded on CRFs. The proposed package insert states, "There have been no reports of overdose following the administration of Surfaxin. If the infant's respiration, ventilation, or oxygenation

is clearly affected after an accidental overdose, as much of the suspension as possible should be aspirated, and the infant should be managed with supportive treatment." *[M1, v 1.1, sec 1.7, p 9]*

7.1.17 Postmarketing Experience

This section is not applicable because Surfaxin is not marketed anywhere in the world.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The primary source of clinical data for the safety review was the studies conducted by the Applicant and included in this application. Unlike the efficacy review, which was restricted to three NRDS studies, the safety review encompassed all studies, including those for MAS and ARDS. Additional clinical information that could not be located in the NDA was obtained from the Applicant in response to Information Requests made during the review process. Those requests and the responses are briefly described in Table 2.

Per patient data were available from four sources: 1) electronic data sets (CRTs) filed in the Electronic Document Room (EDR); 2) case report forms in pdf format in the EDR for NRDS patients who died; 3) hard copy patient data listings included in the NDA; and 4) hard copy patient narratives in the NDA for NRDS patients who died. No CRFs were submitted for ARDS patients who died.

Data developed and submitted under investigator-sponsored INDs using Surfaxin were not used for this review. Two other sources of data were used sparingly for specific purposes: literature reports and data from the INDs and NDAs of the approved surfactants.

Literature reports were used insofar as they were referenced by the Applicant in the designs of their studies,[1,2] or to elucidate or guide the review.[3-12] The reports referenced by the Applicant were reviewed and commented upon as appropriate in the reviews of the studies. Photocopies of some literature reports cited by the Applicant were included in the application.

IND and NDA data, especially the approved labeling, were used as regulatory references. The package inserts for the comparator surfactants in this program - Exosurf, Survanta, and Curosurf - were used thoroughly and frequently.

7.2.1.2 Demographics

Demographic data for the NRDS populations are shown in Table 7 and Table 8, and the relevant demographic information for the safety reviews of MAS and ARDS patients are shown in Table 30 and Table 31.

7.2.1.3 Extent of exposure (dose/duration)

The data in Table 3 are reconfigured in the next two Tables to display dose exposure information more precisely. NRDS and MAS/ARDS studies are separated in the Tables because they were so different in doses and dosing procedures.

Study KL4-IRDS-01 is included in Table 36 to provide a complete picture of dose exposure even though it was a rescue study. The dosing scheme used in the NRDS studies was the same as for other surfactants; i.e., repeat doses were given as needed according to continuing respiratory distress. By this scheme, patients could receive from 1 to four doses. The doses could be given as frequently as every 6 hours. This strategy makes it nearly impossible to draw dose-response conclusions for either efficacy or safety. Because dosing is not fixed, more doses could reflect either a less effective surfactant or a sicker patient or both. And the rapid succession of doses does not provide time to discriminate the relationship of a single dose to an event. Like the other surfactant Sponsors, Discovery did not attempt to draw dose-response conclusions, and justifiably so.

Table 37 illustrates how radically different dosing was for MAS and ARDS patients, using bronchoscopic lavage instead of instillation, and lavaging each of 19 lung segments in the case of ARDS. Multiple doses were tried in the ARDS studies. The situation is complicated further because different concentrations of Surfaxin were used (2.5 mg/mL and 10 mg/mL) making analogy to NRDS doses difficult. Doses are expressed in the Table as mg/kg to find some common ground, although the volume of administration may be more important than the amount of phospholipids administered. In this NDA, where the ARDS studies occupy a secondary place, no explanation or rationale is given by Discovery for these varying approaches to dosing.

Table 36: Dosing Exposure, NRDS Studies (Integrated Safety)

	KL4-IRDS-06			KL4-IRDS-02[a]		KL4-IRDS-05	KL4-IRDS-01
	Surfaxin N=527	Exosurf N=509	Survanta N=258	Surfaxin N=124	Curosurf N=128	Surfaxin N=11	Surfaxin N=47
				N (%)			
175 mg/kg/dose							
0 Dose	3 (0.6)	3 (0.6)	0	5 (4.0)	4 (3.1)	-	
1 Dose	291 (55.2)	268 (52.7)	161 (62.4)	80 (64.5)	92 (71.9)	9 (81.8)	
2 Doses	108 (20.5)	91 (17.9)	49 (19.0)	23 (18.5)	28 (21.9)	-	N.A.
3 Doses	51 (9.7)	55 (10.8)	24 (9.3)	16 (12.0)	4 (3.1)	-	
4 Doses	36 (6.8)	37 (7.3)	7 (2.7)	N.A.	N.A.	2 (18.2)	
5 Doses	38 (7.2)	55 (10.8)	17 (6.6)	N.A.	N.A.	-	
133 mg/kg/dose							
1 Dose				N.A.			7 (14.9)
2 Doses							1 (2.1)
200 mg/kg/dose							
1 Dose				N.A.			27 (57.4)

KL4-IRDS-06	KL4-IRDS-02[a]	KL4-IRDS-05	KL4-IRDS-01
2 Doses			12 (25.5)

[a]Only three doses allowed
Source: M5, v 1.56, sec 5.3.5.3, p 123; M5, v 1.133, sec 5.3.5.3, p 149

Table 37: Dosing Exposure, MAS and ARDS Studies (Integrated Safety)

Study and Dosing Regimen	Surfaxin	Standard of Care Control
KL4-MAS-01		
40 mg/kg (16 ml/kg) by lavage x 3 q 15-60 mins	15	7
KL4-IRDS-MAS-03		
40 mg/kg (16 mL/kg) by lavage x 2 q 15-60 mins	30	25
KL4-ARDS-01		
50 mg/kg ETT instillation	1	1
KL4-ARDS-02		
2- 30 mL (75 mg) aliquots in 19 lung segments	3	N.A.
3- 30 mL (75 mg) aliquots in 19 lung segments	4	
3- 30 mL (75 mg) aliquots in 19 lung segments repeated	5	
KL4-ARDS-03		5
3- 30 mL aliquots (75 mg) in 19 lung segments	6	
3- 30 mL (75 mg) aliquots in 19 lung segments (third aliquot 300 mg)	3	
KL4-ARDS-04		
Part A1: 2- 30 mL (150 mg) + 1- 30 mL (300 mg) lavages in 19 segments	5	
A2: 3- 30 mL (300 mg) lavages in 19 segments	6	
A3: 2- 50 mL (500 mg, 1000 mg) lavages in 19 segments	6	
A4: 2- 50 mL (500 mg, 1000 mg) lavages in 19 segments, combined with 2- 100 mL (2000 mg) boluses	5	
Part B1: 2- 50 mL (500 mg, 1000 mg) lavages in 19 segments	10	
B2: 2- 50 mL (500 mg, 1000 mg) lavages in 19 segments, combined with 2- 100 mL (2000 mg) boluses	13	
B3: SOC		11

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The NDA did not include or refer to any other studies for the evaluation of safety. For the review, studies with other surfactants were reviewed to gather perspective on the Applicant's findings. Where those other sources were used, they were referenced in the review.

7.2.2.2 Postmarketing experience

Surfaxin is not marketed anywhere in the world and no postmarketing data are available.

7.2.2.3 Literature

The application includes a bibliography of 124 citations and reprints of all citations. Almost all references are literature reports, with some FDA correspondence and surfactant package inserts also included. The Applicant's bibliography was generally relevant and helpful. Seminal background papers were included, as well as the major publications of previous surfactant studies. Those were reviewed to the extent they were relevant to the evaluation of the application.

Notably missing from the Applicant's bibliography was any of the literature conveying safety concerns about surfactant therapy. In particular, numerous papers have been published concerning infection, IVH, and pulmonary hemorrhage, and none of those reports is included in the application. Searches in those and other topics of interest were performed for this review and citations are provided when the reports were used in interpreting results in the application or when reaching conclusions.

7.2.3 Adequacy of Overall Clinical Experience

Adequate numbers of patients were included in the program to assess the safety of Surfaxin. Although the evidence for efficacy relies on only one of the studies conducted by the Applicant, the other studies could be used for the safety evaluation. All taken together, the studies provide sufficient exposure to assess safety.

Despite an adequate number of patients, however, two factors somewhat limit the adequacy of the overall clinical experience. This was largely unavoidable. After the plan was made for Exosurf to be the primary comparator in the major efficacy study, Exosurf was withdrawn from the U.S. market. As a result, the studies had to be conducted in other countries, and although the secondary study included some North American centers, the vast majority of patients in the program were from Europe and Latin America. Because of different medical practices, public health practices, and demographic factors in those countries, this reality must inevitably affect the ability of the NDA clinical experience to predict the anticipated clinical experience in the U.S. population. Among the most notable examples is the virtual absence of black patients.

To an extent, a second limiting factor compounded the first. For business reasons, the Applicant chose to use Curosurf as the comparator surfactant in the supporting study. That study included North American patients, but using a different comparator surfactant impaired across-study comparisons.

As a result of these circumstances, the overall clinical experience is an amalgam of international clinical backgrounds, three comparison drugs, and no placebo group. Although the evaluation of the overall safety and efficacy of Surfaxin must recognize these factors, they cannot be quantitatively incorporated into analyses or ultimately into the conclusions. The issues must be addressed in the product labeling.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Adequacy of preclinical testing was limited, but because of the inherent nature of the product and intended population, not through any deficiency in the development program. Because it is instilled intratracheally, local toxic effects of surfactant are of interest and concern. Premature, newborn, or even infant animals are not suitable for preclinical testing, however, and older animals are not surfactant deficient. Consequently, the preclinical testing that can be done can only partially address potential clinical adverse effects.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing for adverse effects was generally appropriate and satisfactory. For the most part, the two broad categories of safety concerns with surfactant, concurrent diagnoses and negative reactions to dose administration, were well handled. Most concurrent diagnoses were defined by the protocol, as were grades or stages of the diagnoses when applicable. There were two exceptions to this. Acquired sepsis was not defined nor was any attempt made to collect causative organisms or other serious infections except by spontaneous AE reporting. As it turned out, this became a significant deficiency in the database available for evaluation. The second weakness in concurrent diagnosis monitoring was in pulmonary hemorrhage. A definition was provided in the protocol, but there was no attempt to grade severity of the hemorrhage, so there was no way to ascertain whether a hemorrhage was mild or life-threatening. The negative reactions to dose administration were appropriately monitored and collected. The available data for this safety outcome should be reliable and comprehensive.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

These assessments are not possible with this drug, as explained in section 5 above.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Refer to section 7.2.5 above.

7.2.8 Assessment of Quality and Completeness of Data

The data and form of the data provided for the safety review were described in section 7.2.1 above. Data collection for very premature neonates is a daunting task and the Applicant generally did a satisfactory job. Many patients in the program were hospitalized for several weeks, if not months. Collecting the significant data while also limiting the data set to manageability is a challenge. The quality of the data reflected the challenge. CRFs were included for patients who died, but when patients had multiple life-threatening events in rapid succession (e.g., air leak, IVH, pulmonary hemorrhage), it was usually impossible to determine from CRFs the relative significance of each event and how they interacted to result in the patient's death.

The Applicant relied on the AC to determine the cause of death in the major efficacy study. Consequently, the records of the AC and their data were a critical component of this review. Unfortunately, this was an area of general weakness of data quality and completeness in the application. No records at all of the AC results or proceedings were included in the initial filing, save as reflected in the results of analyses. The necessary data were eventually obtained over the course of the review through information requests. Although all necessary data were eventually obtained, omitting the data in the first place was a deficiency in the application.

7.2.9 Additional Submissions, Including Safety Update

Additional submissions to the application relevant to safety came in two major forms: responses to information requests and the four-month safety update required by 21 CFR 314.50(d)(5)(vi)(b).

7.2.9.1 Responses to information requests

The primary source of data for the safety review was the studies conducted by the Applicant and included in this application. Additional clinical information that could not be located in the NDA was obtained from the Applicant in response to Information Requests made during the review process. Those requests are briefly described in Table 2. In all cases, the Applicant provided the requested information in usable format and the information was incorporated into the review.

7.2.9.2 Four-month safety update [M5 (9/30/2004), v 2.1]

A four-month safety update was submitted in 42 volumes on September 30, 2004. It had four major components: 1) 6- and 12-month corrected age follow-up reports for study KL4-IRDS-06; 2) 6- and 12-month corrected age follow-up reports for study KL4-IRDS-02; 3) an updated Integrated Summary of Safety; and 4) a summary update of 36 week PCA results for studies KL4-IRDS-06 and KL-IRDS-02. The focus here is on the follow-up reports, which were not included in the initial filing. The other two components of the submission will be briefly summarized with attention to any significant or notable new information.

7.2.9.2.1 6-month corrected age follow-up

Follow-up evaluations at 6 and 12 months corrected age were included in the plans for studies KL4-IRDS-06 and KL4-IRDS-02. The results included in the safety update submission were final for the 6-month evaluations. The procedures and assessments for the follow ups are described in the individual study reports. At 6 months, the evaluation was to be performed by telephone contact with the patient's guardian. This methodology must be considered in interpreting the results. The patient was not examined and information was not obtained from a health care professional. Therefore, all information derives from a lay assessment, which could affect the validity of the characterization of a respiratory illness ("wheezing," "pneumonia," etc). Finally, there was no documentation that the contact was actually made with the guardian vs. other person; for example, a baby-sitter.

There is a perspective that needs to be kept in reviewing results of the early follow-up evaluations in premature neonates. On average, patients in all treatment groups in the two studies spent about 150 days in the hospital after birth *[M5, v 2.1, sec 5.3.5.1, p 48; M5, v 2.16, sec 5.3.5.1, p 43]*. The average gestational age among all patients was 27-28 weeks (Table 8), so their chronological age at the 6-month corrected age time point would have been about 8 months. Therefore, of those 8 months, about 5 were spent in the hospital. In other words, these are patients barely out of the hospital in many cases, and their status will inevitably reflect this.

Dispositions of the patients at 6 months corrected age in the two studies are shown in the next Table. The primary analyses of the follow-up evaluations were of the per protocol (i.e., treated) populations. A notable observation in the results in the Table is the remarkable drop-off in the deaths from 36 weeks PCA through 6 months in the Survanta patients in KL4-IRDS-06 compared to the other two groups. The deaths during that period in all other groups were relatively proportional. The rate of follow-up in Survanta patients was similar to the other groups; there is no obvious explanation for this observation.

Table 38: Disposition of Patients at 6 Months Corrected Age (Integrated Safety)

	KL4-IRDS-06			KL4-IRDS-02	
	Surfaxin	**Exosurf**	**Survanta**	**Surfaxin**	**Curosurf**
In the Study					
Randomized	527	509	258	124	128
Treated	524	506	258	119	124
Alive[a]	375	348	175	97	94
Deaths[a]	133	144[b]	72	21	26
Birth-36 wks PCA	111	119[b]	68	19	23
36 wks PCA-6 mos	22	25	4	2	3
Lost to follow-up/withdrew consent[a]	14/2	13/1	9/2	1/0	4/0

[a]Per protocol population
[b]2 deaths were randomized but not treated
Source: M5 (9/30/2004), v 2.1, sec 5.3.5.1, p 45; M5 (9/30/2004), v 2.16, sec 5.3.5.1, p 40

Table 39 summarizes results of the other health assessments from the 6-month evaluations. There were no differences between Surfaxin and Survanta patients. Statistical comparisons were not done between the Surfaxin and Survanta patients in KL4-IRDS-06, but there were more patients in the Survanta group in "poor" health and fewer in "excellent" health. Combined with the finding of fewer deaths in the Survanta group after 36 weeks PCA, it is possible to speculate that the relatively larger proportion of survivors in the Survanta group is surviving in poorer health. The cautions about these results noted previously, however, must temper any conclusions.

Table 39: Results of 6-Month Telephone Contacts (Integrated Safety)

	KL4-IRDS-06				KL4-IRDS-02		
	Surfaxin N=524	**Exosurf N=506**	**Survanta N=258**	**Surfaxin vs. Exosurf p-value**	**Surfaxin N=119**	**Curosurf N=124**	**Surfaxin vs. Curosurf p-value**
		N (%)				**N (%)**	

	KL4-IRDS-06				KL4-IRDS-02		
Overall Health				0.832			0.297
Poor	173 (33.0)	177 (34.9)	96 (37.2)		25 (21.0)	31 (25.0)	
Fair	31 (5.9)	35 (6.9)	15 (5.8)		6 (5.0)	2 (1.6)	
Good	132 (25.2)	123 (24.3)	78 (30.2)		23 (19.3)	17 (13.7)	
Very good	119 (22.7)	111 (21.9)	54 (20.9)		31 (26.1)	37 (29.8)	
Excellent	69 (13.2)	60 (11.9)	15 (5.8)		34 (28.6)	37 (29.8)	
Respiratory Illnesses	348 (66.4)	335 (66.2)	180 (69.8)	0.756	76 (63.9)	74 (59.7)	0.756
Coughing	304 (58.0)	302 (59.7)	166 (64.3)	0.692	67 (56.3)	66 (53.2)	0.863
Wheezing	268 (51.2)	258 (50.9)	142 (55.0)	0.796	58 (48.7)	52 (41.9)	0.447
Fever	256 (48.9)	259 (51.2)	148 (57.4)	0.641	50 (42.0)	46 (37.1)	0.687
Pneumonia	222 (42.4)	222 (43.9)	122 (47.3)	0.661	31 (26.1)	34 (27.4)	0.494

Source: M5 (9/30/2004), v 2.1, sec 5.3.5.1, pp 47, 49 ; M5 (9/30/2004), v 2.16, sec 5.3.5.1, pp 42,44

Adverse event reports between 36 weeks PCA and 6 months corrected age were summarized in the safety update. As noted, at 6 months many of the patients may still be considered to be only recently recovered from their acute neonatal course, so the 12-month results will have more bearing on the patients' true long-term status. AEs were still quite common at the 6-month evaluation with at least one event in >70% of all patients. Review of the 6-month AE reports found them to be consistent with the reports from the earlier study phases with no evidence of previously undiscovered safety concerns, save one. Deafness NOS was reported in 5 Surfaxin patients vs. 2 Exosurf patients and 1 Survanta patient. The results at 12 months will be more telling about this event. There was no difference in the "hearing impaired" preferred term.

There was no difference at 6 months in infection AEs overall (46.95% Surfaxin, 46.84% Exosurf, 45.74% Survanta, 42.74% Curosurf), but there were differences in some specific events, mostly within the respiratory system. It is not possible to know whether those reports might reflect infectious or pulmonary origins:

- Pharyngitis: 5.15% Surfaxin, 3.36% Exosurf, 3.36% Survanta, 4.84% Curosurf
- Respiratory tract infection NOS : 2.29% Surfaxin, 1.38% Exosurf, 0.78% Survanta, 1.61% Curosurf
- Upper respiratory tract infection NOS: 7.06% Surfaxin, 5.34% Exosurf, 6.59% Survanta, 4.03% Curosurf

On the other hand, there were no differences in the reports of sepsis NOS, neonatal sepsis, or septic shock; in fact the rates of sepsis NOS tended to be lower in Surfaxin patients (2.48% Surfaxin, 3.75% Exosurf, 2.71% Survanta, 3.23% Curosurf).

The pattern of serious AEs at 6 months was consistent with the pattern of all events.

7.2.9.2.2 12-month corrected age follow-up

The 12-month assessments are completed for KL4-IRDS-02, but still in progress for KL4-IRDS-06. As of the cut-off date of May 31, 2004, 12-month results were available for 895 of the 1294 patients enrolled in the study. Evaluations at 12 months corrected age were more thorough and comprehensive than those at 6 months. Patients were examined and a neurological assessment

was included. The next Table shows the dispositions of the patients whose status is currently known. Very few deaths occurred between the 6- and 12-month evaluations.

Table 40: Disposition of Patients at 12 Months Corrected Age (Integrated Safety)

	KL4-IRDS-06			KL4-IRDS-02	
	Surfaxin	**Exosurf**	**Survanta**	**Surfaxin**	**Curosurf**
Treated	372	352	171	119	124
Alive[a]	217	190	93	97	92
Deaths[a]	138	146[b]	72	21	26
Birth-36 wks PCA	111	119[b]	68	19	23
36 wks PCA-6 mos	22	25	4	2	3
6 mos-12 mos	5	2	0	0	0
Lost to follow-up/withdrew consent[a]	14/3	15/1	5/1	1/0	6/0

[a]Per protocol population
[b]2 patients who died were randomized but not treated
Source: M5 (9/30/2004), v 2.1, sec 5.3.5.1, p 45; M5 (9/30/2004), v 2.16, sec 5.3.5.1, p 40

Statistical comparisons have not been made for the 12-month results because all patients have not yet been seen. The results to date are shown in the next Table. It includes findings of the neurological examinations which were not done at 6 months. The data for abnormal neurological findings in KL4-IRDS-06 are artifactually high. According to the statistical plan, all patients not yet seen are imputed to have the worst possible outcome. Final results without the imputations will show true results. In any case, the rates are not different between treatments. Not shown in the Table are the growth assessments that were performed at 12 months. There were no treatment group differences in weight, height, or head circumference.

Table 41: Results of 12 Month Evaluations (Integrated Safety)

	KL4-IRDS-06			KL4-IRDS-02	
	Surfaxin N=372	**Exosurf N=352**	**Survanta N=171**	**Surfaxin N=119**	**Curosurf N=124**
		N (%)			
Overall Health					
Poor	171 (45.9)	177 (50.3)	89 (52.1)	26 (21.90)	35 (28.2)
Fair	18 (4.8)	17 (4.8)	8 (4.7)	8 (6.7)	3 (2.4)
Good	72 (19.4)	55 (15.6)	32 (18.7)	20 (16.8)	19 (15.3)
Very good	70 (18.8)	68 (19.3)	26 (15.2)	24 (20.2)	30 (24.2)
Excellent	41 (11.0)	35 (9.9)	16 (9.4)	41 (34.5)	37 (29.8)
Respiratory Illnesses	269 (72.3)	279 (79.3)	128 (74.9)	72 (60.5)	75 (60.5)
Coughing	260 (69.9)	264 (75.0)	126 (73.7)	63 (52.9)	68 (54.8)
Wheezing	215 (57.8)	229 (65.1)	109 (63.7)	49 (41.2)	59 (47.6)
Fever	232 (62.4)	250 (71.0)	117 (68.4)	45 (37.8)	54 (43.6)
Pneumonia	188 (50.5)	196 (55.7)	93 (54.4)	31 (26.1)	38 (30.7)
Neurological Findings					
Gross tone or reflex abn	155 (55.4)	156 (59.8)	76 (58.9)	23 (21.3)	30 (27.0)
Cerebral palsy	149 (53.2)	150 (57.5)	73 (56.6)	20 (18.5)	26 (23.4)
Hydrocephalus	147 (52.5)	145 (55.6)	73 (56.6)	16 (14.8)	23 (20.7)
Deafness	150 (53.6)	143 (54.8)	71 (55.0)	15 (13.9)	22 (19.8)
Blindness	146 (52.1)	145 (55.6)	72 (55.8)	16 (14.8)	24 (21.6)

	KL4-IRDS-06			KL4-IRDS-02	
Seizures	148 (52.9)	142 (54.4)	72 (55.8)	16 (14.8)	23 (20.7)
Gross motor delay	153 (54.6)	155 (59.4)	75 (58.1)	18 (16.7)	26 (23.4)
Other findings	155 (55.4)	147 (56.3)	72 (55.8)	21 (19.4)	26 (23.6)

Source: M5 (9/30/2004), v 2.1, sec 5.3.5.1, pp 65, 67; M5 (9/30/2004), v 2.16, sec 5.3.5.1, pp 58, 60 ; M5 (9/30/2004), v 2.28, sec 5.3.5.3, pp169-170

Adverse event reports were less common in the period from 6 to 12 months corrected age. About 55% of patients had at least one AE, but for the first time there were more in the Surfaxin patients: 59.3% overall compared to 51.6% in all control patients. The AE reports at 12 months, however, reflect an incomplete data base – there are still patients to be evaluated, so the results might change.

In the patients evaluated so far, the difference in reports of deafness noted at 6 months was still present but there were fewer reports: 4 Surfaxin patients (1.08%), 2 Exosurf patients (0.57%), 0 Survanta or Curosurf patients. The differences in reports of respiratory tract infectious events seen at 6 months changed somewhat at 12 months. Differences were still present for infection events overall (37.9% Surfaxin, 33.2% control), but several of the events occurred in more control patients at 12 months (tonsillitis, otitis media, respiratory tract infection NOS, pharyngitis). Other events were still reported more commonly in Surfaxin patients (bronchitis, pneumonia in study KL4-IRDS-02 but not overall, upper respiratory tract infection NOS). With not all patients evaluated yet, it is premature to draw conclusions, but there is some consistency at 12 months with the types of AEs reported at 6 months and earlier.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

To summarize the AE profile for Surfaxin in the prevention of RDS, several circumstances must be considered.
1) The intended population is physiologically immature in every organ system. The population is also critically and acutely ill during the time of dosing, with multiple adverse and lethal events often occurring nearly simultaneously.
2) Therefore, nearly every patient experiences an AE and most are serious. Because so many factors are contemporaneous, the relationships among drug, event, and disease are difficult to sort out.
3) Surfaxin is applied directly to the lungs and mostly stays there. Pharmacokinetic, toxicokinetic, or ADME information is not available.
4) Preclinical studies were hampered by the need to use young animals whose hardiness is not conducive to long-term studies.
5) The Applicant did not prospectively establish criteria for certain diagnoses that would have aided interpretation of the results; for example, sepsis.
Taking those conditions into account, four events comprised a "problem list" during the course of the review: non-RDS deaths, infection-related events, negative reactions to dose administration, and renal events. The first three events are summarized in this section. Renal events were concluded to be unrelated to the drug (see section 7.1.5.6.1 above).

7.3.1 Non-RDS Deaths

With fewer Surfaxin patients dying because of RDS, but no difference in all-cause mortality, it was not completely surprising to find more non-RDS deaths in Surfaxin patients, but it was nonetheless necessary to determine whether Surfaxin was causing any deaths as opposed to shifting the balance from RDS-related deaths to deaths from all other causes.

For the most part, the non-RDS deaths spanned all causes. Two particular findings were concluded to reflect idiosyncracies in the adjudication process: more renal deaths in Surfaxin patients (the difference diminished at later study time points), and deaths in Surfaxin patients from two causes physiologically related to RDS (IVH and pulmonary hemorrhage) that were adjudicated as not related.

Despite the issues associated with adjudication and cause-specific mortality, the overall results indicate that mortality in Surfaxin patients actually showed a *numerical advantage* that persisted over time with no substantiated evidence to the contrary.

7.3.2 Infection

Suggestions of higher rates of infection-related events in Surfaxin patients were found in:

- slightly higher number of deaths caused by sepsis in KL4-IRDS-06
- more serious AEs of sepsis and pneumonia in NRDS studies
- more infection AEs in one MAS study

Contrary evidence was observed in:

- no difference in sepsis deaths in KL4-IRDS-02
- no difference in all infection AEs
- no difference in infection AEs in the other MAS study

The signal for a safety concern about infection is not strong enough to preclude approval of the drug, but the relevant information should be made available in product labeling.

7.3.3 Negative reactions to dose administration

Most likely because the volume of Surfaxin was relatively larger than other surfactants, its administration was reproducibly associated with more negative reactions. The reactions included obstruction of the ETT and interruption or discontinuation of dosing, events with important clinical implications. These findings need to be included in product labeling.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Pooling was used little for this review, although the Applicant used it frequently. In its Integrated Safety Summary, the Applicant pooled all Surfaxin and all control patients together for display of AEs and other safety outcomes in the NRDS studies. Pooling the Surfaxin patients was reasonable and this review examined the pooled Surfaxin patients to obtain the largest data base possible for estimating the frequency of events, especially rare ones. Pooling control patients, on the other hand, is not considered appropriate and the pooled control data were not used. Each of the surfactants used in control groups is different and each is associated with a unique safety profile. Pooling their results could hide differences from Surfaxin that might be informative.

Data from MAS and ARDS studies were not pooled with NRDS studies. Those patient populations and the methods of dosing were so different that pooling them made no clinical sense, even though it would enlarge the exposed group. By the same token, even pooling the ARDS patients was risky because the dosing regimens within and among those studies were quite different.

Because of these factors, possible drug-related adverse effects were detected by comparing rates of the events in Surfaxin patients to each of the various control groups. The disadvantages of this method were reduced precision of an incidence estimate (i.e., smaller sample), and interpreting the varying incidences among all the groups (i.e., drug-related differences vs. clinical setting differences).

The patient level data that were provided by the Applicant were generally satisfactory and sufficient for exploring safety concerns that arose. The exception, previously noted, was the information provided about the adjudication process. That information was obtained through information requests. When provided, the information was in usable form.

7.4.1.2 Combining data

When data were combined, the numerators and denominators were simply combined.

7.4.2 Explorations for Predictive Factors

Some of the difficulties and challenges of this drug, disease, and intended population have been frequently discussed. The various issues all converge when attempting to sort out drug-event relationships:

▪ Dose dependency and time dependency of events: The number of doses varies by patient and depends on degree of illness. The doses are administered in rapid succession every 6 hours during the same period of time when many AEs are likely to occur.
▪ Drug-disease interactions: Many of the concurrent diagnoses occur simultaneously with each other, the underlying illness, and with dosing.
▪ Drug-drug interactions: PK, metabolic, and clearance data cannot be obtained.

The single interaction in which some explorations are possible is drug-demographic.

7.4.2.1 Explorations for dose dependency for adverse findings

See section 7.4.2 above.

7.4.2.2 Explorations for time dependency for adverse findings

See section 7.4.2 above.

7.4.2.3 Explorations for drug-demographic interactions

The Applicant provided results of safety outcomes for the gender and birth weight demographic subgroups in a manner that allowed adequate review. For the racial subgroups, the "non-white" patients were all collapsed into one group. In fact, there were very few patients in the neonatal program who were not either white or Hispanic, so the Applicant may have believed the numbers in other groups would have been unreliably small for analysis. Although this might be true, not providing the information represents a deficiency in the presentation of safety results for the application. This should be addressed in the product labeling.

7.4.2.4 Explorations for drug-disease interactions

See section 7.4.2 above.

7.4.2.5 Explorations for drug-drug interactions

Not surprisingly for a critically ill population, concomitant medications were given to most patients in the studies and usually simultaneously with the surfactant dosing period. The frequency of use for classes of drugs is shown in the next Table. Because of findings noted elsewhere in this review about infection and deafness, some specific antibiotics are singled out. The Table probably reflects some regional differences in drug use between the two studies, but between surfactants within studies the pattern of use seems to be similar. With such high use of concomitant medications in so many patients, drug-drug interactions are difficult to evaluate.

Table 42: Concomitant Medications (Integrated Safety)

	KL4-IRDS-06			KL4-IRDS-02	
	Surfaxin N=524	Exosurf N=506	Survanta N=258	Surfaxin N=119	Curosurf N=124
		N (%)			

	KL4-IRDS-06			KL4-IRDS-02	
Vasopressors	305 (58.2)	289 (57.1)	147 (57.0)	63 (52.9)	71 (57.3)
Paralytics	33 (6.3)	45 (8.9)	15 (5.8)	11 (9.2)	10 (8.1)
Sedatives	299 (57.1)	299 (59.1)	147 (57.0)	107 (89.9)	98 (79.0)
Steroids	150 (28.6)	162 (32.0)	81 (31.4)	52 (43.7)	49 (39.5)
Bronchodilators	386 (73.7)	371 (73.7)	182 (70.5)	69 (58.0)	65 (52.4)
Antibiotics	508 (96.9)	489 (96.6)	249 (96.5)	117 (98.3)	122 (98.4)
Amikacin	322 (61.5)	313 (61.9)	168 (65.1)	38 (31.9)	40 (32.3)
Gentamicin	170 (32.4)	168 (33.2)	89 (34.5)	71 (58.8)	75 (60.5)
Tobramycin	19 (3.6)	19 (3.8)	8 (3.1)	9 (7.6)	7 (5.6)
Diuretics	301 (57.4)	299 (59.1)	147 (57.0)	69 (58.0)	82 (66.1)
Furosemide	280 (53.4)	286 (56.5)	141 (54.7)	65 (54.6)	77 (62.1)
Source: M5, v 1.89, sec 5.3.5.3, p 389					

7.4.3 Causality Determination

Refer to section 7.3 above. Of the four events discussed there, one is considered causally related to the drug with certainty: negative reactions to dose administration. For another, the causality is inconclusive but the evidence is sufficiently suggestive to warrant including the information in product labeling. Causality could not be established for the other two events.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosages and dosing regimens of surfactants have mostly been derived empirically. The very first significant human use reported good results and the dose used then became a standard from which all subsequent products developed.[9] The Table below shows the approved doses of the surfactant products used in this program. There are some differences in their compositions but three of the products use very similar volume doses. Curosurf has concentrated its product to reduce the volume, and in fact it is the only product with an estimable effort to refine dosing,[10] although its package insert did not change accordingly. For each product, the doses that were ultimately developed came about because of formulation issues or early clinical study results that were encouraging. None of the products underwent significant dose-finding and some underwent none at all.

Table 43: Surfactant Product Dosages (Integrated Safety)

	Surfaxin	Exosurf	Survanta	Curosurf
Concentration (mg phospholipids/mL)	30 mg/mL	13.5 mg/mL	25 mg/mL	80 mg/mL
Dose (mg phospholipids/kg birth weight)	175 mg/kg	67.5 mg/kg	100 mg/kg	1st dose: 200 mg/kg Repeat doses: 100 mg/kg
Dose (mL/kg birth weight)	5.8 mL/kg	5.0 mL/kg	4.0 mL/kg	1st dose: 2.2 mL/kg Repeat doses: 1.25 mL/kg
Source: M5, v 1.2, sec 5.3.5.1, p 477-8; M5, v 1.1, sec 5.3.5.1, 29 ; M5, v 1.41, sec 5.3.5.1, p 26				

The Applicant selected an initial clinical dose of 133 mg/kg phospholipids based on results in primate studies. Later primate studies showed that a higher dose of 200 mg/kg produced more consistent and longer-lasting effects. A clinical dosing study then compared those two doses, but the study was in the rescue strategy and only eight patients received the lower dose. Then, the dose selected for Phase 3 development was 175 mg/kg with no obvious rationale.

Administering additional doses of surfactant after the first dose depends on the patient's continuing respiratory status, so patients may receive from 1 to 4 doses. This strategy makes dose-response determinations quite difficult, especially for safety outcomes, because only relatively sicker patients receive more doses. The situation is well illustrated in the following dose-mortality data provided in the application for the two major studies.

Table 44: Number of Surfactant Doses and Mortality

	KL4-IRDS-06						KL4-IRDS-02			
	Surfaxin		Exosurf		Survanta		Surfaxin		Curosurf	
	Died N=111	Alive N=416	Died N=121	Alive N=388	Died N=68	Alive N=190	Died N=19	Alive N=100	Died N=23	Alive N=101
	N (%)									
0 Dose	0	3 (0.7)	2 (1.7)	1 (0.3)	0	0	0	0	0	0
1 Dose	42 (37.8)	249 (59.9)	39 (32.2)	229 (59.0)	33 (48.5)	1128 (67.4)	8 (42.1)	72 (72.0)	12 (52.2)	80 (79.2)
2 Doses	27 (24.3)	81 (19.5)	32 (26.4)	59 (15.2)	16 (23.5)	33 (17.4)	11 (57.9)[a]	28 (28.0)	11 (47.8)	21 (20.8)
3 Doses	19 (17.1)	32 (7.7)	16 (13.2)	39 (10.1)	9 (13.2)	15 (7.9)				
4 Doses	12 (10.8)	24 (5.8)	13 (10.7)	24 (6.2)	2 (2.9)	5 (2.6)				
5 Doses	11 (9.9)	27 (6.5)	19 (15.7)	36 (9.3)	8 (11.8)	9 (4.7)				

[a]Data were only provided as 2 or more doses for this study
Source: M5, v 1.7, sec 5.3.5.1, p2148; M5, v 1.48, sec 5.3.5.1, p 2629

More than half the patients in the studies only received one dose of surfactant and more than half of those survived. The balance of survival immediately reversed for patients who received two or more doses. With three or more doses the proportions of patients who survived changed relatively little but there were always more who died. These observations are true for all the surfactants and raise a question about the value of the doses after the first. It could even be possible that repeat doses are harmful, but the strategy used does not allow conclusions to be drawn about that possibility. A study in which patients are randomized to different numbers of doses would be necessary.

Despite the reality that clinical dose-ranging in the clinical circumstances of NRDS is extremely challenging, additional information about doses and dose regimens is warranted. In particular, as noted above, additional information could help to determine whether any of the associated safety concerns might be modified by using other doses.

8.2 Drug-Drug Interactions

See section 7.4.2.5 above.

8.3 Special Populations

The entire intended population for Surfaxin is a special population. As noted in section 8.1 above, although the available information is limited, there is no basis for establishing special dosing or other considerations for population subgroups.

8.4 Pediatrics

This section is not applicable because the intended indication is by definition pediatric and confined to the neonatal population. Pediatric considerations will be warranted for use of Surfaxin in ARDS or other diseases.

8.5 Advisory Committee Meeting

No Advisory Committee meeting related to this application was held or is planned.

8.6 Literature Review

The application includes a bibliography of 124 citations and reprints of all citations. Almost all references are literature reports, with some FDA correspondence and surfactant package inserts also included. The Applicant's bibliography was generally relevant and helpful. Seminal background papers were included, as well as the major publications of previous surfactant studies. Those were reviewed to the extent they were relevant to the evaluation of the application.

Notably missing from the Applicant's bibliography was any of the literature conveying safety concerns about surfactant therapy. In particular, numerous papers have been published about infection, IVH, and pulmonary hemorrhage, and none of those reports is included in the application. Searches in those and other topics of interest were performed for this review and citations are provided when the reports were used in interpreting results in the application or when reaching conclusions.

8.7 Postmarketing Risk Management Plan

The Applicant included a risk management plan in the application. The components described for the plan are:

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8.8 Other Relevant Materials

Consultations were provided for this application by the Division of Scientific Investigations (DSI); the Division of Drug Marketing, Advertising, and Communication (DDMAC); and the Division of Medication Errors and Technical Support (DMETS).

Results of the DSI consultation are summarized in section 4.4 above. The DDMAC consultation recommended a number of changes in the proposed package insert which are all contained within the Labeling Review in section 9.4 below. The DMETS consultation is also reported under the Labeling Review below.

9 OVERALL ASSESSMENT

9.1 Conclusions

This review finds evidence to support demonstrated effectiveness of Surfaxin in:

- the prevention of RDS, the indication proposed by the Applicant, and

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Results for the co-primary efficacy endpoints were statistically persuasive. The incidence of RDS was about 17% less in patients treated with Surfaxin, and RDS-related mortality was approximately half the rate in Surfaxin patients compared to Exosurf patients (4.7 vs. 9.6%). The criteria for efficacy were fairly met, and moreover, the results were consistent across population subgroups based on birth weight, gender, and race.

Although results for the secondary endpoints showed them to generally support the primary effects of Surfaxin on RDS and RDS-mortality and there were no results that contradicted those

effects, [redacted] (b) (4)

Evaluation of the results for BPD is more complicated. BPD was an endpoint discussed with the Division, indeed, was supported as a primary endpoint by the Division, but the Applicant's definition of the condition was not sufficiently refined. In a correspondence dated September 26, 2001, the Division stated that "…BPD should be defined by peripheral oxygen saturation parameters that specify when an infant requires supplemental oxygen…" [redacted] (b) (4)

There was one major efficacy study in the application and two supportive studies. The results from the supportive studies generally provided evidence of *consistency* with the major efficacy study. Although there were no significant differences in incidence of RDS or RDS-related deaths in the supportive studies, they were not designed or powered to detect them, and the rates of the events, as well as secondary outcomes, were similar to those in the major efficacy study.

Among the secondary efficacy endpoints was all-cause mortality, and the results for this outcome were not at all straightforward. Despite the difference in RDS-related mortality, there was no difference in all-cause mortality at any time point in the study, and in fact the incidence of non-RDS-related mortality (all the deaths besides those RDS-related) was significantly higher in Surfaxin patients that Exosurf patients. Finding more non-RDS-related deaths in Surfaxin patients made it the most important focus of the safety evaluation of the application.

The Applicant did not examine the non-RDS-related deaths separately, so the analyses and conclusions from that review rested solely with the FDA. The review of deaths from the perspective of safety is found in section 7.1.1 above and mortality data are summarized best in Table 12 and Table 22. For the most part, the non-RDS deaths spanned all causes. Two particular findings were concluded to reflect idiosyncracies in the adjudication process that was used to determine cause of death: more renal deaths in Surfaxin patients (the difference diminished at later study time points), and deaths in Surfaxin patients from two causes physiologically related to RDS (IVH and pulmonary hemorrhage) that were adjudicated as not related. Despite the issues associated with adjudication and cause-specific mortality, the overall results indicate that mortality in Surfaxin patients actually showed a *numerical advantage* that persisted over time with no substantiated evidence to the contrary.

The Applicant concluded that no safety issues of concern were identified in the clinical studies. This review identified two concerns. First, suggestions of higher rates of infection-related events

in Surfaxin patients were found in the slightly higher number of deaths caused by sepsis in one NRDS study; more serious AEs of sepsis and pneumonia in NRDS studies pooled; and more infection AEs in one MAS study. Other data indicated no increased risk of infection, so while causality between Surfaxin and increased risk of infection is inconclusive, the information should be provided in product labeling. The other area of concern is in negative reactions to administration of Surfaxin. Most likely because the volume of Surfaxin was relatively larger than other surfactants, its administration was reproducibly associated with more negative reactions. The reactions included obstruction of the ETT and interruption or discontinuation of dosing, events with important clinical implications. These findings also need to be included in product labeling.

9.2 Recommendation on Regulatory Action

From the clinical standpoint, the recommended action is **Approval** with labeling changes, enumerated in section 9.4. The recommendation is founded in the demonstrated effectiveness of Surfaxin in preventing RDS and deaths related to RDS. These effects were accompanied by two areas of concern, the possibility for increased infection and relatively more negative reactions to dose administration than other surfactants, but neither risk overrules the beneficial effects of the drug as long as the risks are disclosed in product labeling.

For the first surfactant approved, the benefit/risk was compellingly positive compared to placebo. In assessing benefit/risk for this application, the ratio is naturally made different by availability of other products, but the essence remains the same. Preventing a serious disease with its associated lethality in the most fragile of all populations is of great clinical benefit. It was a natural consequence that a critical component of this review was to examine whether there was evidence of any "trade-off" in that benefit; i.e., increasing the risk to suffer or die for another reason. In a clinical setting of such high acuity, it is difficult to determine for certain a single cause of death and the adjudication process employed in this program amply demonstrated the difficulties. After exhaustive examination, however, this review concludes that there is no evidence for the hypothetical trade-off. That is, the benefit is real. The safety findings of concern summarized in the section above are also real, to be sure, but do not overrule the appreciable benefit of the product.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The Risk Management Plan proposed by the Applicant (section 8.7 above) is satisfactory. The (b) (4)

9.3.2 Required Phase 4 Commitments

No Phase 4 commitments will be required of the Applicant.

9.3.3 Other Phase 4 Requests

The Applicant will be encouraged to consider further clinical investigation of the dose of Surfaxin. Despite the reality that clinical dose-ranging in the clinical circumstances of NRDS is extremely challenging, additional information about doses and dose regimens is warranted. In particular, additional information could help to determine whether any of the associated safety concerns might be modified by using other doses.

9.4 Labeling Review

9.4.1 Trade Name

DMETS recommended against the use of the trade name Surfaxin because of concerns about confusion with look-alike and sound-alike terms, specifically "surfactant." The clinical scenario of concern is the delivery room setting where the first dose of Surfaxin would be administered. The situation is frequently emergent and as many as 8-10 health care personnel might be in the room, all issuing verbal orders. (At birth a neonate does not have a name or hospital identification number). There are no written orders at that time. A person caring for the newborn might issue an instruction to "give a dose of surfactant" (neonatal care-givers frequently use the generic term) or "give a dose of Surfaxin". In the first instance, if "Surfaxin" is heard instead of "surfactant," it would be given when the caregiver actually intended another product on formulary to be given (e.g., Infasurf) and a medication error could result. In the second instance, if "surfactant" is heard instead of "Surfaxin," another surfactant on the formulary could be erroneously given. If Surfaxin were the only surfactant available, no error would occur in either instance. Each of these scenarios has clinical legitimacy, but it is impossible to predict how frequently they might occur; presumably not highly frequently. The recommendation of this reviewer is to follow the DMETS recommendation.

9.4.2 Package Insert

The recommended changes are organized below according to the format and content of the proposed package insert included in the application *[M1, v 1.1, sec 1.7, p 1]*.

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10 APPENDICES

10.1 Individual Study Report: KL4-IRDS-06. A Multinational, Multicenter, Randomized, Masked, Controlled, Prophylaxis Superiority Trial of the Safety and Effectiveness of Surfaxin® (Lucinactant) Compared to Exosurf® (Colfosceril Palmitate) in the Prevention of Respiratory Distress Syndrome (RDS) in Premature Neonates

10.1.1 Protocol

This section describes the study protocol as originally written. Changes effected by protocol amendments are discussed separately in section 10.1.2.

10.1.1.1 Study administrative information

Protocol Issue Date:	May 9, 2001
Protocol Amendment Dates:	October 10, 2001; November 29, 2001; November 10, 2003
Study Dates:	July 2, 2001 to December 16, 2003
Study Sites:	57 centers in U.S., Europe, and Latin America received IRB approval. 54 centers in Europe and Latin America participated in the study.
Study Report Date:	March 21, 2004
Source:	*M5, v 1.1, sec 5.3.5.1, p 1*

10.1.1.2 Objectives/Rationale [M5, v 1.2, sec 5.3.5.1, p 476]

This was the major efficacy study for the clinical program. There were two objectives: 1) to determine the difference in efficacy between Surfaxin and Exosurf in the prevention of RDS in premature neonates, and 2) to assess the safety profile of Surfaxin compared to that of Exosurf.

Exosurf was the primary comparator in the study; however, owing to its infrequent use in the U.S. at the time of initiating the study, Survanta was included as a reference comparator in order to inform U.S. prescribers.

10.1.1.3 Study design overview

This was a multinational, multicenter study. Patients were enrolled in Chile, Ecuador, Uruguay, Panama, Mexico, Brazil, Russia, Hungary, and Poland. One U.S. center was recruited for the study but did not enroll any patients.

The study was randomized, masked, controlled, and event-driven. Premature neonates at high risk for RDS were to be randomized immediately after birth to receive Surfaxin, Exosurf, or Survanta. Surfaxin vs. Exosurf was the primary superiority comparison; Survanta was included as a reference product. No placebo was used. The first surfactant dose was to be given as soon as possible after randomization, and no later than 30 minutes of age. Additional doses of the same assigned surfactant could then be given at protocol-established minimum intervals if RDS occurred and persisted at protocol-specified severity. Treatments were to be administered by unblinded dosing administrators who did not otherwise participate in the patient's care. Investigators and other personnel caring for the patients were blind to the surfactant administered.

The study was designed with two stages. An early stage encompassed all events and evaluations through 28 days of age, 36 weeks post-conceptual age (PCA), and hospital discharge. The second stage was comprised of follow-up evaluations at 6- and 12-months adjusted ages.

10.1.1.4 Study population

Patients could be entered into the study if they met all the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria: *[M5, v 1.2, sec 5.3.5.1, p 478]*
1) A legally authorized representative provides written permission by signing and dating the informed consent form.
2) The birth weight is 600-1250 grams.
3) The patient has been successfully intubated.

Exclusion Criteria : *[M5, v 1.2, sec 5.3.5.1, p 478]*
1) Heart rate cannot be stabilized above 100 within 5 minutes of birth
2) 5 minute APGAR score ≤ 3
3) Major congenital malformation(s) diagnosed antenatally or noted immediately after birth
4) Other disease(s) potentially interfering with cardiopulmonary function (e.g., hydrops fetalis, or congenital infection)
5) Neonates born to a mother with suspected chorioamnionitis (uterine tenderness, maternal fever, fetal tachycardia)
6) Neonates born to a mother with prolonged rupture of membranes > 5 days
7) Known or suspected chromosomal abnormality
8) Gestational age > 32 weeks

10.1.1.5 Study treatments

Study patients were randomized to receive one of three surfactants: Surfaxin, Exosurf, or Survanta. There was no placebo.

Table 45: Study Treatments: KL4-IRDS-06

	Surfaxin	Exosurf	Survanta
Concentration (mg	30 mg/mL	13.5 mg/mL	25 mg/mL

	Surfaxin	Exosurf	Survanta
phospholipids/mL)			
Dose (mg phospholipids/kg birth weight)	175 mg/kg	67.5 mg/kg	100 mg/kg
Dose (mL/kg birth weight)	5.8 mL/kg	5.0 mL/kg	4.0 mL/kg
Source: M5, v 1.2, sec 5.3.5.1, p 477-8; M5, v 1.1, sec 5.3.5.1, 29			

Multiple doses of each surfactant could be given if the patient met specified retreatment criteria that were based on continuing severity of disease. Patients could receive up to four doses of Surfaxin or Survanta, but only three doses of Exosurf, as allowed by the package insert. The retreatment procedures, including the ways the product differences were handled for the study, are described in section 10.1.1.5.4 below.

10.1.1.5.1 Randomization

Exosurf was the active comparator and Survanta was a reference product, so half the number of patients was randomized to Survanta, resulting in a randomization ratio of 2:2:1 for the three products. A unique randomization list was provided to each center. Patients were stratified within each center by birth weight: stratum 1 – 600-800 grams; stratum 2 – 801-1000 grams; stratum 3 – 1001-1250 grams. Treatment assignments were sealed in sequentially numbered opaque envelopes to be opened after randomization.

10.1.1.5.2 Masking

The three surfactants are distinguishable by appearance and by dosage form. Surfaxin and Survanta are refrigerated suspensions that need to be warmed before administration and Exosurf is a lyophilized powder reconstituted with sterile water. Therefore, the protocol describes a system of procedures and personnel to maintain the blinded design of the study.

Upon determining eligibility and enrolling a patient in the study, the investigator notified a *Dosing Preparer*. This was an individual who was not involved in determining the patient's eligibility nor would be otherwise involved in the patient's care. The Dosing Preparer determined the assigned treatment by opening the next sequential opaque envelope for the patient's birth weight stratum. The Dosing Preparer then prepared the assigned treatment according to specific directions in a protocol appendix. The preparation instructions for Exosurf and Survanta conformed to those products' package inserts. The surfactant was prepared in a location not visible to the patient's caregivers, preferably the pharmacy. The surfactant was drawn into a syringe that was wrapped in an opaque label to mask the surfactant's appearance. The label had gradations to permit accurate dosing.

The prepared dosing syringe was delivered to a *Dosing Administrator* who would give the surfactant to the patient. The Dosing Administrator was also an individual not involved in determining the patient's eligibility or involved in the care. The Dosing Administrator could be the same person as the Dosing Preparer. Surfactant administration had to be performed in a location or in a manner not visible to the patient's caregivers.

10.1.1.5.3 Surfactant administration [M5, v 1.2, sec 5.3.5.1, p 4482]

The three surfactants were to be administered in the same manner, which was identical to the procedure prescribed in the Survanta package insert. (The package insert for Exosurf recommends a different administration procedure which will be described following.) The surfactant administration procedures were:

- The ETT is in place with mechanical or manual hand-bag ventilation ongoing
- A 5 French end-hole catheter is passed into the ETT through a Bodai or equivalent valve (a device with a side-entry valve, placed between the ETT and ventilator or bag outlet).
- Ventilation continues at ≥ 30 breaths/minute, PEEP 4-5 cm H_2O, and FiO_2 sufficient to prevent cyanosis or desaturation
- Position the patient with head and body 5-10° down, head turned to the right
- Inject ¼ of the total dose of surfactant
- Ventilate the patient until stable (O_2 saturation 85-90%, heart rate > 120)
- Reposition the patient to head and body 5-10° down and head turned to the left
- Inject another quarter-dose of surfactant
- Ventilate until stable
- Reposition the patient to head and body 5-10° up and head turned to the right
- Inject the next quarter-dose of surfactant
- Ventilate until stable
- Reposition the patient to head and body 5-10° up and head turned to the left
- Inject the last quarter-dose of surfactant
- Remove the catheter from the ETT
- Do not suction the infant's ETT for 1 hour unless signs of significant airway obstruction occur
- Resume usual care. Elevate the head of the patient's bed at least 5° for 1-2 hours.

The administration procedure described in the Exosurf package insert differs from the above procedure in that the total dose is divided into two half-doses rather than four quarter-doses; the patient is not repositioned; and the surfactant is injected with the patient's head at midline. After injection of each half-dose, the patient's head is turned briefly to the right, then left, respectively. These procedures were not followed for the study so that all surfactants would be administered similarly.

Reviewer's Comment: ***Only one study has compared different surfactant dosing procedures, using Survanta, and demonstrated no differences in 72-hour outcomes with the different procedures.[11] Exosurf has not been so studied nor have longer term outcomes, but the likelihood is that the change in Exosurf administration used in this study would not significantly influence the results.***

10.1.1.5.4 Retreatments [M5, v 1.2, sec 5.3.5.1, p 481,484]

Patients could receive additional doses of the assigned surfactant if they met protocol-specified criteria, which were intended to restrict retreatment to patients with disease of certain severity. Patients assigned to Surfaxin or Survanta could receive up to three additional doses (four total) at minimum 6-hour intervals. Owing to the different labeling for Exosurf, patients assigned to

receive that product could receive no more than two additional doses (three total) at minimum 12-hour intervals. Because of the different treatment intervals for the products, to maintain the study blind all patients were to be evaluated for retreatment at fixed intervals: 6 ± 0.5, 12 ± 0.5, 18 ± 0.5, and 24 ± 0.5 hours after the first treatment.

The criteria to receive retreatment, regardless of surfactant, were

- the patient is still intubated;
- at least 6 hours have passed since the previous Surfaxin/Survanta dose or at least 12 hours have passed since the previous Exosurf dose; and
- the patient continues to require mechanical ventilation with a mean airway pressure of ≥ 6 cm H_2O and $FiO_2 \geq 0.30$ to maintain a PaO_2 between 50 and 80 mm Hg or an oxygen saturation (measured by pulse oximetry) between 88 and 95% and a chest radiograph consistent with RDS.

Because patients assigned to Exosurf were not allowed to receive doses at less than 12 hour intervals, if they met retreatment criteria before the necessary elapsed time they received a "sham" treatment in which all procedures were followed as described in section 10.1.1.5.3 above, but air was injected into the ETT instead of surfactant.

As a consequence of the various requirements, several possibilities existed at each retreatment time point, as summarized in Table 2. For Surfaxin and Survanta, evaluation of retreatment at each time point was independent of the previous time point; that is, a patient might not qualify for retreatment at one time but qualify at the next time. For Exosurf, the retreatment actions at the 18 ± 0.5 and 24 ± 0.5 hour time points were dependent on previous actions. As the last column in the Table indicates, according to this schema patients could receive varying numbers of doses of each surfactant.

Table 46: Retreatment Schema: KL4-IRDS-06

Dose Number	Time Point After First Dose	Drug	Action	Cumulative Doses
2	**6 ± 0.5 h**	Surfaxin/Survanta	▪ Retreat if criteria met ▪ No action if criteria not met	1 or 2
		Exosurf	▪ Sham treatment if criteria met ▪ No action if criteria not met	1
3	**12 ± 0.5 h**	Surfaxin/Survanta	▪ Retreat if criteria met ▪ No action if criteria not met	1, 2, or 3
		Exosurf	▪ Retreat if criteria met ▪ No action if criteria not met	1 or 2
4	**18 ± 0.5 h**	Surfaxin/Survanta	▪ Retreat if criteria met ▪ No action if criteria not met	1, 2, 3, or 4
		Exosurf	▪ Sham if criteria met and dose given at 12 h ▪ Retreat if criteria met and no dose given at 12 h ▪ No action if criteria not met	1, 2, or 3
5	**24 ± 0.5 h**	Surfaxin/Survanta	▪ Sham if criteria met and 4 previous doses given ▪ Retreat if criteria met and < 4 previous doses given	1, 2, 3, or 4

Dose Number	Time Point After First Dose	Drug	Action	Cumulative Doses
			▪ No action if criteria not met	
		Exosurf	▪ Sham if criteria met and 18 h dose given ▪ Retreat if criteria met and no dose since initial or 12 h ▪ No action if criteria not met	1, 2, or 3
Source: M5, v 1.1, sec 5.3.5.1, p 30				

For any treatment, initial or retreatment, the protocol prominently provided the following advice for post-dosing management of the patients.

> **"Ventilator settings need to be closely monitored and adjustments in the ventilator pressure, FiO_2, and rates need to be made in response to the beneficial effects of the treatment in order to maintain arterial blood gases with PaO_2 of 50 to 65 mm Hg or oxygen saturation between 88 and 95% and $PaCO_2$ of 45 to 55 mm Hg. To attain these goals, the peak inspiratory pressure (PIP) should be decreased initially, with subsequent adjustments to include a reduction in FiO_2, ventilator rate, inspiratory time, and positive end expiratory pressure (PEEP). Chest expansion should be monitored carefully."** *[M5, v 1.2, sec 5.3.5.1, p 485]*

10.1.1.6 Study procedures

A previous, small, single-center study had tested the logistics and feasibility of procedures used in this study (section 6.1.3.1.3 above). The study protocol contained detailed instructions for many procedures, but the study report does not mention any specific training or preparation of study personnel.

10.1.1.6.1 Randomization and masking

These procedures were integrally related to study treatments and are described in that section. The protocol provides for breaking of the blind if "specific urgent treatment would be dictated by knowing the treatment status of the patient". In that case, the investigator would contact the study monitor or could open the sealed randomization envelope in the event the monitor was not available. Breaking of the blind was required to be reported.

10.1.1.6.2 Study discontinuation

Patients could discontinue from the study at any time by voluntary withdrawal of the parent or guardian. An investigator could withdraw a patient at any time if he/she believed it in the best medical interest of the patient.

The protocol describes several circumstances whereby the study could be terminated:

- The local health authority requests it
- A determination is made by an independent Data Safety Monitoring Board that the risk level of the drug is significant
- The Sponsor may terminate the study for reasons other than safety by written 30-day notice of intended termination

- The clinical investigator or IRB may terminate participation for reasons other than safety by written 30-day notice
- Abrogation of any clause in the Clinical Study Agreement

10.1.1.6.3 Concomitant medications

Concomitant medications are not described or discussed in the original protocol except in a list of variables to be analyzed.

10.1.1.6.4 Study assessments and evaluations

The study was organized in five phases: Screening, Treatment, Retreatment, Post-dosing, and Follow-up. The Post-dosing phase had several key time points for assessments: 28 days of age, 36 weeks PCA, hospital discharge, and death if it occurred. Follow-up evaluations were to be at 6 and 12 months. The assessments and procedures to be performed during these phases and at the specified time points are shown in the Table. Descriptions of the assessments and procedures follow the Table.

Table 47: Study Assessments: KL4-IRDS-06

	Screening	Treatment	Retreatment	Post-Dosing Phase				Follow-up Phase	
				Post-dosing[a]	28 Days of Age	36 weeks PCA	Discharge	6 months	12 months
Maternal & birth history	X								
Entry criteria	X								
Dosing assessments[b]		X	X						
Vital signs		X	X						
Length, weight, head circumference	X				X (collected at whichever came first)	X	X		X
Physical Exam	X				X (collected at whichever came first)	X	X		X
Arterial blood gases		X	X	X	X	X	X		
Ventilator settings		X	X	X	X	X	X		
Supplemental oxygen				X	X	X	X	X	X
Chest x-ray		X	X	X					
Adverse experiences		X	X	X	X	X	X	X	X
Concomitant meds		X	X	X	X	X	X	X	X
Overall patient status						X	X		
Assessment of respiratory illnesses								X	X
Hospitalizations/death								X	X

[a]Post-dosing time points began after initiation of Dose 1 and did not change with subsequent doses
[b]Dosing assessments included heart, rate, oxygen saturation, blood pressure, and negative reactions to dose administration
Source: M5, v 1.1, sec 5.3.5.1, p 26

Screening Phase

▪ Maternal and birth history variables included:

Maternal age	Mode of delivery, date and time of birth
Gravidity and parity	Single or multiple birth
Antenatal steroid treatment	Sex
Labor history	Ethnicity (white, black, other)
Tocolytic therapy	Birth weight (grams)
Pregnancy-induced hypertension	Head circumference (cm)
Gestational diabetes	Length (cm)
Ruptured amniotic membranes	Apgar score (1, 5, 10 minutes)
Chorioamnionitis	Congenital anomaly
Oligohydramnios > 21 days	Gestational age, by Ballard method
Date of last menstrual period	

Treatment Phase

For purposes of timing the assessments, "Time 0" occured at the initiation of the first quarter-dose of the first dose.

▪ Dosing Assessments. For each dose, assessments included lowest heart rate, lowest SaO_2 (obtained from pulse oximetry), blood pressure (systolic, diastolic, mean) after completion of dosing, and the occurrence of specified negative dose-related events (**obstruction of ETT, ETT reflux, pallor, or interruption of drug administration**).

▪ Vital signs were recorded at 2 and 6 hours post-Time 0. They included SaO_2, heart rate, spontaneous respirations if off mechanical ventilation, and blood pressure (systolic, diastolic, mean).

▪ Arterial blood gases were recorded at 2, 6, and 24±8 hours post-Time 0 and included pH, PaO_2, and $PaCO_2$, and HCO_3. Only one gas was required during the 24±8 hour interval.

▪ Ventilator settings were recorded concurrently with obtaining arterial blood gases and included FiO_2, set positive end expiratory pressure (PEEP), mean airway pressure (MAP), peak inspiratory pressure (PIP), set ventilator rate, mode (IMV, patient-triggered), inspiratory time, and expiratory time.

▪ Chest x-ray was to be obtained within a 24±8 hour period post-Time 0.

Retreatment Phase

The protocol stipulates that patients enrolled and treated initially will continue to receive repeat doses if they meet retreatment criteria, even if exclusion criteria are found to be true (except in the cases of withdrawal of parental permission or if the treating physician believes treatment would be harmful). In the Retreatment Phase, recording of the Dosing Assessments, Vital signs, Arterial blood gases, and Ventilator settings are identical with those in the Treatment Phase.

▪ Chest x-ray was obtained at 24±8 hours post-Time 0 and then daily through Day 7 if on mechanical ventilation. The daily chest x-ray is not required if the patient is off mechanical ventilation, but is required on Day 7.

Post-dosing Phase

▪ Arterial blood gases were recorded daily as long as the patient required mechanical ventilation or until death, 36 weeks PCA, or discharge, whichever came first. The blood gas closest in time to 8 a.m. each day was used for analyses. If an arterial line was not available, SaO_2 was recorded.

▪ Ventilator settings were recorded daily as long as the patient required mechanical ventilation or until death, 36 weeks PCA, or discharge, whichever came first.

▪ Supplemental oxygen was recorded three times daily (00:00, 08:00, 16:00 hours) until the patient was off oxygen, death, 36 weeks PCA, or hospital discharge, whichever came first. Oxygen delivery mode, FiO_2, flow rate, and SaO_2 were recorded.

▪ Adverse experiences and Concomitant medications were to be recorded through 36 weeks PCA. If a patient was discharged before that time, the treating physician or guardian were to be contacted to obtain the information.

▪ Overall patient status was recorded at 36 weeks PCA. It included:

- worst stage retinopathy of prematurity and any therapies
- worst grade IVH
- presence of cystic periventricular leukomalacia
- presence of patent ductus arteriosus and any treatments
- presence of necrotizing enterocolitis and any treatments
- occurrence of air leaks
- occurrence of pulmonary hemorrhage
- occurrence of acquired sepsis
- occurrence of apnea
- continuation of supplemental oxygen or date of discontinuance
- date of hospital discharge
- date, time, and cause of death

Follow-up Phase

▪ 6-month Follow-up. The patient's guardian was to be contacted to determine the following:

- mode of oxygen delivery, set FiO_2, flow rate if the patient is receiving oxygen
- number of respiratory illnesses since discharge from the birth hospitalization
- characterizations of the child's respiratory illnesses (wheezing, cough, pneumonia, etc)
- respiratory medications the child has needed since birth hospitalization
- number of hospitalizations since discharge from the birth hospitalization
- death
- adverse experiences, new and follow-up

▪ 12-month Follow-up. The patient was to return to the clinic or physician office for the following assessments:

- mode of oxygen delivery, set FiO_2, flow rate if the patient is receiving oxygen
- number of respiratory illnesses since discharge from the birth hospitalization
- characterizations of the child's respiratory illnesses (wheezing, cough, pneumonia, etc)
- respiratory medications the child has needed since birth hospitalization

- number of hospitalizations since discharge from the birth hospitalization
- death
- adverse experiences, new and follow-up
- weight, length, head circumference
- physical exam including neurologic

10.1.1.7 Efficacy parameters [M5, v 1.2, sec 5.3.5.1, p 499]

The study, as amended (See section 10.1.2.3), had co-primary efficacy variables: incidence of RDS at 24 hours and incidence of RDS-related mortality at 14 days. Both were based on findings of an Adjudication Committee.

10.1.1.7.1 Adjudication Committee [M5, v 1.2, sec 5.3.5.1, p 505; M5, v 1.39, sec 5.3.5.1, p12667]

The Adjudication Committee (AC) was established by the Applicant to obtain independent evaluation of several key study endpoints and to standardize the quality and consistency of endpoint classifications.

A Standard Operating Procedures Manual for the Committee was issued in April, 2002. The Manual stated that the committee would be comprised of seven members who were neonatologists or pediatric radiologists. They could not be investigators or sub-investigators in the study and had to declare in writing that there was no conflict of interest with the Sponsor. The members were reimbursed for their expenses in performance of their duties and received "reasonable" remuneration for the time.

All AC members were voting members. They appointed a Chair. The AC met throughout the course of the study, generally on a monthly basis. More frequent meetings could occur at the instigation of the members or the Sponsor. Endpoint data were reviewed on an ongoing basis. AC members were blind to study treatments. Adjudication data packages (ADP) were prepared by the Sponsor for AC members, with treatment-revealing information removed. The information that was provided included copies of CRFs containing the relevant endpoint data, digital copies of x-rays stored on CD-R media, serious AEs reports, and autopsy reports if available. The packages also included a ballot by which AC members reported their assessments.

Procedures for the AC pertaining to specific endpoints will be discussed with each endpoint below. General procedures were as follows. Two members reviewed each ADP and independently cast their votes on the endpoint under consideration by completing and signing the ballot. The endpoint would be considered adjudicated if both members agreed. If there was disagreement on the RDS or air leak endpoints, the pediatric radiologist adjudicated independently as a tie-breaker. If there was disagreement on the mortality endpoints, the endpoint was adjudicated by "peer consultation". At the beginning of the process, committee members reviewed a series of chest x-rays to agree on rules of interpretation that would be used throughout the process.

10.1.1.7.2 Primary efficacy variables

10.1.1.7.2.1 Incidence of RDS at 24 hours

Reviewer's Comment: ***As detailed later, the criteria for RDS changed during the course of the study. This section reflects the original definition and rules as stated in the first protocol. The changes made through amendments are detailed in section 10.1.2.***

This endpoint was time-specific and based on chest x-ray and FiO_2 data. RDS was defined as requiring FiO_2 plus the demonstration of a reticulogranular pattern consistent with RDS on a chest x-ray obtained between 16 and 32 hours of age. The Table summarizes the criteria.

Table 48: Definition of RDS: KL4-IRDS-06

Diagnosis	Chest x-ray at 24±8 hrs	FiO_2 at 24±8 hrs
RDS	Positive changes	≥ 30% on mechanical ventilation at 24±8 hrs
No RDS	Positive or indeterminate	< 30% on or off mechanical ventilation
	If no chest x-ray at 24±8 hrs	FiO_2 after 24±8 hrs was < 30% on or off mechanical ventilation
Source: M5, v 1.2, sec 5.3.5.1, p 499		

Rules that applied to this endpoint were:

- Patients with a chest x-ray positive for RDS before 16 hours and a repeat positive chest x-ray after 32 hours and an FiO_2 > 30% before 16 hours and a repeat FiO_2 > 30% after 32 hours were to be counted as having RDS. All other patients outside the time windows in the table were to be counted as not having RDS.
- Patients who died before 32 hours and whose death was due to RDS were to be counted as having RDS. Patients whose death was due to other causes were not be counted as having RDS.

  Reviewer's Comment: ***The second instance was changed in the AC SOP Manual to state that patients whose death was due to another cause but had evidence of RDS would be counted as having RDS. Patients whose death was due to another cause and had no evidence of RDS would not be counted as having RDS.***
- Patients lost to follow-up before 32 hours without the requisite data were to be counted as having RDS.
- Patients whose RDS diagnosis is missing were to be counted as having RDS.

  Reviewer's Comment: ***All the time windows indicated here are those stated in the original study protocol. The AC SOP Manual and protocol amendment changed them to a 24±4 hour window.***

To adjudicate the incidence of RDS at 24 hours, AC members first reviewed the appropriate time-specific chest x-ray obtained according to the rules above. Then members reviewed the CRF page that contained the appropriate FiO_2 data to establish the definition of RDS.

10.1.1.7.2.2 Incidence of RDS-related mortality at 14 days [M5, v 1.39, sec 5.3.5.1, p 12672]

The cause of death was adjudicated by the AC and the results were used in the analyses of this endpoint. AC members reviewed all chest x-rays and CRF ventilator setting data for all patients who died through day 14. Serious AE reports and available autopsy reports were also reviewed. The following rules applied to this endpoint:

- A patient who died as a result of pulmonary hemorrhage was to be classified as an RDS-related death, if the patient had RDS that had not resolved before the hemorrhage. The diagnosis of RDS could occur at any time before death and did not have to meet the 24±8 hour definition.
- In the case of intracranial hemorrhage, death was to be classified as RDS-related if the RDS was clinically significant enough that it was likely to have contributed to the hemorrhage. The diagnosis of RDS could occur at any time before death and did not have to meet the 24±8 hour definition.
- Sepsis could be diagnosed based on substantial clinical evidence of infection even in the absence of positive blood cultures. Positive blood cultures could be considered contaminated if the organism was one not commonly associated with early onset sepsis and there was no clinical or other laboratory evidence of sepsis.
- Patients lost to follow-up before and including Day 14 were to be counted as having died due to RDS.
- Patients whose data were missing were to be counted as having died due to RDS.

10.1.1.7.3 Secondary efficacy variables

10.1.1.7.3.1 All-cause mortality

All-cause mortality was analyzed for each of the study assessment time points described in section 10.1.1.6.4 above. Patients who were lost to follow-up prior to the data time point were to be counted as having died. Patients whose data were missing were to be counted as having died.

10.1.1.7.3.2 Air leaks [M5, v 1.39, sec 5.3.5.1, p 12673]

Air leak was originally a component of the co-primary endpoint, but was relegated to a secondary endpoint when the primary endpoints were changed (see section 10.1.2.3 below). The presence of pulmonary air leak through 7 days of age was adjudicated by the AC for purposes of efficacy analyses, but the events were also reported by the clinical investigators. For the AC, pulmonary air leak was defined as chest radiographic evidence of air leak (pneumothorax, pulmonary interstitial emphysema (PIE), pneumomediastinum, subcutaneous emphysema) resulting from lung parenchymal disease. AC members reviewed all chest x-rays available through Day 8 to determine the presence or absence of air leak. Rules for adjudicating this endpoint were

- Patients who died due to RDS or other respiratory causes prior to and including 7 days of age were to be counted as having air leaks. Patients who died prior to and including 7 days of age without evidence of air leak due to other causes were to be counted as not having air leak.
- Patients who were lost to follow-up prior to and including 7 days of age were to be counted as having air leak.

- Patients whose data were missing were to be counted as having air leak.

10.1.1.7.3.3 Composite endpoints

There were several composite endpoints using those previously described: RDS-related mortality or air leak, RDS-related mortality and air leak, incidence of RDS and RDS-related mortality, incidence of RDS and RDS- related mortality and air leak.

10.1.1.7.3.4 Severity of RDS

The determination of this endpoint was based on "longitudinal assessment of FiO_2 and MAP through 72 hours of age," not otherwise specified in the study protocol.

10.1.1.7.3.5 Number of surfactant doses

The total number of doses of each of the surfactants administered was to be compared.

10.1.1.7.3.6 Bronchopulmonary dysplasia [M5, v 1.2, sec 5.3.5.1, p 501]

Bronchopulmonary dysplasia was defined as the continuing need for supplemental oxygen (with the exception of infants who required supplemental oxygen only during feedings) at two time points: 28 days of age and 36 weeks PCA. Patients who died due to RDS or other respiratory causes were to be counted as having BPD. Patients who died due to other causes were to be counted as not having BPD. Patients who were lost to follow-up prior to 28 days or 36 weeks PCA were to be counted as having BPD. Patients whose data were missing were to be counted as having BPD.

Reviewer's Comment: ***The definition of BPD used in the study was not ideal. The current standard is to not consider BPD to be present until 36 weeks PCA. Oxygen requirement earlier than that probably often represents lingering effects of prematurity rather than chronic lung injury. In addition, basing the diagnosis on oxygen use alone is probably unreliable considering the variability in clinical practices. Requiring radiographic changes and/or some demonstration of a "physiologic" need for oxygen are the more widely accepted criteria.***

10.1.1.7.3.7 Days on mechanical ventilation through 36 weeks PCA [M5, v 1.2, sec 5.3.5.1, p 501]

Rules governing determination of this endpoint were that if a patient died or was lost to follow-up, the last known status for mechanical ventilation would be carried forward to the end of 36 weeks PCA; if a patient was reintubated for respiratory reasons after being off mechanical ventilation for ≥ 24 hours, only those days of mechanical ventilation would be counted; if a patient was reintubated for non-respiratory reasons after being off mechanical ventilation ≥ 24 hours, the patient would be considered off mechanical ventilation.

10.1.1.7.3.8 Duration of supplemental oxygen through 36 weeks PCA [M5, v 1.2, sec 5.3.5.1, p 502]

The total number of days alive and on supplemental oxygen through 36 weeks PCA was determined using the following rules: if a patient died or was lost to follow-up, the last known status for oxygen therapy would be carried forward to the end of 36 weeks PCA; if a patient was returned to oxygen therapy for respiratory reasons after being off oxygen for ≥ 24 hours, only those days of oxygen therapy would be counted; if a patient was returned to oxygen therapy for non-respiratory reasons after being off oxygen ≥ 24 hours, the patient would be considered off oxygen therapy.

Reviewer's Comment: ***For purposes of the two previous endpoints, the protocol does not define a "day"; i.e., whether the therapy was required for 24 hours entire or some portion of it.***

10.1.1.7.3.9 Duration of hospitalization through 36 weeks PCA [M5, v 1.2, sec 5.3.5.1, p 502]

If a patient died or was lost to follow-up, the patient was to be counted as being hospitalized through Day 28 or 36 weeks PCA, whichever came later.

10.1.1.8 Efficacy/safety parameters

In RDS and the population of this study, some endpoints cannot be clearly demarcated as indicators of efficacy or safety. Their occurrence is influenced by the effect of surfactant on lung function, however, they also may reflect events that have adverse consequences on the patient's well-being. Because they do not fall easily into a pure efficacy or safety category, those events are described separately in this section.

10.1.1.8.1 Concurrent diagnoses

The following conditions, with their protocol definitions, are known to occur in premature neonates with or without RDS. Their occurrence may be influenced by the presence of RDS and its severity.

10.1.1.8.1.1 Intraventricular hemorrhage (IVH)

Detected by cranial ultrasound and graded I-IV according to protocol. Cranial ultrasounds were not required by the protocol because study centers were required to have procedures in place to perform ultrasounds on every patient. The day of life on which an ultrasound were performed could vary, however.

10.1.1.8.1.2 Necrotizing enterocolitis (NEC)

Staged according to protocol as Stage I, IIA, IIB, IIIA, or IIIB.

10.1.1.8.1.3 Periventricular leukomalacia (PVL)

The presence of one or more echolucent cysts in and around the cerebral ventricles on cranial ultrasound

10.1.1.8.1.4 Apnea

No definition provided

10.1.1.8.1.5 Patent ductus arteriosus (PDA)

No definition provided

10.1.1.8.1.6 Retinopathy of prematurity (ROP)

Graded according to protocol in Stages I-IV

10.1.1.8.1.7 Pulmonary hemorrhage

The presence of bright red blood in a tracheal aspirate deemed not to be the result of tracheal trauma, associated with clinical deterioration and x-ray changes

10.1.1.8.2 Follow-up evaluations [M5, v 1.2, sec 5.3.5.1, p 502]

10.1.1.8.2.1 6-month follow-up

The assessments at this evaluation included need for oxygen, number of respiratory illnesses, character of respiratory illnesses, respiratory medications, number of hospitalizations, and survival.

10.1.1.8.2.2 12-month follow-up

The assessments at this evaluation included need for oxygen, number of respiratory illnesses, character of respiratory illnesses, respiratory medications, number of hospitalizations, weight, length, head circumference, neurologic examination, and survival.

10.1.1.9 Safety evaluations [M5, v 1.1, sec 5.3.5.1, p 34-5]

The following categories of endpoints were characterized by the Applicant as specific to evaluation of the safety of Surfaxin.

Reviewer's Comment: ***It should be noted that arterial blood gases, chest x-rays, and ventilator settings could be considered, and have been by other surfactant product applicants and sponsors, as measures of effectiveness rather than safety.***

10.1.1.9.1 Adverse experiences

Definitions, reporting requirements, and relationship to study therapy were all adequately defined in the study protocol. The original term used in the CRF report of the investigator was coded to preferred terms using the MedDRA dictionary.

10.1.1.9.2 Negative reactions to dose administration

These were treated as a separate category of "adverse experiences" specific to the dosing procedure and were defined as: obstruction of the ETT, ETT reflux, pallor, apnea, and interruption of dose administration.

10.1.1.9.3 Concomitant medication use

Concomitant medications were to be recorded from the time of first dose administration through 36 weeks PCA or premature study termination; however, the date and time of concomitant medication use were not recorded, only the use per se.

10.1.1.9.4 Arterial blood gases

The protocol defined this category to include pH, PaO_2, and $PaCO_2$, and HCO_3. They were collected 2 and 6 hours after completing doses 1-5 if an arterial line was present, and at 24±4 hours after Time 0. They were also collected daily through Day 7 if an arterial line was present and the patient was on mechanical ventilation. SaO_2 was collected if an arterial line was not present.

10.1.1.9.5 Ventilator settings

This category was comprised of FiO_2, set positive end expiratory pressure (PEEP), mean airway pressure (MAP), peak inspiratory pressure (PIP), set ventilator rate, mode (IMV, patient-triggered), inspiratory time, and expiratory time. The values were recorded simultaneously with collected arterial blood gases.

10.1.1.9.6 Chest x-rays

Chest x-rays were obtained as needed for retreatments and at 24±4 hours after Time 0. They were also obtained daily through Day 7 if the patient was on mechanical ventilation, and at Day 7 regardless.

10.1.1.9.7 Vital signs

Vital signs included SaO_2, heart rate, spontaneous respirations if off mechanical ventilation, and blood pressure (systolic, diastolic, mean). They were collected 2 and 6 hours after completing Doses 1-5.

10.1.1.9.8 Physical examination

Results of the physical examination were recorded on the day of discharge, Day 28, or 36 weeks PCA, whichever came first.

10.1.1.10 Statistical plan [M5, v 1.2, sec 5.3.5.1, p 496 ff]

10.1.1.10.1 Randomization

Randomization was previously described in section 10.1.1.5.1 above.

10.1.1.10.2 Sample size

This study was designed to be event-driven. The sample size estimate was based on data from a published study comparing Exosurf to Infasurf, an approved bovine-derived surfactant.[2] The rates of relevant events in that study, from which estimates were made for the present study, were:

Table 49: Published Event Rates

	Infasurf	Exosurf
Incidence of RDS at 24 hrs	15%	47%
Incidence of air leaks	10%	15%
RDS-related death at 14 days	2%	5%
Source: M5, v 1.1, sec 5.3.5.1, p 42		

The Applicant estimated the anticipated rates for these events in its study and then calculated sample size estimates as described in the next Table.

Table 50: Sample Size Estimates: KL4-IRDS-06

	Surfaxin	Exosurf	Sample Size Calculations
Estimated incidence of RDS	30%	40%	Two-sided, α=0.05 Power ≈ 94%

	Surfaxin	Exosurf	Sample Size Calculations
Estimated RDS-related deaths or air leaks through 7 days[a]	10%	17%	**N = 600/group** **# of events = 420 (30% of 600 Surfaxin + 40% of 600 Exosurf)** Two-sided, α=0.05 Power ≈ 93% **N = 600/group** **# of events = 162 (10% of 600 Surfaxin + 17% of 600 Exosurf)**

[a] Note: In the protocol, the co-primary endpoint was RDS-death through 14 days or air leaks through 7 days.
Source: M5, v 1.2, sec 5.3.5.1, p 498

According to the event-driven design, therefore, the study would continue until 420 RDS events and 162 RDS-death or air leak events occurred. It was estimated these numbers of events would require 600 patients in each treatment group.

10.1.1.10.3 Analytical plan

According to the protocol, the primary analyses would be intent-to-treat, using data from all randomized patients. All tests would use two-sided testing at the 0.05 level of significance. No p-value adjustment was planned for multiple comparisons between any two of the three treatment arms.

Statistical models were to include terms for surfactant treatment, birth weight, study center, and terms for the interaction of surfactant treatment with birth weight and center, as well as terms for other baseline variables that might be found to be significantly different between treatment groups. Data from centers with fewer than 10 patients in either treatment group would be combined and analyzed as a single site.

The plan was to compare groups using the two-tailed Student's t-test (normal distributions) or the Wilcoxon rank sum test (non-normal distributions) for continuous variables and the Chi-square, Fisher's exact, or Mantel-Haenszel tests for categorical variables. The point estimate of relative risk ratios (Surfaxin:Exosurf) and the 95% confidence intervals would be calculated.

Secondary analyses of outcome measures of efficacy would be performed for infants who received an initial study treatment.

The last value carried forward method was to be used for missing values.

10.1.1.10.4 Data Safety Monitoring Board (DSMB)[M5, v 1.2, sec 5.3.5.1, p 504]

The protocol called for creation of an independent Data Safety Monitoring Board consisting of one statistician and two to three clinicians to evaluate the safety and conduct of the study. A standard operating procedure manual was to be issued. The DSMB would have the authority to recommend halting the study for reasons of safety or overwhelming efficacy. The DSMB would also inform the Sponsor when the required number of primary events had occurred.
Reviewer's Comment: ***Although the DSMB was to monitor the safety and progress of the study, neither the protocol nor statistical and analytical plan mention or describe "interim***

analyses" per se. Two such analyses are in fact provided, however, in the study report (See section 10.1.3.5.1.4 below).

10.1.2 Changes to the Protocol or Plan

The original protocol was issued on May 9, 2001, and was subsequently amended three times. All amendments occurred after the study had begun.

10.1.2.1 Amendment #1 [M5, v 1.1, sec 5.3.5.1, p 41]

The first amendment was enacted on October 10, 2001, and affected several important elements of study design:

- narrowed the window for administering the first dose of surfactant from within 30 minutes of birth to 15-30 minutes
- added acquired sepsis to the list of concurrent conditions (10.1.1.8.1 Concurrent diagnoses)
- increased the number of study sites
- removed suspected maternal chorioamnionitis as an exclusion criterion
- changed the exclusion criterion for duration of ruptured membranes from > 5 days to > 2 weeks
- added a new exclusion criterion of neonates who require chest compression, epinephrine, bicarbonate, or fluid bolus in the delivery room for resuscitation
- altered the position of neonates for surfactant dosing to ensure delivery of surfactant to the dependent lung and to reduce the risk of reflux
- added guidelines for ventilator management in a protocol appendix to try to standardize ventilator management across study centers
- made the timing of arterial blood gases, ventilator settings and vital signs consistent for all doses; i.e., specified time after completion of dosing rather than after Time 0
- narrowed the time window for assessment of RDS from 24±8 hours to 24±4 hours
- allowed the DSMB to recommend a sample size recalculation in order to maintain study power
- specified that data provided to the DSMB should be initially masked to treatment
- added peripheral oxygen saturation values to the definition of BPD
- standardized the definitions of "off mechanical ventilation" and "off supplemental oxygen" to not requiring the modality for ≥ 24 hours
- specified that the 6- and 12-month follow-up evaluations were to be performed according to corrected age, not chronological age
- modified a part of the definition of RDS to specify that patients who died before 28 hours from non-RDS causes but who have RDS will be considered to have had RDS
- a section was added to Statistical Analyses to state that the database would be locked down in the same two phases of the study design: after the first short-term phase through 36 weeks PCA and again after completion of the follow-up phase.
- analysis of Survanta data was specified as comparisons only to Exosurf as reference, not to Surfaxin

10.1.2.2 Amendment #2 [M5, v 1.2, sec 5.3.5.1, p 41]

Fewer changes were made with Amendment #2 enacted on November 29, 2001.

- amplified the information collected when patients stopped or re-started supplemental oxygen
- specified information to be collected at follow-ups: only pulmonary information at 6-months; time intervals for intercurrent events; and specific elements of neurologic assessment at 12-months (tone and reflexes, hydrocephalus, cerebral palsy, deafness, blindness, gross motor delay, seizures)
- again altered the definition of RDS as follows

Table 51: Definition of RDS - Revised (KL4-IRDS-06)

Diagnosis	Chest x-ray at 24±4 hrs	FiO_2 at 24±4 hrs
RDS	Positive changes	≥ 30% at 24±4 hrs
No RDS	Positive or indeterminate If no chest x-ray at 24±4 hrs	FiO_2 < 30% prior to or after 24±4 hours
Patients with a chest x-ray positive for RDS between 16 and 20 hours and a repeat positive chest x-ray between 28 and 32 hours and an FiO_2 > 30% at the time of these x-rays were to be counted as having RDS. All other patients outside the time windows in the table were to be counted as not having RDS. **Source: M5, v 1.1, sec 5.3.5.1, p 247**		

- provided definitions of respiratory and non-respiratory reasons for requiring oxygen
- clarified that severity of RDS would be assessed using FiO_2 and MAP between 1 and 72 hours of age
- changed the membership of the AC from 4-6 to 6-10 members
- added collection of arterial blood gases at 24±4 hours post Time 0

10.1.2.3 Amendment #3 [M5, v 1.2, sec 5.3.5.1, p 42]

The final protocol amendment was enacted on November 10, 2003.

Reviewer's Comment: ***Even though this amendment occurred near the end of the study, the changes were agreed to by the Division in a facsimile correspondence of November 14, 2003.***

- the primary efficacy endpoint of the study was changed from "incidence of RDS at 24 hours, and RDS-related mortality through 14 days of age and/or air-leak through 7 days of age, or either of the two components alone" to "incidence of RDS at 24 hours, and RDS-related mortality through 14 days of age"
- restated the sample size estimation to be consistent with the amended efficacy endpoint and recalculated the number of required RDS-death events:

Table 52: Sample Size Estimates – Revised: KL4-IRDS-06

	Surfaxin	Exosurf	Sample Size Calculations
Estimated incidence of RDS	30%	40%	Two-sided, α=0.05 Power ≈ 94% **N = 600/group** **# of events = 420 (30% of 600 Surfaxin + 40% of 600 Exosurf)**

	Surfaxin	Exosurf	Sample Size Calculations
Estimated RDS-related deaths through 14 days	3.5%	7.5%	Two-sided, α=0.05 Power ≈ 83% **N = 600/group** **# of events = 66 (3.5% of 600 Surfaxin + 7.5% of 600 Exosurf)**
Source: M5, v 1.1, sec 5.3.5.1, p 43			

- added composite endpoints of RDS-mortality, air leaks, and incidence of RDS as secondary endpoints

10.1.3 Results

Patients were enrolled in the study from July 2, 2001, until September 29, 2003, at 49 study centers in Ecuador, Chile, Russia, Uruguay, Panama, Mexico, Brazil, Hungary, and Poland. Enrollment was stopped when the DSMB notified the Applicant that the required number of events had occurred. Five centers which had IRB approval and were approved by the Sponsor never enrolled any patients.

10.1.3.1 Study patients

At completion of the study, 1294 patients had been randomized. Across the centers, the number of patients randomized ranged from 119 patients at one Polish center to three patients at each of two centers. The disposition of the randomized patients through completion of the early stage of the study (i.e., not including 6- and 12-month follow-ups) is summarized in Table 53. "Completed" patients were those who were evaluated at 28 days of age, 36 weeks PCA, discharge, or death, whichever came latest.

Table 53: Patient Disposition: KL4-IRDS-06

Disposition	Surfaxin N (%)	Exosurf N (%)	Survanta N (%)	Total
Randomized	527	509	258	1294
Treated	524 (99.4)	506 (99.4)	258 (100)	1288 (99.5)
Discontinued due to:				
Death	111 (21.1)	121 (23.8)	68 (26.4)	300 (23.2)
AE	3 (0.6)	3 (0.6)	1 (0.4)	7 (0.5)
Completed	522 (99.1)	505 (99.2)	258 (100)	1285 (99.3)
Source: M5, v 1.1, sec 5.3.5.1, p 45				

Reviewer's Comment: ***Table 53 reproduces the Applicant's table and indicates that patients were discontinued due to AEs in each treatment group. This is in fact not true. The patients in the table represent patients for whom one or more doses was discontinued because of an AE. There were no patients in this study who discontinued because of AEs. See section 10.1.3.6.2.2 below.***

The six patients who were randomized but not treated, and the reasons, were:

- Surfaxin

◦ Patient 052001 had a 5-minute APGAR of 3, which was recognized after randomization as an exclusion criterion, so the patient was not treated.
◦ Patient 081007 was not treated when it was discovered that the study drug refrigerator temperature had not been properly maintained.
◦Patient 312001 was not intubated, which was required for study drug delivery.

- Exosurf
  ◦ Patient 023008 was mistakenly randomized despite an exclusion criterion.
  ◦ Patient 732005 experienced problems with intubation and could not be treated.
  ◦ Patient 781002 developed a pulmonary hemorrhage at 28 minutes after birth and died shortly thereafter.

Under the intent-to-treat plan, all six patients were included in efficacy analyses, despite not receiving treatment. They were not included in the safety analyses, however, which were confined to patients who actually received treatment.

Patients who died will be considered in the appropriate sections of this review.

10.1.3.2 Protocol deviations

The Table below shows the number of patients in each treatment group who represented deviations from protocol-specified entry criteria.

Table 54: Protocol Deviations: KL4-IRDS-06

Deviation	Surfaxin (N)	Exosurf (N)	Survanta (N)
Birth weight not 600-1250 g	0	0	1
Not intubated successfully within 30 mins	6	1	1
5-minute APGAR ≤ 3	2	0	1
Major congenital malformation	0	3	0
Disease interfering with cardiopulmonary function	0	0	1
Mother with rupture of membranes > 2 wks	1	0	1
Gestational age > 32 wks	0	1	0
Delivery room resuscitation	1	0	0
Incorrect surfactant given	0	0	1 (Exosurf)

Source: M5, v 1.1, sec 5.3.5.1, p 46

The preponderance of Surfaxin patients among those who were not successfully intubated within 30 minutes is apparent, but nothing in the data listings reveals an obvious reason; for example, only one of the patients was < 1000 g birth weight, which could make intubation more difficult. There were too few patients who deviated from any other single criterion to reasonably affect efficacy results.

10.1.3.3 Data sets analyzed

All randomized patients were analyzed for efficacy as intention-to-treat. The study protocol indicated that a "per protocol" subset population who received at least one dose of surfactant

would also be analyzed, but this analysis was not carried out. No reason was given in the study report. Safety analyses included only the patients who received a treatment.

10.1.3.4 Demographic and baseline characteristics

Patients were stratified by birth weight, an important prognostic factor in neonatal RDS. The next Table shows the birth weights (i.e., pre-randomization weights) in the three treatment groups, along with several other factors that might influence outcomes. There were no differences between the Surfaxin and Exosurf patients in any of these characteristics.
Reviewer's Comment: ***The Applicant's analyses of the baseline factors, as well as the efficacy endpoints, included comparisons of results between Survanta- and Exosurf-treated patients. These comparisons were not part of the statistical plan for the study, nor were they discussed with FDA before filing the NDA. Comparisons between these two approved drugs are not relevant to this application and will not be included in this review.***

Table 55: Neonatal Baseline and Demographic Characteristics: KL4-IRDS-06

Characteristic	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
	N (%)			
Birth Status				0.940
Single	426 (80.8)	412 (80.9)	206 (79.8)	
Multiple	101 (19.2)	97 (19.1)	52 (20.2)	
Congenital anomaly	4 (0.8)	9 (1.8)	4 (1.6)	0.144
Mode of delivery				0.600
Vaginal spontaneous	132 (25.0)	122 (24.0)	69 (26.7)	
Vaginal assisted	9 (1.7)	4 (0.8)	1 (0.4)	
Elective C-section	2 (0.4)	2 (0.4)	0	
Emergency C-section	384 (72.9)	381 (74.9)	188 (72.9)	
Race				0.339
White	409 (77.6)	397 (78.0)	204 (79.1)	
Black	3 (0.6)	4 (0.8)	3 (1.2)	
Other	115 (21.8)	108 (21.2)	51 (19.8)	
Gender				0.892
Male	263 (49.9)	254 (49.9)	129 (50.0)	
Female	264 (50.1)	255 (50.1)	129 (50.0)	
Apgar – 1 min				0.909
Mean (S.D.)	5.3 (2.16)	5.3 (2.15)	5.3 (2.12)	
Apgar – 5 min				0.971
Mean (S.D.)	7.1 (1.43)	7.2 (1.42)	7.1 (1.41)	
N	526	508	257	
Apgar – 10 min				0.479
Mean (S.D.)	7.4 (1.32)	7.5 (1.27)	7.4 (1.38)	
N	448	438	221	
Gestational age (weeks)				0.976
Mean (S.D.)	28.2 (1.95)	28.2 (2.03)	28.1 (2.12)	
N	522	507	256	

Characteristic	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
Weight (g)				0.685
Mean (S.D.)	973.3 (183.41)	970.5 (185.85)	966.6 (187.03)	
N	527	509	258	
Length (cm)				0.471
Mean (S.D.)	36.0 (3.26)	35.8 (3.22)	35.9 (3.26)	
N	525	506	258	
Head circumference (cm)				0.894
Mean (S.D.)	25.3 (2.00)	25.4 (1.97)	25.3 (1.94)	
N	525	504	258	
Source: M5, v 1.1, sec 5.3.5.1, p 48				

For neonates, certain baseline characteristics related to the mother and her pregnancy are important to neonatal status and outcome. Those characteristics are displayed in the following Table. Again, there were no differences between the Surfaxin and Exosurf groups.

Table 56: Maternal Characteristics: KL4-IRDS-06

Characteristic	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
Maternal age (yr)				0.229
Mean (S.D.)	28.4 (6.79)	27.9 (6.42)	28.2 (6.51)	
Gravidity				0.709
Mean (S.D.)	2.5 (2.06)	2.6 (1.89)	2.5 (1.59)	
Parity				0.847
Mean (S.D.)	2.0 (1.36)	2.0 (1.37)	1.9 (1.20)	
	N (%)			
Clinical chorioamnionitis	23 (4.4)	19 (3.8)	13 (5.0)	0.613
Gestational diabetes	17 (3.2)	10 (2.0)	5 (2.0)	0.243
Pregnancy-induced hypertension	142 (27.0)	146 (28.7)	62 (24.0)	0.612
Insulin-dependent diabetes	8 (1.5)	3 (0.6)	4 (1.6)	0.162
Labor				0.939
Spontaneous	255 (80.4)	233 (81.5)	133 (83.6)	
Induced	62 (19.6)	53 (18.5)	26 (16.4)	
Missing	210	223	99	

Characteristic	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
Oligohydramnios > 21 days	7 (1.3)	6 (1.2)	1 (0.4)	0.873
Antenatal steroids (missing)	415 (79.2) 3	394 (78.5) 7	191 (74.3) 1	0.684
Tocolytic therapy	200 (38.0)	198 (39.2)	129 (50.0)	0.571
Diabetes, gestational or insulin-dependent	22 (4.2)	12 (2.4)	9 (3.5)	0.127

Source: M5, v 1.1, sec 5.3.5.1, p 46

10.1.3.5 Efficacy endpoint outcomes

All the results presented in this section are from the intent-to-treat data set of all randomized patients.

10.1.3.5.1 Primary efficacy endpoints

As amended (section 10.1.2), there were co-primary endpoints for this study, incidence of RDS at 24 hours and RDS-related mortality at 14 days. According to agreement with the Division *[M1, v 1.1, sec 1.5, p5]*, both endpoints would have to be significant at the 5% level, two-sided, to establish efficacy of Surfaxin.

10.1.3.5.1.1 Endpoint definitions

As noted in section 10.1.1.7.2.1 above, the original definition of the co-primary efficacy endpoint, incidence of RDS at 24 hours, was changed by protocol amendments. The modified definition that was applied in the analyses is shown just below. It should be noted that the changes in the definition of the endpoint were prompted by the Division, so this final, amended definition will be accepted in this review to establish the drug's efficacy.

Diagnosis	Chest x-ray at 24±4 hrs	FiO_2 at 24±4 hrs
RDS	Positive changes	≥ 30% at 24±4 hrs
No RDS	Positive or indeterminate	< 30%
	If no chest x-ray at 24±4 hrs	FiO_2 < 30% prior to or after 24±4 hours

For the other co-primary endpoint, RDS-related deaths at 14 days, the attributions of cause of death used in the primary analyses were those adjudicated by the AC. Pre-specified rules governing some of the decisions were:

- A patient who died as a result of pulmonary hemorrhage was to be classified as an RDS-related death, if the patient had RDS that had not resolved before the hemorrhage.

The diagnosis of RDS could occur at any time before death and did not have to meet the 24±8 hour definition.

- In the case of intracranial hemorrhage, death was to be classified as RDS-related if the RDS was clinically significant enough that it was likely to have contributed to the hemorrhage. The diagnosis of RDS could occur at any time before death and did not have to meet the 24±8 hour definition.
- Sepsis could be diagnosed based on substantial clinical evidence of infection even in the absence of positive blood cultures. Positive blood cultures could be considered contaminated if the organism was one not commonly associated with early onset sepsis and there was no clinical or other laboratory evidence of sepsis.
- Patients lost to follow-up before and including Day 14 were to be counted as having died due to RDS.
- Patients whose data were missing were to be counted as having died due to RDS.

10.1.3.5.1.2 Incidence of RDS at 24 hours

Based on the AC results, significantly fewer patients treated with Surfaxin than Exosurf had RDS at 24 hours of age (Table 57 below). The Applicant also determined the incidence of RDS from the CRFs; i.e., from the FiO_2 and chest x-ray results recorded by the investigators. Those CRF results are also shown in the Table.

According to protocol, the results from the AC are considered the primary results; however, as the Table shows, members of the AC clearly identified more patients with RDS than would have been determined from the CRF data alone. Inspection of data listings reveals that the difference is in interpretation of the chest x-ray *[M5, v 1.39, sec 5.3.5.1, Table B.9, p 7103 & Table B.19, p 12543]*. Fewer investigators than members of the AC reported chest x-ray results consistent with RDS. The differences in incidences of RDS between the two methods do not appear to be treatment-biased; the proportion of RDS by CRF is approximately 40% that of AC determinations in each treatment group. Despite the different rates of RDS by the two methods, the difference between Surfaxin and Exosurf patients remains statistically significant. It should also be noted that the rates of RDS based on AC results are more consistent with published rates than those based on CRF's.[12]

Table 57: Incidence of RDS at 24 Hours: KL4-IRDS-06

	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
		N (%)		
RDS at 24 hours – Adjudication Committee	206 (39.1)	240 (47.2)	86 (33.3)	0.005
RDS at 24 hours – CRF	83 (15.7)	102 (20.0)	31 (12.0)	0.041

Source: M5, v 1.1, sec 5.3.5.1, p 51

Table 58 shows the incidences of RDS at 24 hours based on AC results for gender, race, and weight subgroups. The Table also shows results of logistic regression analyses in each group, adjusting for study center, gender, race, and weight. The treatment effect remains significant in the gender groups, in white patients, and in the largest patients. In the other groups, the effect is

consistent with the overall results and not contradictory, if not statistically significant. The tendencies that would be expected of RDS; i.e., more in non-white and smaller patients, are observed in these results.

Table 58: Subgroup Analyses of Incidence of RDS Based on Adjudication Committee Results: KL4-IRDS-06

Group	Surfaxin N (%)	Exosurf N (%)	Survanta N (%)	p-value Surfaxin vs. Exosurf
Overall	206/527 (39.1)	240/509 (47.2)	86/258 (33.3)	T=0.004 C<0.001 B<0.001 R=0.062 S=0.860
Males	104/263 (39.5)	120/254 (47.2)	43/129 (33.3)	T=0.026 C=0.111 B<0.001 R=0.177
Females	102/264 (38.6)	120/255 (47.1)	43/129 (33.3)	T=0.031 C=0.017 B=0.086 R=0.115
White	141/409 (34.5)	166/397 (41.8)	57/204 (27.9)	T=0.021 C<0.001 B<0.001 S=0.936
Non-white	65/118 (55.1)	74/112 (66.1)	29/54(53.7)	T=0.056 C=0.389 B=0.804 S=0.521
600-800 g	55/119 (46.2)	63/112 (56.3)	31/58 (53.4)	T=0.097 C=0.992 R=0.771 S=0.075
801-1000 g	76/178 (42.7)	79/166 (47.6)	29/84 (34.5)	T=0.408 C=0.704 R=0.136 S=0.476
1001-1250 g	75/230 (32.6)	98/231 (42.4)	26/116 (22.4)	T=0.029 C=0.027 R=0.026 S=0.549

T=treatment, C=study center, B=weight stratum, R=race, S=gender
Source: M5, v 1.7, sec 5.3.5.1, p 1815

10.1.3.5.1.3 Incidence of RDS-related mortality at 14 days

Analyzing the causes of death based on AC results demonstrated significantly fewer RDS-related deaths in Surfaxin patients than Exosurf patients. As with the incidence of RDS, however, the RDS-related deaths as attributed by investigators were far fewer. Both results are displayed in the Table below.

Table 59: Incidence of RDS-related Mortality at 14 Days: KL4-IRDS-06

	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
		N (%)		
RDS-related mortality at 14 days – Adjudication Committee	25 (4.7)	49 (9.6)	27 (10.5)	0.001
RDS-related mortality at 14 days – CRF	1 (0.2)	3 (0.6)	0	0.309

Source: M5, v 1.1, sec 5.3.5.1, p 51

AC members were charged "to establish if cause of death *is associated with RDS"* (emphasis added by reviewer), and then to indicate on the ballot whether there was "RDS-related" mortality. A separate section of the ballot asked the AC member to indicate "Cause of death (primary)". For most patients counted by the AC as experiencing RDS-related mortality, a cause other than RDS was assigned, and this cause was in most cases the same as indicated by the investigator on the CRF. In other words, the AC determined whether RDS was *related to* or *influenced* the ultimate cause of death, not necessarily was the cause of death, and this was the basis of the primary analysis. This was allowed by the pre-specified rules noted above (10.1.3.5.1.1); for example, *"In the case of intracranial hemorrhage, death was to be classified as RDS-related if the RDS was clinically significant enough that it was likely to have contributed to the hemorrhage."*

Subgroup analyses for RDS-related mortality are presented in Table 60 below. As with incidence of RDS, the subgroup analysis results are consistent with the overall results, failing to reach significance only in the small non-white group of patients and in the largest patients where there were very few deaths.

Table 60: Subgroup Analyses of RDS-related Mortality at 14 Days According to Adjudication Committee Results: KL4-IRDS-06

Group	Surfaxin N (%)	Exosurf N (%)	Survanta N (%)	p-value Surfaxin vs. Exosurf
Overall	25/527 (4.7)	49/509 (9.6)	27/258 (10.5)	T=0.001 C=0.998 B<0.001 R=0.216 S=0.058
Males	16/263 (6.1)	28/254 (11.0)	14/129 (10.9)	T=0.041 C=1.000 B<0.001 R=0.834
Females	9/264 (3.4)	21/255 (8.2)	13/129 (10.1)	T=0.012 C=1.000 B=0.007 R=0.923
White	16/409 (3.9)	37/397 (9.3)	18/204 (8.8)	T=0.001 C=1.000 B<0.001 S=0.069
Non-white	9/118 (7.6)	12/112 (10.7)	9/54 (16.7)	T=0.549

Group	Surfaxin N (%)	Exosurf N (%)	Survanta N (%)	p-value Surfaxin vs. Exosurf
				C=1.000 B=0.004 S=0.560
600-800 g	14/119 (11.8)	21/112 (18.8)	16/58 (27.6)	T=0.148 C=1.000 R=0.291 S=0.036
801-1000 g	9/178 (5.1)	20/166 (12.0)	9/84 (10.7)	T=0.023 C=1.000 R=0.964 S=0.052
1001-1250 g	2/230 (0.9)	8/231 (3.5)	2/116 (1.7)	T=0.072 C=1.000 R=0.853 S=0.126

T=treatment, C=study center, B=weight stratum, R=race, S=gender
Source: M5, v 1.7, sec 5.3.5.1, p 1822

10.1.3.5.1.4 Interim analyses

Two formal interim analyses of the co-primary endpoints were performed by the Applicant at 33% and 66% of the planned complete enrollment. The study report states that the Applicant remained blind to the results. The significance levels at the interim analyses are shown in the next Table. The significance levels were based on the O'Brien-Fleming boundaries generated by the Lan-DeMets alpha-spending function, where the overall significance level across all analyses was set to 0.05 for each endpoint. As noted, the co-primary endpoints changed during the course of the study, after the two interim analyses. The significance level of the final results stayed in place because those particular endpoints had not previously been analyzed.

Table 61: Results of Interim Analyses: KL4-IRDS-06

Interim (Proportion of Planned Enrollment)	Z-Critical Value	Significance Level
33%	3.50	0.00047
66%	2.52	0.01190
100%	1.99	0.04623

Source: M5, v 1.1, sec 5.3.5.1, p 63

10.1.3.5.2 Secondary efficacy endpoints

There was an array of secondary endpoints in the study, all related to clinical status or lung function. The endpoints were not ordered for importance, nor were there any statistical adjustments for multiple comparisons. Among the secondary endpoints were several composites of other single primary or secondary endpoints. Also considered secondary efficacy endpoints were several concurrent diagnoses which the Applicant considered as indicators of effectiveness. The same concurrent diagnoses could be considered, and have been by other surfactant sponsors, to indicate safety of the therapy. They will be considered in both contexts in this review, as appropriate.

The secondary endpoints were determined at different time points in the study, depending on the pathophysiologic and prognostic characteristics of the endpoint. Many of the secondary

endpoints were analyzed in two ways to account for deaths occurring through the course of the study. In one analysis, the event was "**imputed for death**;" that is, if death occurred before the time point of determination, the patient was counted as having the event. In the other analysis, not imputed for death, the last observation of the event before death was carried forward for the analysis. With an overall mortality rate about 20%, the results when imputed for death give a distorted perspective on the rates of relatively uncommon events. Therefore, in most cases, the results not imputed for death will be the focus in this review.

10.1.3.5.2.1 All-cause mortality

The rates of death from any cause; i.e., all deaths, are shown for each evaluation time and for subgroups in Table 62. There were no treatment group differences for all-cause mortality, although Surfaxin patients in the largest weight group tended ($0.05 < p < 0.10$) to have fewer deaths beyond the 14 day time point.

Table 62: All-Cause Mortality: KL4-IRDS-06

	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
	N (%)			
	14 Days of Age			
Overall	84 (15.9)	86 (16.9)	48 (18.6)	0.468
Male	45 (17.1)	52 (20.5)	26 (20.2)	0.328
Female	39 (14.8)	34 (13.3)	22 (17.1)	0.879
White	63 (15.4)	69 (17.4)	34 (16.7)	0.251
Non-white	21 (17.8)	17 (15.2)	14 (25.9)	0.473
600-800 g	45 (37.8)	40 (35.7)	25 (43.1)	0.679
801-1000 g	26 (14.6)	29 (17.5)	16 (19.0)	0.429
1001-1250 g	13 (5.7)	17 (7.4)	7 (6.0)	0.474
	28 Days of Age			
Overall	100 (19.0)	109 (21.4)	61 (23.6)	0.188
Male	57 (21.7)	64 (25.2)	30 (23.3)	0.295
Female	43 (16.3)	45 (17.6)	31 (24.0)	0.560
White	76 (18.6)	87 (21.9)	47 (23.0)	0.124
Non-white	24 (20.3)	22 (19.6)	14 (25.9)	0.768
600-800 g	52 (43.7)	40 (35.7)	25 (43.1)	0.679
801-1000 g	33 (18.5)	36 (21.7)	20 (23.8)	0.434
1001-1250 g	15 (6.5)	26 (11.3)	9 (7.8)	0.071
	36 Weeks PCA			
Overall	111 (21.1)	121 (23.8)	68 (26.4)	0.166
Male	64 (24.3)	71 (28.0)	32 (24.8)	0.213
Female	47 (17.8)	50 (19.6)	36 (27.9)	0.554
White	83 (20.3)	95 (23.9)	52 (25.5)	0.095
Non-white	28 (23.7)	26 (23.2)	16 (29.6)	0.784
600-800 g	55 (46.2)	50 (44.6)	33 (56.9)	0.575
801-1000 g	39 (21.9)	42 (25.3)	22 (26.2)	0.428
1001-1250 g	17 (7.4)	29 (12.6)	13 (11.2)	0.057
	Discharge			
Overall	110 (20.9)	119 (23.4)	66 (25.6)	0.166
Male	63 (24.0)	71 (28.0)	32 (24.8)	0.169
Female	47 (17.8)	48 (18.8)	34 (26.4)	0.672
White	83 (20.3)	94 (23.7)	50 (24.5)	0.116
Non-white	27 (22.9)	25 (22.3)	16 (29.6)	0.928
600-800 g	54 (45.4)	50 (44.6)	32 (55.2)	0.700
801-1000 g	39 (21.9)	40 (24.1)	22 (26.2)	0.492
1001-1250 g	17 (7.4)	29 (12.6)	12 (10.3)	0.057

Source: M5, v 1.7, sec 5.3.5.1, p 1992ff

The next Table illustrates the contrast between rates of RDS-related mortality and all-cause mortality at 14 days in this study. The difference between treatments for RDS-related deaths disappears when all-cause mortality is analyzed.

Table 63: RDS-Related Mortality vs. All-Cause Mortality at 14 Days: KL4-IRDS-06

	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
		N (%)		
RDS-related mortality at 14 days	25 (4.7)	49 (9.6)	27 (10.5)	0.001
All-cause mortality at 14 days	84 (15.9)	86 (16.9)	48 (18.6)	0.468

Source: M5, v 1.1, sec 5.3.5.1, p 51

The five most common causes of death in each treatment group are shown in the next Table, which illustrates how the non-RDS causes of death distribute. The causes of death shown in the Table account for almost all study deaths; no other cause occurred in more than one or two patients in total.

Reviewer's Comment: ***The large difference in renal deaths and difference in sepsis deaths are reviewed and discussed in detail in the Integrated Review of Safety (section 7).***

Table 64: Causes of Death Through 14 Days of Age: KL4-IRDS-06

Cause of Death	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)
		N (%)	
Air leak	8 (1.5)	10 (2.0)	4 (1.6)
IVH	17 (3.2)	28 (5.5)	18 (7.0)
NEC	4 (0.8)	2 (0.4)	4 (1.6)
Pulmonary hemorrhage	15 (2.8)	12 (2.4)	11 (4.3)
Renal failure	7 (1.3)	1 (0.2)	0
Sepsis	23 (4.4)	18 (3.5)	4 (1.6)

Source: M5, v 1.1, sec 5.3.5.1, p 75

10.1.3.5.2.2 Air leaks

The presence of air leaks (pneumothorax, pneumopericardium, pneumomediastinum, subcutaneous emphysema, and PIE) through 7 days of age was determined by the AC, and also recorded by investigators at 7 days of age and at 36 weeks PCA. The results not imputed for death through 7 days are shown in the next Table.

Table 65: Air Leaks Through 7 Days of Age: KL4-IRDS-06

	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
		N (%)		
		By Adjudication Committee		
Overall	82 (15.6)	93 (18.3)	42 (16.3)	0.152
PIE	56 (10.6)	64 (12.6)	24 (9.3)	0.236
Pneumomediastinum	2 (0.4)	1 (0.2)	5 (1.9)	1.000
Pneumopericardium	1 (0.2)	0	0	0.764
Pneumothorax	34 (6.5)	34 (6.7)	13 (5.0)	0.823
Subcutaneous emphysema	0	0	0	-
		By Investigator/CRF		

	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
Overall	80 (15.2)	89 (17.5)	35 (13.6)	0.221
PIE	48 (9.1)	51 (10.0)	25 (9.7)	0.512
Pneumomediastinum	2 (0.4)	2 (0.4)	0	0.924
Pneumopericardium	1 (0.2)	0	0	0.818
Pneumothorax	18 (3.4)	22 (4.3)	6 (2.3)	0.395
Subcutaneous emphysema	0	1 (0.2)	0	0.801
Source: M5, v 1.1, sec 5.3.5.1, p53; M5, v 1.7, sec 5.3.5.1, p 1845				

Rates of air leaks at the 36 week PCA time point are only slightly higher (1-3%) and there are no treatment differences.

10.1.3.5.2.3 Composite endpoints

Several composite endpoints using RDS-deaths, all-cause deaths, incidence of RDS, and air leaks were analyzed. The results according to AC determinations are displayed in Table 66.

Table 66: Composite Secondary Endpoint Results: KL4-IRDS-06

	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
	N (%)			
RDS-death Day 14:				
OR air leak Day 7	92 (17.5)	110 (21.6)	49 (19.0)	0.045
AND air leak Day 7	15 (2.8)	32 (6.3)	20 (7.8	0.006
RDS at 24 hours and:				
All-cause death Day 14	42 (8.0)	63 (12.4)	29 (11.2)	0.009
All-cause death Day 14 or air leak Day 7	102 (19.4)	123 (24.2)	51 (19.8)	0.024
All-cause death Day 14 and air leak Day 7	22 (4.2)	33 (6.5)	20 (7.8)	0.076
RDS-death Day 14 and air leak Day 7	14 (2.7)	30 (5.9)	17 (6.6)	0.008
Source: M5, v 1.1, sec 5.3.5.1, p 52				

The intention of the composite endpoints is to estimate some sort of meaningful global clinical effect on the patient, but such a panoply of composites is hard to unravel, particularly considering that there was no protection from multiplicity in the comparisons. There is also not a clear-cut clinical connection among events in some of the composites. Air leak is itself a composite of several different events and those events have different clinical implications; i.e., PIE often bodes much worse for the patient that a pneumomediastinum. Several of the air leak manifestations may have relatively benign clinical consequences and do not increase the likelihood of death, so assessing that event or death has questionable clinical meaning. In other words, combining with death an event which does not necessarily predict death contributes little to understanding the effects of the drug. In addition, analytically, it is also possible that the observed treatment differences are being primarily driven by the co-primary endpoints which are the foundations of the two sets of composites.

The most noteworthy aspect of these composite endpoints is that one of them, RDS-death through Day 14 or air leaks through Day 7, was the original co-primary endpoint until the strategy was modified by protocol amendment #3 (section 10.1.2.3).

10.1.3.5.2.4 Severity of RDS

Severity of RDS was evaluated by FiO_2 and MAP measurements at several time points after the first dose of surfactant. There were a few significant differences in mean values between Surfaxin- and Exosurf-treated patients, but most values were not different. The contribution of this endpoint to evaluating the effectiveness of the drug is considered to be minimal for two reasons: 1) the management of respiratory support is highly non-standardized among clinicians and although "guidelines" were incorporated into the protocol by the first amendment, the guidelines were not binding and still allowed considerable flexibility of management; and 2) these endpoints pale beside the other more clinically meaningful endpoints of the study.

10.1.3.5.2.5 Number of surfactant doses

The Applicant designated this endpoint as an indicator of efficacy, presumably on the basis that the more effective surfactant needs to be given less often. This may be contraverted to some extent by the re-treatment criteria which required fairly mild disease ($FiO_2 \geq 30\%$ and MAP ≥ 6) to give additional doses. The proportions of patients who received different numbers of doses are shown in the next Table. There were no significant differences between treatments.

Table 67: Number of Surfactant Doses: KL4-IRDS-06

	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
Number of Doses[a]		**N (%)**		
0	3 (0.6)	3 (0.6)	0	0.881
1	291 (55.2)	268 (52.7)	161 (62.4)	0.606
2	108 (20.5)	91 (17.9)	49 (19.0)	0.177
3	51 (9.7)	55 (10.8)	24 (9.3)	0.584
4	36 (6.8)	37 (7.3)	7 (2.7)	0.704
5	38 (7.2)	55 (10.8)	17 (6.6)	0.066
Overall				0.393

[a] Doses 2 and 4 could have been sham air for Exosurf patients. Dose 5 could have been sham air for Surfaxin and Survanta patients.
Source: M5, v 1.1, sec 5.3.5.1, p 58

10.1.3.5.2.6 Bronchopulmonary dysplasia

The presence of BPD was determined at 28 days of age and 36 weeks PCA and the diagnosis only required needing oxygen; there was no requirement for radiographic or other clinical criteria. Analyses were performed imputed for death, but that method makes no difference in this case because the diagnosis was time-dependent; i.e., required being alive at 28 days or 36 weeks PCA, so the diagnosis could not be imputed for previous deaths. Results of analyses are in the next Table.

Reviewer's Comment: ***The endpoint "Alive without BPD" was not explicitly planned in the protocol, but represents a best outcome that is important in assessing the effect of a surfactant. It should be noted, however, that the current standard is to not consider BPD to be present until 36 weeks PCA. Oxygen requirement earlier than that probably often represents***

lingering effects of prematurity rather than chronic lung injury. The almost 20% drop in "BPD" between 28 days and 36 weeks PCA in this study reflects that reality.

Table 68: Incidence of Bronchopulmonary Dysplasia: KL4-IRDS-06

	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
	N (%)			
BPD Not Imputed for Death				
Day 28	304 (57.7)	316 (62.1)	149 (57.8)	0.055
36 wks PCA	212 (40.2)	229 (45.0)	110 (42.6)	0.046
Alive without BPD				
Day 28	221 (41.9)	190 (37.3)	106 (41.1)	0.044
36 wks PCA	313 (59.4)	274 (53.8)	144 (55.8)	0.022

Source: M5, v 1.1, sec 5.3.5.1, p 54

10.1.3.5.2.7 Duration of mechanical ventilation, oxygen, and hospitalization

The results of these endpoints through 36 weeks PCA are summarized in Table 69. There were no treatment group differences. This is not surprising because the durations of these events are typically more a function of the neonate's gestational maturity than lung function per se. In other words, other elements (alveolarization, thoracic muscle strength and recoil, central respiratory center, etc.) will continue to be delayed even if surfactant function is effectively restored. So, for example, patients might require prolonged ventilation for apnea rather than for atelectasis.

Table 69: Days of Ventilation, Oxygen, and Hospitalization: KL4-IRDS-06

	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
	Mean (SD)			
Mechanical Ventilation	21.7 (26.28)	22.7 (26.49)	24.8 (27.88)	0.278
Supplemental Oxygen	33.7 (25.73)	35.7 (25.87)	35.7 (26.94)	0.111
Hospitalization	53.1 (14.54)	53.1 (15.12)	54.1 (15.45)	0.893

Source: M5, v 1.1, sec 5.3.5.1, p 57

10.1.3.5.2.8 Concurrent diagnoses

Reviewer's Comment: ***The Applicant considers these events to be indicators of efficacy of Surfaxin, but it should be noted that at least three of the events, IVH, PDA, and pulmonary hemorrhage, have been reported to increase with surfactant therapy and consequently have been considered as indicators of safety. Acquired sepsis, for some reason included here, is clearly so.***

Rates of the eight events, not imputed for death, are shown in the next Table. Where an event has stages or grades, the worst observed stage or grade was used for the analysis.

Table 70: Concurrent Diagnoses Through 36 Weeks PCA: KL4-IRDS-06

	Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf

		Surfaxin (N=527)	Exosurf (N=509)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
Diagnosis	**Stage/ Grade**		**N (%)**		
IVH	None	253 (48.0)	222 (43.6)	118 (45.7)	0.570
	Grade 1	59 (11.2)	86 (16.9)	30 (11.6)	
	Grade 2	114 (21.6)	109 (21.4)	57 (22.1)	
	Grade 3	61 (11.6)	44 (8.6)	26 (10.1)	
	Grade 4	40 (7.6)	48 (9.4)	27 (10.5)	
	Overall	274 (52.0)	287 (56.4)	140 (54.3)	0.120
NEC	None	440 (83.5)	424 (83.3)	210 (81.4)	0.676
	Stage I	53 (10.1)	43 (8.4)	13 (5.0)	
	Stage IIa	12 (2.3)	15 (2.9)	13 (5.0)	
	Stage IIb	3 (0.6)	5 (1.0)	6 (2.3)	
	Stage IIIa	4 (0.8)	4 (0.8)	3 (1.2)	
	Stage IIIb	15 (2.8)	18 (3.5)	13 (5.0)	
	Overall	87 (16.5)	85 (16.7)	48 (18.6)	0.873
PVL	Yes	53 (10.1)	51 (10.0)	32 (12.4)	0.829
	No	474 (89.9)	458 (90.0)	226 (87.6)	
Apnea	Yes	271 (51.4)	264 (51.9)	119 (46.1)	0.993
	No	256 (48.6)	245 (48.1)	139 (53.9)	
PDA	Yes	192 (36.4)	177 (34.8)	95 (36.8)	0.486
	No	335 (63.6)	332 (65.2)	163 (63.2)	
ROP	None	387 (73.4)	375 (73.3)	193 (74.8)	0.789
	Stage 1	57 (10.8)	55 (10.8)	27 (10.5)	
	Stage 2	48 (9.1)	44 (8.6)	22 (8.5)	
	Stage 3	34 (6.5)	32 (6.3)	16 (6.2)	
	Stage 4	1 (0.2)	3 (0.6)	0	
	Overall	140 (26.6)	134 (26.3)	65 (25.2)	0.915
Pulmonary hemorrhage	Yes	54 (10.2)	59 (11.6)	36 (14.0)	0.494
	No	473 (89.8)	450 (88.4)	222 (86.0)	
Acquired sepsis	Yes	232 (44.0)	224 (44.0)	113(43.8)	0.967
	No	295 (56.0)	285 (56.0)	145 (56.2)	

Source: M5, v 1.1, sec 5.3.5.1, p 61-2

The results (not shown) when the events were imputed for death showed higher rates for some of the events, but with one exception there were no treatment group differences. The exception was a significantly different distribution among the stages of ROP favoring Surfaxin; i.e., fewer Surfaxin patients in the more severe stages. Otherwise, these analyses, whether considered for efficacy or safety, demonstrated little difference among the surfactants in these concurrent diagnoses. There is no apparent advantage or disadvantage for any of the products in these outcomes.

10.1.3.6 Safety outcomes

Evaluating the safety of a therapy in this population is complicated. The patients are not only pre-verbal but they are also not under the care of their parents, so that many possible symptomatologies (pain, distress, nausea, etc.) are undetectable and unreported. In addition, by virtue of prematurity, many events that would be considered "abnormal" or "adverse" in other patients would be considered "physiologic" or at least expected in these patients (e.g., hyperbilirubinemia, apnea).

In addition, the occurrence of some AEs (e.g., intracranial hemorrhage) can be somewhat common because of the underlying disease itself. Differentiating whether the event is due to the underlying disease or therapy not only requires a high level of discrimination, but also means some events can be considered indicators of both *efficacy* and *safety*.
These issues are reflected in the Applicant's somewhat inconsistent descriptions of the parameters used to evaluate safety. The protocol states that safety variables are AEs (AEs), negative reactions to dose administration, concomitant medications, physical examination findings, vital signs, arterial blood gases, ventilator settings, and chest radiographs. Arterial blood gases, ventilator settings, and chest radiographs, however, were also used to indicate efficacy and were already discussed in this review in that context (refer to section 10.1.3.5.2.4 above), and in fact the application does not report the chest radiograph results in assessing safety, referring back instead to their use in the efficacy results.
It is important to note that in this study, no clinical laboratory testing was used to monitor patients, except for blood gases; that is, there was no requirement to check hematological, chemical, etc. parameters. Abnormalities that occurred in those laboratory tests were only reported as AEs.

In this review, the following parameters will be considered as primarily indicative of safety:

- AEs
- Negative reactions to dose administration
- Concomitant medications

Physical findings and vital signs, so closely linked as they are to cardiopulmonary function, cannot be clearly demarcated as indicators of safety vs. efficacy, but are discussed here as safety outcomes.

Finally, another safety parameter considered in this review is the results of the 6- and 12-month follow-up results, reviewed in section 7.2.9 above.

10.1.3.6.1 Exposure

Of the 1294 randomized patients, 1288 received treatment and were included in the safety analyses. Descriptions of the six patients who were not treated, three Surfaxin and three Exosurf, are given in section 10.1.3.1 above. All randomized Survanta patients received treatment.

The dosing regimen for surfactants allows multiple doses up to a maximum if RDS continues. The numbers of patients who received various doses of each surfactant are shown in Table 67. Slightly more than half the Surfaxin patients only received one dose and three-fourths only required two. The nature of the dosing regimen that only allows repeat doses if respiratory distress continues, makes it somewhat difficult to correlate outcomes with the number of doses. That is, the frequency of an AE, for example, might be higher in patients who received more doses, but so is the severity of the illness which might also predispose to a higher rate of the AE.

10.1.3.6.2 Adverse events

As Table 71 shows, virtually every patient in this study had at least one AE. The ubiquity of AEs makes it difficult to distinguish treatments by occurrence of AEs. It is most likely that any

differences would show up in the rare events. Therefore, it is somewhat puzzling that the Applicant chose to display only the AEs that occurred in ≥10% of patients. For this review, the Applicant's summary was augmented by including events that occurred in ≥1% of patients and more commonly in Surfaxin patients. Also, the Tables show the MedDRA organ classes regardless of whether any single event met the criteria for display. For easier display, the information is divided into two tables.

Table 71: Adverse Events (Part 1): KL4-IRDS-06

MedDRA Organ Class/ MedDRA Preferred Term	Surfaxin (N=524)	Exosurf (N=506)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
	N (%)			
ANY EVENT	522 (99.6)	505 (99.8)	258 (100)	1.000
Blood and lymphatic system	420 (80.2)	414 (81.8)	213 (82.6)	0.526
Anemia NOS	10 (1.9)	5 (1.0)	2 (0.8)	0.299
Anemia neonatal	404 (77.1)	401 (79.2)	204 (79.1)	0.408
Disseminated intravascular coagulation	13 (2.5)	10 (2.0)	6 (2.3)	0.675
Leukocytosis NOS	31 (5.9)	22 (4.3)	9 (3.5)	0.263
Leukopenia NOS	24 (4.6)	23 (4.5)	10 (3.9)	1.000
Cardiac disorders	187 (35.7)	171 (33.8)	69 (26.7)	0.556
Bradycardia NOS	66 (12.6)	51 (10.1)	22 (8.5)	0.238
Cardiac murmur NOS	37 (7.1)	30 (5.9)	16 (6.2)	0.528
Tricuspid valve incompetence	5 (1.0)	2 (0.4)	1 (0.4)	0.452
Ventricular septal defect NOS	12 (2.3)	10 (2.0)	5 (1.9)	0.831
Congenital, familial, genetic disorders	203 (38.7)	195 (38.5)	99 (38.4)	0.949
Patent ductus arteriosus	188 (35.9)	175 (34.6)	95 (36.8)	0.696
Ear and labyrinth disorders	1 (0.2)	1 (0.2)	0	1.000
Endocrine disorders	32 (6.1)	20 (4.0)	19 (7.4)	0.120
Eye disorders	139 (26.5)	135 (26.7)	64 (24.8)	1.000
Retrolental fibroplasia[a]	137 (26.1)	133 (26.3)	63 (24.4)	1.000
Gastrointestinal disorders	187 (35.7)	169 (33.4)	84 (32.6)	0.871
Abdominal distention	28 (5.3)	19 (3.8)	10 (3.9)	1.000
Gastrointestinal hemorrhage NOS	15 (2.9)	7 (1.4)	4 (1.6)	0.131
Inguinal hernia NOS	24 (4.6)	22 (4.3)	6 (2.3)	0.881
Necrotizing enterocolitis	87 (16.6)	84 (16.6)	47 (18.2)	1.000
General disorders	63 (12.0)	53 (10.5)	36 (14.0)	0.490
Edema NOS	19 (3.6)	15 (3.0)	9 (3.5)	0.603
Edema peripheral	7 (1.3)	4 (0.8)	1 (0.4)	0.547
Hepato-biliary disorders	332 (63.4)	308 (60.9)	154 (59.7)	0.441
Hepatomegaly	6 (1.1)	5 (1.0)	2 (0.8)	1.000
Hypoproteinemia	28 (5.3)	24 (4.7)	13 (5.0)	0.672
Jaundice neonatal	326 (62.2)	297 (58.7)	151 (58.5)	0.252
Immune system disorders	0	1 (0.2)	0	0.491
Infections and infestations	357 (68.1)	346 (68.4)	181 (70.2)	0.947
Fungal infection NOS	11 (2.1)	3 (0.6)	2 (0.8)	0.056
Infection NOS	8 (1.5)	4 (0.8)	2 (0.8)	0.386
Mycotic sepsis	6 (1.1)	5 (1.0)	1 (0.4)	1.000
Pneumonia NOS	129 (24.6)	126 (24.9)	78 (30.2)	0.942
Respiratory tract infection NOS	5 (1.0)	2 (0.4)	1 (0.4)	0.452
Sepsis neonatal	196 (37.4)	195 (38.5)	93 (36.0)	0.748
Septic shock	20 (3.8)	10 (2.0)	7 (2.7)	0.095
Injury and poisoning	11 (2.1)	6 (1.2)	3 (1.2)	0.330

[a] Retrolental fibroplasia = retinopathy of prematurity
Source: M5, v 1.8, sec 5.3.5.1, p 2447ff

Table 72: Adverse Events (Part 2): KL4-IRDS-06

MedDRA Organ Class/ MedDRA Preferred Term	Surfaxin (N=524)	Exosurf (N=506)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
	N (%)			
Investigations	179 (34.2)	159 (31.4)	87 (33.7)	0.354
Blood creatine increased	12 (2.3)	9 (1.8)	4 (1.6)	0.661
Blood urea increased	7 (1.3)	5 (1.0)	2 (0.8)	0.774
Oxygen saturation decreased	149 (28.4)	127 (25.1)	65 (25.2)	0.232
Metabolism and nutrition disorders	315 (60.1)	327 (64.6)	154 (59.7)	0.140
Acidosis NOS	30 (5.7)	20 (4.0)	13 (5.0)	0.195
Hypercalcemia	8 (1.5)	7 (1.4)	3 (1.2)	1.000
Hyperglycemia NOS	137 (26.1)	138 (27.3)	66 (25.6)	0.725
Hypernatremia	29 (5.5)	21 (4.2)	11 (4.3)	0.314
Hypocalcemia	76 (14.5)	54 (10.7)	39 (15.1)	0.074
Hypoglycemia neonatal	85 (16.2)	76 (15.0)	36 (14.0)	0.608
Hypokalemia	31 (5.9)	24 (4.7)	10 (3.9)	0.410
Hyponatremia	93 (17.7)	110 (21.7)	39 (15.1)	0.117
Malnutrition NOS	5 (1.0)	1 (0.2)	1 (0.4)	0.218
Musculoskeletal, connective tissue, bone	12 (2.3)	7 (1.4)	6 (2.3)	0.356
Neoplasms	4 (0.8)	1 (0.2)	0	0.374
Nervous system disorders	130 (24.8)	124 (24.5)	65 (25.2)	0.942
Convulsion neonatal	56 (10.7)	46 (9.1)	27 (10.5)	0.406
Hydrocephalus NOS	18 (3.4)	14 (2.8)	6 (2.3)	0.593
Neurological disorder NOS	53 (10.1)	47 (9.3)	32 (12.4)	0.675
Pregnancy and perinatal conditions	12 (2.3)	6 (1.2)	6 (2.3)	0.235
Psychiatric disorders	0	2 (0.4)	2 (0.8)	0.241
Renal and urinary	75 (14.3)	70 (13.8)	38 (14.7)	0.858
Reproductive system	4 (0.8)	2 (0.4)	2 (0.8)	0.687
Respiratory, thoracic, mediastinal	460 (87.8)	447 (88.3)	231 (89.5)	0.848
Atelectasis neonatal	60 (11.5)	72 (14.2)	30 (11.6)	0.193
BPD	196 (37.4)	207 (40.9)	85 (32.9)	0.251
Cardio-respiratory arrest neonatal	5 (1.0)	2 (0.4)	2 (0.8)	0.452
Cyanosis NOS	8 (1.5)	4 (0.8)	1 (0.4)	0.386
Mediastinal emphysema	7 (1.3)	5 (1.0)	2 (0.8)	0.774
Neonatal apneic attack	266 (50.8)	260 (51.4)	118 (45.7)	0.852
Neonatal hypoxia	70 (13.4)	59 (11.7)	35 (13.6)	0.452
Neonatal respiratory acidosis	78 (14.9)	71 (14.0)	33 (12.8)	0.724
Neonatal RDS	247 (47.1)	253 (50.0)	103 (39.9)	0.383
Pulmonary hemorrhage	54 (10.3)	57 (11.3)	34 (13.2)	0.688
Pulmonary interstitial emphysema	67 (12.8)	75 (14.8)	35 (13.6)	0.367
Skin and subcutaneous tissue	30 (5.7)	21 (4.2)	11 (4.3)	0.254
Skin lesion NOS	5 (1.0)	2 (0.4)	1 (0.4)	0.452
Surgical and medical procedures	5 (1.0)	3 (0.6)	1 (0.4)	0.726
Vascular disorders	342 (65.3)	344 (68.0)	171 (66.3)	0.390
Hypertension neonatal	50 (9.5)	44 (8.7)	22 (8.5)	0.666
Intracranial hemorrhage NOS	9 (1.7)	7 (1.4)	4 (1.6)	0.803
IVH neonatal	265 (50.6)	272 (53.8)	135 (52.3)	0.319
Neonatal hypotension	87 (16.6)	97 (19.2)	52 (20.2)	0.291
Pulmonary artery stenosis	8 (1.5)	7 (1.4)	2 (0.8)	1.000
Source: M5, v 1.8, sec 5.3.5.1, p 2447ff				

The Tables demonstrate that many events were double-reported in this study; i.e., as AEs but also in one or more of the efficacy assessments. For example, RDS and several of the concurrent

diagnoses are among the most common AEs. This again reflects the overlap of these events as indicators of efficacy and safety in the opinions of investigators.

Investigators considered AEs to be severe more than half the time in all the treatment groups: 60.1% for Surfaxin, 62.3% for Exosurf, and 61.2% for Survanta. The majority of AEs were considered not related to drug by the investigators: 60.9% for Surfaxin, 64.8% for Exosurf, and 63.2% for Survanta.

10.1.3.6.2.1 Deaths and serious adverse events

Death is an efficacy outcome in this study and is wholly considered in that section of the review.

The Applicant summarized in tabular form the serious AEs that occurred in 3% or more of patients. As was done in the consideration of AEs, the Applicant's summary information is included in the next table, but the Table also includes serious AEs in ≥1% of patients and more common in Surfaxin patients.

Table 73: Serious Adverse Events: KL4-IRDS-06

MedDRA Organ Class/ MedDRA Preferred Term	Surfaxin (N=524)	Exosurf (N=506)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
	N (%)			
ANY EVENT	392 (74.8)	395 (78.1)	194 (75.2)	0.240
Blood and lymphatic system	20 (3.8)	21 (4.2)	10 (3.9)	0.874
Cardiac disorders	33 (6.3)	31 (6.1)	10 (3.9)	1.000
Bradycardia NOS	11 (2.1)	8 (1.6)	2 (0.8)	0.645
Cardiac failure NOS	5 (1.0)	5 (1.0)	1 (0.4)	1.000
Congenital, familial, genetic disorders	74 (14.1)	76 (15.0)	38 (14.7)	0.724
Patent ductus arteriosus	67 (12.8)	68 (13.4)	37 (14.3)	0.782
Endocrine disorders	2 (0.4)	1 (0.2)	0	1.000
Eye disorders	26 (5.0)	34 (6.7)	14 (5.4)	0.235
Retrolental fibroplasia	26 (5.0)	34 (6.7)	14 (5.4)	0.235
Gastrointestinal disorders	46 (8.8)	46 (9.1)	26 (10.1)	0.913
Necrotizing enterocolitis	27 (5.2)	32 (6.3)	23 (8.9)	0.425
General disorders	6 (1.1)	6 (1.2)	8 (3.1)	1.000
Hepato-biliary disorders	5 (1.0)	5 (1.0)	3 (1.2)	1.000
Infections and infestations	151 (28.8)	126 (24.9)	73 (28.3)	0.160
Pneumonia NOS	43 (8.2)	31 (6.1)	24 (9.3)	0.228
Sepsis neonatal	86 (16.4)	80 (15.8)	37 (14.3)	0.800
Septic shock	18 (3.4)	10 (2.0)	7 (2.7)	0.181
Injury and poisoning	4 (0.8)	0	1 (0.4)	0.125
Investigations	22 (4.2)	11 (2.2)	5 (1.9)	0.077
Oxygen saturation decreased	22 (4.2)	11 (2.2)	5 (1.9)	0.077
Metabolism and nutrition disorders	13 (2.5)	13 (2.6)	4 (1.6)	1.000
Acidosis NOS	5 (1.0)	2 (0.4)	1 (0.4)	0.452
Musculoskeletal, connective tissue, bone	1 (0.2)	0	1 (0.4)	1.000
Nervous system disorders	32 (6.1)	32 (6.3)	13 (5.0)	0.898
Convulsion neonatal	11 (2.1)	6 (1.2)	2 (0.8)	0.330
Pregnancy and perinatal	2 (0.4)	0	1 (0.4)	0.500
Renal and urinary	19 (3.6)	16 (3.2)	7 (2.7)	0.733
Renal failure neonatal	13 (2.5)	11 (2.2)	2 (0.8)	0.838
Respiratory, thoracic, mediastinal disorders	327 (62.4)	326 (64.4)	156 (60.5)	0.518
BPD	97 (18.5)	101 (20.0)	47 (18.2)	0.580
Cardio-respiratory arrest neonatal	5 (1.0)	2 (0.4)	2 (0.8)	0.452
Neonatal apneic attack	35 (6.7)	35 (6.9)	22 (8.5)	0.902

MedDRA Organ Class/ MedDRA Preferred Term	Surfaxin (N=524)	Exosurf (N=506)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
	N (%)			
Neonatal respiratory acidosis	5 (1.0)	5 (1.0)	1 (0.4)	1.000
Neonatal RDS	238 (45.4)	243 (48.0)	100 (38.8)	0.417
Neonatal respiratory failure	5 (1.0)	5 (1.0)	1 (0.4)	1.000
Pneumothorax NOS	37 (7.1)	32 (6.3)	13 (5.0)	0.709
Pulmonary hemorrhage	43 (8.2)	39 (7.7)	24 (9.3)	0.818
Pulmonary interstitial emphysema	28 (5.3)	33 (6.5)	10 (3.9)	0.432
Surgical and medical	1 (0.2)	2 (0.4)	0	0.618
Vascular disorders	99 (18.9)	97 (19.2)	51 (19.8)	0.937
IVH neonatal	90 (17.2)	82 (16.2)	44 (17.1)	0.738
Source: M5, v 1.8, sec 5.3.5.1, p 2435ff				

10.1.3.6.2.2 Discontinuations due to adverse events

No patients were discontinued from the study because of AEs, despite a table in the application showing "Discontinuation due to AE" occurring in seven patients *[M5, v 1.1, sec 5.3.5.1, p 66]*. On examination, those were instances of interruption of a dose of surfactant or a decision not to give a dose and those events are more properly considered in the section on negative reactions to dose administration.

10.1.3.6.3 Negative reactions to dose administration

This is an important component in the safety evaluation of an intratracheally instilled suspension. The tidal volume of a premature neonate is approximately 10 mL/kg and the dose volume of surfactant is approximately half that.

The Applicant pre-specified five reactions to dose administration that investigators had to report if they occurred: obstruction of the ETT, ETT reflux, apnea, pallor, and interruption of dose administration. Without explanation, the results do not include apnea. The results are summarized in Table 74.

Table 74: Negative Reactions to Dose Administration: KL4-IRDS-06

	Surfaxin	Exosurf	Survanta	p-value Surfaxin vs. Exosurf
	N (%)			
Dose 1	**N=524**	**N=506**	**N=257**	
Interruption	38 (7.3)	18 (3.6)	13 (5.1)	0.009
Pallor	37 (7.1)	15 (3.0)	21 (8.2)	0.003
ETT reflux	97 (18.5)	111 (21.9)	48 (18.7)	0.187
ETT obstruction	30 (5.7)	10 (2.0)	8 (3.1)	0.002
Dose 2	**N=219**	**N=209**	**N=86**	
Interruption	26 (11.9)	4 (1.9)	5 (5.8)	<0.001
Pallor	18 (8.2)	9 (4.3)	8 (9.3)	0.113
ETT reflux	35 (16.0)	7 (3.3)	10 (11.6)	<0.001
ETT obstruction	14 (6.4)	0	4 (4.7)	<0.001
Dose 3	**N=117**	**N=143**	**N=46**	
Interruption	14 (12.0)	10 (7.0)	6 (13.0)	0.199
Pallor	15 (12.8)	11 (7.7)	5 (10.9)	0.213
ETT reflux	25 (21.4)	18 (12.6)	5 (10.9)	0.066
ETT obstruction	6 (5.1)	5 (3.5)	6 (13.0)	0.550
Dose 4	**N=68**	**N=101**	**N=27**	
Interruption	5 (7.4)	4 (4.0)	3 (11.1)	0.488
Pallor	10 (14.7)	2 (2.0)	3 (11.1)	0.004
ETT reflux	13 (19.1)	7 (7.0)	4 (14.8)	0.027

	Surfaxin	Exosurf	Survanta	p-value Surfaxin vs. Exosurf
		N (%)		
ETT obstruction	2 (2.9)	1 (1.0)	1 (3.7)	0.566
Dose 5	**N=66**	**N=79**	**N=28**	
Interruption	4 (6.1)	10 (12.7)	3 (10.7)	0.260
Pallor	8 (12.1)	9 (11.4)	1 (3.6)	1.000
ETT reflux	13 (19.7)	18 (22.8)	0	0.689
ETT obstruction	3 (4.5)	5 (6.3)	0	0.728
Source: M5, v 1.1, sec 5.3.5.1, p 71				

There were significantly more negative reactions in patients receiving Surfaxin, sometimes 2-3 times the frequency of Exosurf or Survanta. The preponderance of differences occurred with the first two doses, which is the total number of doses most patients received. The Applicant chose to focus on ETT obstruction in providing additional summary results. Those results are summarized in the next Table.

Table 75: ETT Obstruction Events: KL4-IRDS-06

	Patients with ETT Obstruction	Weight Groups of Affected Patients	Obstruction Resulting in Dose Interruption	Death by Day 14
Surfaxin	44 (8.4%)	600-800 g: 11/44 (25.0%) 801-1000 g: 15/44 (34.1%) 1001-1250 g: 18/44 (40.9%)	17/44 (39%)	7/44 (16%)
Exosurf	19 (3.8%)	600-800 g: 6/19 (31.6%) 801-1000 g: 5/19 (26.3%) 1001-1250 g: 8/19 (42.1%)	9/19 (47%)	3/19 (15.8%)
Survanta	17 (6.6%)	600-800 g: 5/17 (29.4%) 801-1000 g: 7/17 (41.2%) 1001-1250 g: 5/17 (29.4%)	4/17 (23.5)	5/17 (29.4%)
Source: M5, v 1.1, sec 5.3.5.1, p 70				

Although ETT obstruction is an important event, limiting the analysis to this event is insufficient. A fuller examination of this outcome is found in the Integrated Review of Safety (section 7 above).

10.1.3.6.4 Concomitant medications

Table 76 displays the classes of medications that were administered to study patients through 36 weeks PCA. There were no differences between treatments for any class of medication, but there were for three single medications: thiopental (1.3% Surfaxin, 0 Exosurf, p=0.015); betamethasone (0.8% Surfaxin, 2.2% Exosurf, p=0.070); and fluticasone (0.8% Surfaxin, 2.2% Exosurf, p=0.07). The overall concomitant medication results again demonstrate the high degree of acute illness of the patients in the study, but do not differentiate the surfactants.

Table 76: Summary of Concomitant Medications: KL4-IRDS-06

Drug Class	Surfaxin (N=524)	Exosurf (N=506)	Survanta (N=258)	p-value Surfaxin vs. Exosurf
		N (%)		
Vasopressors	305 (58.2)	289 (57.1)	147 (57.0)	0.753
Sedatives	299 (57.1)	299 (59.1)	147 (57.0)	0.528
Paralytics	33 (6.3)	45 (8.9)	15 (5.8)	0.126

Steroids	150 (28.6)	162 (32.0)	81 (31.4)	0.249
Bronchodilators	386 (73.7)	371 (73.3)	182 (70.5)	0.944
Antibiotics	508 (96.9)	489 (96.6)	249 (96.5)	0.860
Diuretics	301 (57.4)	299 (59.1)	147 (57.0)	0.613
Source: M5, v 1.8, sec 5.3.5.1, p 2553ff				

10.1.3.6.5 Vital signs and physical findings [M5, v 1.1, sec 5.3.5.1, p 79]

There were a few differences in blood pressures and heart rates in the study, but none was clinically significant (i.e., < 3 mmHg or 3 bpm). Investigators reported many physical findings that would be expected in these premature neonates with high rates of concurrent illnesses. The more meaningful physical findings are those detected at the long-term follow-up assessments, reviewed in section 7.2.9 above.

10.1.4 Study Summary and Discussion

KL4-IRDS-06 is the major efficacy study for this NDA. Of the two other efficacy studies, one can be considered supportive at best and the other was too small to contribute to the overall assessment of Surfaxin, so this study provides the preponderance of evidence for efficacy and safety.

With the evidence of effectiveness coming from this single study, KL4-IRDS-06 was reviewed and evaluated according to the guidance for "Providing Clinical Evidence of Effectiveness for Human Drugs and biological Products." The study met the standards set forth in that guidance. It was a large, adequately designed multicenter study. It was randomized and appropriately stratified for birth weight within each of the many international centers. Because of the route of administration of surfactant, blinding is difficult, but appropriate and diligent efforts were made to accomplish and maintain blinding in the study. The comparator products were appropriate and consistent with the Division's recommendations. Similarly, the primary efficacy endpoints and the superiority design of the study were compliant with the Division's recommendations, even though the definition of the co-primary endpoints underwent changes by protocol amendments after initiation of the study. By the time of analysis, the endpoints were those agreed upon with the Division. The adjudication of the endpoints via the mechanism of an independent committee was appropriate, and diligent efforts were made to ensure that the committee members received all data and information necessary to perform their duties. There were multiple secondary efficacy endpoints involving different events, satisfying another criterion of the guidance. In addition, the secondary endpoints were generally similar to those used for other surfactant products.

The study was designed to be event-driven and was completed when 1294 patients had been randomized. There were no subsets of the population for the primary efficacy analyses – all 1294 patients were included in the intent-to-treat analyses. Six who never received treatment were excluded from safety analyses. The treatment groups were balanced at baseline for critical demographic and prognostic characteristics.

Results for the co-primary efficacy endpoints were statistically persuasive, again meeting the guidance's standards. In both endpoints, incidence of RDS at 24 hours and RDS-related

mortality at 14 days, Surfaxin was significantly superior to the comparator Exosurf. Moreover, the results were consistent across population subgroups based on birth weight, gender, and race.

Thus, this study provides the necessary level of confidence for the effectiveness of Surfaxin in preventing RDS and RDS-related deaths. Results for the safety outcomes were less clear-cut. When all causes of death were considered, there was no treatment difference and in fact the number of non-RDS-related deaths was significantly greater in the Surfaxin patients. Differences were most notable for two particular causes of death, renal failure and sepsis. These results raise the possibility of an adverse effect of Surfaxin. The issue is addressed more comprehensively from the perspective of the entire clinical program in the Integrated Reviews of Efficacy and Safety.

The AE profiles and the incidences of concurrent diagnoses were generally similar for the three surfactants in this study. On the other hand, the administration of Surfaxin is clearly accompanied by more negative reactions (i.e., reflux, ETT obstruction, dose interruption) than Exosurf or Survanta. This is most likely due to the relatively larger dose volume of Surfaxin and needs to be detailed in the product labeling.

10.2 Individual Study Report: KL4-IRDS-02. A Masked, Multicenter, Randomized, Controlled Trial Comparing the Safety and Effectiveness of Surfaxin® (Lucinactant) to Curosurf (Poractant Alfa) in the Prevention and Treatment of Respiratory Distress Syndrome (RDS) in Premature Infants

This study was performed to compare Surfaxin to Curosurf, a natural porcine lung-derived surfactant, approved in the U.S. and the leading surfactant used in Europe. This study had several essential similarities to study KL4-IRDS-06:

- The patient population was the same: premature neonates 600-1250 grams birth weight at high risk for RDS
- A prevention strategy of surfactant administration was used
- There were several common efficacy endpoints
- The safety endpoints were the same

On the other hand, there were critical differences:

- The comparator surfactant was different
- The primary efficacy endpoint was different
- There was a different dosing regimen for Surfaxin, with fewer doses given
- There was a non-inferiority design, rather than superiority
- The study was stopped before completion

The differences in this study outweigh the similarities and render it unable to stand with KL4-IRDS-06 as a major efficacy study. In this review, it is considered minimally supportive for efficacy and contributory to safety.

10.2.1 Protocol

Where elements of study design are similar, electronic cross-reference links in **bold font** direct the reader to the relevant sections of the review of KL4-IRDS-06.

The final protocol for KL4-IRDS-02 was issued on January 30, 2001, and amended several times. The study was conducted from August 17, 2001, through May 28, 2003. Thirty-five centers in the U.S., Canada, the U.K., and several European countries received IRB approval for the study. The final study report was issued March 15, 2004, and it is located in the NDA at *[M5, v 1.41, sec 5.3.5.1, p 1]*.

10.2.1.1 Objective/Rationale [M5, v 1.41, sec 5.3.5.1, p 14]

The objective of the study was to demonstrate the safety and non-inferiority efficacy of Surfaxin compared to Curosurf when given prophylactically to premature neonates at high risk for RDS.

Curosurf is an organic solvent extract surfactant from porcine lungs and was approved in 1999 in the U.S. for treatment ("rescue") of neonatal RDS (NDA 20-744). It is not approved for

prevention, the indication sought for Surfaxin. Curosurf is the leading brand of surfactant in Europe.

10.2.1.2 Study design overview

This was a multicenter, international, randomized, masked, non-inferiority study modeled after a published collaborative rescue study in Europe.[1]
Reviewer's Comment: ***Modeling the design of this prevention study after a rescue study raises some important issues, which are detailed in section 10.2.1.7.1 belowand summarized in section 10.2.4 below.***

The study was designed in two phases: a short-term efficacy and safety phase through 28 days of age, hospital discharge, or 36 weeks PCA, whichever came latest; and a long-term phase of 6- and 12-month follow-up.

Premature neonates at high risk for RDS were randomized to receive either Surfaxin or Curosurf between 15 and 30 minutes after birth. Up to two additional doses could be given during the first 48 hours of life if retreatment criteria were met. Masking of the treatments was to be accomplished with a separate group of personnel responsible for dose preparation and administration.

Patient eligibility criteria were the same as for study KL4-IRDS-06 (See **sections 10.1.1.4 above** and **10.1.2 above**), except that mothers with chorioamnionitis were not excluded and there was an additional inclusion criterion: gestational age had to be ≥24 weeks but <29 weeks.

10.2.1.3 Study treatments [M5, v 1.41, sec 5.3.5.1, p 176ff]

The treatments in this study were Surfaxin or Curosurf, whose dose characteristics are described in Table 77. The dose of Curosurf prescribed in the original protocol was 200 mg/kg for the first dose and 100 mg/kg for the repeat doses. This is the dose of Curosurf approved in the U.S. and Europe. The dose was modified by protocol amendment, however, to agree with a publication[10] indicating no advantage of a higher dose over a lower, and also to make the phospholipid dosages of the two surfactants the same for the study *[M5, v 1.41, sec 5.3.5.1, p 36]*. The Table below shows the lower, amended dose of Curosurf.

Table 77: Study Treatments: KL4-IRDS-02

	Surfaxin	Curosurf[a]
Concentration (mg phospholipids/mL)	30 mg/mL	80 mg/mL
Dose (mg phospholipids/kg birth weight)	175 mg/kg	1st dose: 175 mg/kg Repeat doses: 100 mg/kg
Dose (mL/kg birth weight)	5.8 mL/kg	1st dose: 2.2 mL/kg Repeat doses: 1.25 mL/kg
[a] As modified by protocol amendment **Source: M5, v 1.41, sec 5.3.5.1, p 26**		

Patients were randomized to the surfactants in a 1:1 ratio. There were two birth weight strata: 600-1000 grams and 1001-1250 grams. Study KL4-IRDS-06 had three strata: 600-800, 801-1000, and 1001-1250 grams.

Masking of the treatments was accomplished in the same manner as in KL4-IRDS-06; i.e., by using designated Dosing Preparers and Dosing Administrators who were not otherwise involved in the patient's care or in study decision-making. Refer to **section 10.1.1.5.2 above**.

The method of administration was the same for the two study surfactants, and was the same as that used in KL4-IRDS-06 (refer to **section 10.1.1.5.3 above**) except that
▪ the total dose was divided into two half-doses, rather than four quarter-doses, and
▪ the half-doses were administered with the patient in right lateral decubitus and then left lateral decubitus positions, head elevated 30°.

This study also differed from KL4-IRDS-06 in the total number of treatments allowed. Patients could receive up to two additional doses (three total vs. four total in KL4-IRDS-06) after the first dose if they met criteria:

- ▪ the patient is still intubated;
- ▪ at least 6 hours have passed since the previous dose;
- ▪ no more than 48 hours have passed since birth; and
- ▪ the patient continues to require mechanical ventilation for RDS with $FiO_2 \geq 0.30$ to maintain arterial $PaO_2 \geq 50$ mmHg or an oxygen saturation ≥90% and radiographic confirmation of RDS.

Reviewer's Comment: ***Dosage and administration of the two surfactants were made equivalent in this study's design, which resulted in two important deviations from the Curosurf package insert:***

- ▪ ***the first dose of Curosurf was lower than the approved dose (175 mg/kg vs. 200 mg/kg), and***
- ▪ ***the dosing interval was shorter (6 hours vs. 12 hours)***

10.2.1.4 Study procedures

The procedures and assessments for this study were virtually identical to those of study KL4-IRDS-06, except that vital signs, arterial blood gases, and ventilator settings were recorded slightly more frequently in this study. Refer to **section 10.1.1.6 above.**

10.2.1.5 Efficacy parameters [M5, v 1.41, sec 5.3.5.1, p 173 & 194-197]

The efficacy parameters differed in two significant ways from KL4-IRDS-06: there was a different primary efficacy variable, and no Adjudication Committee was used. Investigators made all diagnostic and causal determinations, guided in some cases by protocol stipulations.

10.2.1.5.1 Primary efficacy variable

There was a single primary efficacy variable in this study: the incidence of being alive without BPD at Day 28. The presence of BPD was determined by the investigator according to the

protocol definition (as amended): requirement for mechanical ventilation or supplemental oxygen in order to maintain oxygen saturation ≥90%, except during feedings. (The amended definition of BPD added the requirement for mechanical ventilation and the oxygen saturation criterion.)

Reviewer's Comment: ***As in KL4-IRDS-06, the definition of BPD used in the study was not ideal. The current standard is to not consider BPD to be present until 36 weeks PCA. Oxygen requirement earlier than that probably often represents lingering effects of prematurity rather than chronic lung injury. In addition, basing the diagnosis on oxygen use alone is probably unreliable considering the variability in clinical practices. Requiring radiographic changes and/or some demonstration of a "physiologic" need for oxygen are the more widely accepted criteria.***

10.2.1.5.2 Secondary efficacy variables

The secondary efficacy variables in this study were almost entirely the same as in study KL4-IRDS-06 (**section 10.1.1.7.3)**. They are listed below and any differences from KL4-IRDS-06 are noted, otherwise the definitions and rules governing the variables are the same as in KL4-IRDS-06.

▪ **Incidence of RDS at 24 hours**: this was a co-primary efficacy variable in KL4-IRDS-06. In this study, it was defined as needing mechanical ventilation at 24 hours with $FiO_2 > 0.30$, combined with a chest x-ray showing a reticulogranular pattern obtained between 20 and 28 hours of age (later amended to 24 ± 6 hours). If a patient died before 24 hours of age, presence of RDS would be determined by the last chest x-ray and FiO_2 before death.
▪ **Total number of surfactant doses required**
▪ **RDS-related mortality through 14 days of age**: this variable was not included in the original protocol, but was added by amendment. Cause of death was determined by the investigator.
▪ **Incidence of death at 28 days of age**
▪ **Incidence of BPD at 28 days of age**
▪ **Incidence of death at 36 weeks PCA**
▪ **Incidence of BPD at 36 weeks PCA**
▪ **Number of days requiring mechanical ventilation through 36 weeks PCA**
▪ **Duration of supplemental oxygen through 36 weeks PCA**
▪ **Occurrence of air leaks through 7 days of age and 36 weeks PCA**
▪ **Incidence of concurrent diagnoses through 36 weeks PCA**: as in KL4-IRDS-06, the presence of these diagnoses was imputed for death or loss to follow-up.
  ◦ PDA
  ◦ NEC
  ◦ acquired sepsis
  ◦ apnea
  ◦ severe IVH
  ◦ PVL
  ◦ ROP
  ◦ pulmonary hemorrhage
▪ **Duration of hospitalization through 36 weeks PCA**
▪ **Incidence of pre-discharge death**

10.2.1.5.3 Follow-up evaluations [M5, v 1.41, sec 5.3.5.1, p 186]

As in KL4-IRDS-06, 6- and 12-month adjusted age follow-up evaluations were planned for this study and the assessments at each are the same as in the previous study. Refer to **section 10.1.1.8.2.**

10.2.1.6 Safety evaluations [M5, v 1.41., sec 5.3.5.1, p 198]

The protocol named four parameters that would be used to evaluate the safety of the treatments in this study:

- Adverse experiences
- Vital signs and Physical examination
- Negative reactions to dose administration
- Concomitant medications

These variables were also used in KL4-IRDS-06, along with several others, and the rules governing them were the same in the two studies. Refer to **section 10.1.1.9.**

10.2.1.7 Statistical considerations

10.2.1.7.1 Sample size [M5, v 1.41, sec 5.3.5.1, p 193]

The planned sample size for the study was 248 patients per treatment group. It was intended to provide the evidence for a non-inferiority comparison of the two surfactants in the primary efficacy variable using a two-sided type I error of 0.05 and type II error of 0.10. The margin for non-inferiority was set at 14.5% and was established in the following manner.

The statistical design of the study was based on that of the Collaborative European Multicenter Study Group.[1] In that study, 55% of patients treated with Curosurf were alive without BPD at 28 days vs. 26% of patients who received placebo. To preserve 50% of that 29% superiority gap, the non-inferiority margin was set at 14.5%. In order to claim non-inferiority, the lower limit of the two-sided 95% confidence interval for being alive without BPD at Day 28 would need to be ≥ -14.5%. A total of 496 patients would be required to satisfy this objective.

Reviewer's Comment: ***The basis for the non-inferiority margin and therefore the sample size calculation for this study is not supportable. The referenced study used a rescue strategy in patients 700-2000 grams birth weight who were treated with a single 200 mg/kg dose of Curosurf. The study was designed to evaluate three endpoints, none of which was survival without BPD, although that endpoint was reported. Therefore, the result from that study upon which the statistical plan of KL4-IRDS-02 was based was unplanned and obtained from a different patient population who were treated with a different dosage of Curosurf. Of all these factors, the most critical one is the patient population. The patients in the referenced study were larger and more mature and had established RDS at the time of treatment, as opposed to the population in KL4-IRDS-02 who were at risk for RDS but inevitably included patients who never would have developed the disease. In other words, better outcomes would be expected in the population of a preventive strategy than a rescue strategy. That is substantiated in the***

results of study KL4-IRDS-06 where 41.9% of Surfaxin-treated patients were alive without BPD at 28 days (See Table 68), in contrast to the 55% incidence hypothesized in the sample size calculations above. These concerns were communicated by the Division to the Sponsor in a letter dated September 26, 2001 [M1, v 1.1, sec 1.5, p 41]. The plan was carried out despite the Division's stated concerns.

10.2.1.7.2 Analytical plan

The primary analyses in this study were planned to be based on the per-protocol data set; i.e., all patients who received at least one treatment. Supportive analyses were intended to be the intent-to-treat data set. Safety analyses included all patients who received at least one treatment. All analyses would use two-sided testing and a significance level of 0.05.

The analytical plan called for switching from a non-inferiority to superiority comparison if the lower confidence interval of the treatment effect on the primary efficacy variable should lie entirely above zero, using the intent-to-treat data set.

10.2.1.7.3 Data Safety Monitoring Board (DSMB) [M5, v 1.41, sec 5.3.5.1, p 198]

The protocol called for creation of an independent Data Safety Monitoring Board consisting of one statistician and two clinicians to evaluate the safety and conduct of the study. A standard operating procedure manual was to be issued. The DSMB would have the authority to recommend halting the trail for reasons of safety.

No interim analyses were planned or performed in this study.

10.2.2 Changes to the Protocol or Plan

10.2.2.1 Protocol amendments

The original protocol was amended four times, all during the course of the study. Protocols in different countries were amended different numbers of times, depending on when they joined the project relative to the ongoing amendment process. Ultimately, all centers in all countries adhered to the same protocol. The clinically significant amendments (excluding typographical corrections, changes in personnel, etc.) are shown in the next Table.

Table 78: Protocol Amendments: KL4-IRDS-02

Issue	Original	Amended	Comment
Timing of first dose	Within 15 mins of birth	Between 15 and 30 minutes after birth	
Curosurf dosage	200 mg/kg for first dose	175 mg/kg for first dose	To agree with publication (see 10.2.1.3 above)
Randomization	Straight randomization scheme	Randomized with birth weight stratification	
Gestational age requirement	24-29 weeks	24 to <29 weeks	
Retreatment dosage	Based on actual weight	Based on initial estimated weight	

Issue	Original	Amended	Comment
Timing of chest x-ray	20-28 hrs of age	24 ± 6 hrs	"To avoid unnecessary x-rays"
BPD definition	Require supplemental oxygen	Also require mechanical ventilation and require oxygen to maintain oxygen saturation > 90%	
Timing for air leaks	Through 36 weeks PCA	Through 7 days of age and 36 weeks PCA	For consistency with other Surfaxin studies
Post-dose ventilator management	Elevate head of bed 5°	Elevate head of bed 10°	"To be more in accordance with standard practices"
Arterial blood gas measurements	None prior to first dose	Required prior to first dose	
RDS-related mortality	None	RDS-related mortality through 14 days added as secondary endpoint	For consistency with other Surfaxin studies
Air leak	None	Air leak from parenchymal lung disease added	
Statistical analysis	None	AUC measurements analyzed for FiO_2 and MAP	To minimize variation associated with time point measurements
Source: M5, v 1.41, sec 5.3.5.1, p 36			

10.2.2.2 Early termination [M5, v 1.41, sec 5.3.5.1, p 38]

The study was stopped before the planned enrollment was reached because the study had gone on longer than anticipated and "priority and resources were shifted to the pivotal KL4-IRDS-06 study."

10.2.3 Results

The study's short-term phase was conducted from August 17, 2001, through May 28, 2003. The 6- and 12-month follow-up evaluations continued on. Results of the follow-up phases were submitted to the NDA in the 4-month safety update and are reviewed in section 7.2.9 above.

10.2.3.1 Study patients

At the time of premature termination, 252 of the planned 496 patients had been enrolled in 22 study centers in the U.S., Canada, Poland, Hungary, Spain, U.K., Portugal, and France. Disposition of the patients is shown in the next Table.

Table 79: Patient Disposition: KL4-IRDS-02

	Surfaxin	Curosurf	Overall
Randomized (ITT population)	124	128	252
Treated (Per Protocol population)	119	124	243
Discontinued	0	0	0
Died (ITT)	21	25	46
Completed (ITT)	103	103	206
Died (per protocol)	19	23	42
Completed (per protocol)	100	101	201
Source: M5, v 1.41, sec 5.3.5.1, pp 38-39			

Nine patients were randomized but not treated. The reasons by treatment and patient number were:

- Surfaxin
  - 081001 – medication did not arrive in the NICU within the specified time for treatment
  - 422001 – randomization was in error, the birth weight was 1325 grams
  - 431008 – the patient was not treated because of "a misunderstanding about the gestational age requirement"
  - 471007 – the necessary personnel for treatment were not available
  - 511010 – a congenital anomaly was detected after randomization
- Curosurf
  - 401002 – the randomization envelope was opened before assigning the APGAR score which was ≤3 and excluded the patient from the study
  - 402002, 472001 – the patients did not need to be intubated
  - 431004 – a congenital anomaly was detected after randomization

The enrollment by country is shown in Table 80.

Table 80: Enrollment by Country: KL4-IRDS-02

Country	Surfaxin	Curosurf	Total
U.K.	11	8	19
Poland	16	16	32
Hungary	30	31	61
Spain	23	23	46
Portugal	4	6	10
France	24	25	49
U.S.	14	16	30
Canada	2	3	5
Source: M5, v 1.41, sec 5.3.5.1, p 53			

10.2.3.2 Protocol deviations

The protocol deviations as reported by the Applicant are summarized in Table 81.

Table 81: Protocol Deviations: KL4-IRDS-02

Deviation	Surfaxin (N)	Curosurf (N)
Birth weight not 600-1250 g/ gestational age outside limits	2	1
Not intubated successfully prior to randomization	1	4
5-minute APGAR ≤ 3	2	1
Major congenital malformation	1	1
Informed consent not signed	1	2
Heart rate not stabilized	0	1
Delivery after 2 weeks ruptured membranes	2	2
Delivery room resuscitation	0	1
Source: M5, v 1.41., sec 5.3.5.1, p 39		

The only noticeable difference in the protocol deviations is that slightly more Curosurf patients were not intubated successfully before randomization. The data listings were reviewed to determine whether any reason was apparent for that difference, and in the course of that review several errors were noted in the information provided in the application from which the above Table was constructed. Curosurf patient 402002 is represented in the source information with several protocol deviations but the data listings do not confirm three of the deviations. One of the deviations reported for the patient is birth weight outside the allowed range, but the data listings show a weight within the range; while another patient's weight is outside the range but not indicated as such in the study report. In other words, there appear to be several errors in the data from which Table 81 is derived, making it unreliable.

10.2.3.3 Demographic and baseline characteristics

Baseline neonatal and maternal characteristics for all randomized patients are shown in the next two Tables.

Table 82: Neonatal Baseline and Demographic Characteristics: KL4-IRDS-02

Characteristic	Surfaxin (N=124)	Curosurf (N=128)	p-value
	N (%)		
Birth Status			0.701
Single	90 (72.6)	91 (71.1)	
Multiple	34 (27.4)	37 (28.9)	
Congenital anomaly	3 (2.4)	5 (3.9)	0.532
Mode of delivery			0.598
Vaginal spontaneous	46 (37.1)	39 (30.5)	
Vaginal assisted	4 (3.2)	5 (3.9)	
Elective C-section	3 (2.4)	2 (1.6)	
Emergency C-section	71 (57.3)	82 (64.1)	
Race			0.554
White	105 (84.7)	104 (81.3)	
Black	4 (3.2)	7 (5.5)	
Hispanic	9 (7.3)	7 (5.5)	
Other	6 (4.8)	10 (7.8)	
Gender			0.731
Male	60 (48.4)	66 (51.6)	
Female	64 (51.6)	62 (48.4)	
Apgar – 1 min			0.814
Mean (S.D.)	5.8 (2.08)	5.8 (2.16)	
N	124	127	
Apgar – 5 min			0.648
Mean (S.D.)	7.9 (1.54)	7.9 (1.45)	
N	123	127	
Gestational age (weeks)			0.663
Mean (S.D.)	26.9 (1.21)	27.0 (1.42)	
N	122	126	

Characteristic	Surfaxin (N=124)	Curosurf (N=128)	p-value
Weight (g)			0.909
Mean (S.D.)	931.7 (190.55)	937.1 (194.22)	
N	124	128	
Length (cm)			0.934
Mean (S.D.)	34.9 (3.15)	35.0 (3.47)	
N	112	119	
Head circumference (cm)			0.196
Mean (S.D.)	24.9 (1.70)	25.1 (2.21)	
N	122	127	
Source: M5, v 1.48, sec 5.3.5.1, p 2604ff			

Table 83: Maternal Characteristics: KL4-IRDS-02

Characteristic	Surfaxin (N=124)	Curosurf (N=128)	p-value
Maternal age (yr)			0.796
Mean (S.D.)	29.7 (5.77)	29.8 (5.81)	
Gravidity			0.604
Mean (S.D.)	2.7 (1.84)	2.6 (1.71)	
Parity			0.980
Mean (S.D.)	2.0 (1.27)	2.0 (1.20)	
	N (%)		
Clinical chorioamnionitis	23 (18.5)	27 (21.1)	0.359
Gestational diabetes	1 (0.8)	7 (5.6)	0.036
Pregnancy-induced hypertension	15 (12.3)	13 (10.2)	0.499
Insulin-dependent diabetes	2 (1.6)	3 (2.3)	0.705
Labor			0.300
Spontaneous	75 (83.3)	87 (87.0)	
Induced	15 (16.7)	13 (13.0)	
Missing	34	28	
Oligohydramnios > 21 days	5 (4.0)	4 (3.2)	0.652
Antenatal steroids	109 (87.9)	107 (83.6)	0.358
Tocolytic therapy	73 (59.3)	80 (62.5)	0.656
Diabetes, gestational or insulin-dependent	2 (1.6)	7 (5.5)	0.097

Source: M5, v 1.48, sec 5.3.5.1, p 2596ff

The only treatment group difference in any of these characteristics is the higher incidence of maternal diabetes in the Curosurf patients. Although maternal diabetes is a poor prognostic factor for the neonate, the actual number of affected patients is most likely too low to account for any clinical difference, despite the statistical difference.

The results for these characteristics in the per protocol population are consistent with those in the randomized population, including the difference in maternal diabetes.

10.2.3.4 Efficacy endpoint outcomes

The primary results presented by the Applicant were for the per protocol population and those results are represented in this review. Despite the protocol plan to also provide results of intent-to-treat analyses, those are not included in the Application.

10.2.3.4.1 Primary efficacy endpoint

Results for the primary efficacy analysis are shown in Table 84. The Applicant concluded that non-inferiority in the endpoint was demonstrated because the lower confidence interval limit did not fall outside the established margin of -14.5%.

Table 84: Patients Alive Without BPD at 28 Days: KL4-IRDS-02

	Surfaxin (N=119)	Curosurf (N=124)	Surfaxin Minus Curosurf
Alive Without BPD at 28 Days			
N (%)	45 (37.82)	41 (33.06)	4.75 %
95% C.I.	(29.10, 46.53)	(24.78, 41.34)	(-7.27, 16.77)

Source: M5, v 1.41, sec 5.3.5.1, p 42

Inexplicably, subset analyses were not presented for the primary endpoint at the 28-day time point, but were for 36 weeks PCA, which was a secondary endpoint. Those subset results were consistent with the 28-day overall results in showing no difference between treatments, although confidence intervals were not presented for the results.

10.2.3.4.2 Secondary efficacy endpoints

Although they were secondary endpoints in this study, incidence of RDS at 24 hours and RDS-related mortality were primary endpoints in KL4-IRDS-06, so they are displayed separately in the next Table to allow easier reference back to results in the other study. Several of the other secondary endpoints are then shown in the following Table. Determination of cause of death was made by the investigator in this study. There were no differences between any of the treatments for any of the secondary endpoints displayed in Table 85 and Table 86, however, non-inferiority analyses were not performed for any of these endpoints so the possible conclusions about comparative efficacy are limited.

Table 85: Incidence of RDS and RDS-Related Mortality: KL4-IRDS-02

Endpoint	Surfaxin (N=119)	Curosurf (N=124)	p-value Surfaxin vs. Curosurf
	N (%)		

Endpoint	Surfaxin (N=119)	Curosurf (N=124)	p-value Surfaxin vs. Curosurf
Incidence of RDS at 24 Hours	22 (18.5)	19 (15.3)	0.508
RDS-Related Mortality at 14 Days	1 (0.8)	0	0.779
Source: M5, v 1.41, sec 5.3.5.1, p 46			

Table 86: Secondary Efficacy Endpoint Results: KL4-IRDS-02

Endpoint	Surfaxin (N=119)	Curosurf (N=124)	p-value Surfaxin vs. Curosurf
	N (%)		
Number of Surfactant Doses			0.211
1 dose only	80 (67.2)	92 (74.2)	
≥ 2 doses	39 (32.8)	32 (25.8)	
All-cause Mortality			
14 Days	13 (10.9)	17 (13.7)	0.498
28 Days	14 (11.8)	20 (16.1)	0.266
36 Weeks PCA	19 (16.0)	23 (18.5)	0.478
Discharge	19 (16.0)	23 (18.5)	0.478
BPD – Not Imputed for Death			
28 Days	74 (62.2)	79 (63.7)	0.632
36 Weeks PCA	42 (35.3)	36 (29.0)	0.314
Alive Without BPD at 36 Weeks PCA	77 (64.7)	84 (67.7)	0.737
Air Leaks at 7 Days – Not imputed for Death			
Overall	11 (9.2)	9 (7.3)	0.538
PIE	3 (2.5)	6 (4.8)	0.309
Pneumomediastinum	0	1 (0.8)	0.843
Pneumothorax	5 (4.2)	1 (0.8)	0.059
Air Leaks at 36 Weeks PCA – Not imputed for Death			
Overall	17 (14.3)	13 (10.5)	0.378
PIE	6 (5.0)	9 (7.3)	0.351
Pneumomediastinum	0	1 (0.8)	0.843
Pneumothorax	7 (5.9)	2 (1.6)	0.055
	Mean (S.D.)		
Severity of RDS			
FiO_2 AUC	0.30 (0.14)	0.29 (0.15)	0.426
MAP AUC	5.92 (3.41)	5.32 (3.38)	0.209
Number of Days Through 36 Weeks PCA For:			
Mechanical Ventilation	23.6 (26.14)	22.6 (25.87)	0.968
Oxygen	37.5 (26.81)	36.4 (25.76)	0.754
Hospitalization	59.3 (13.33)	59.0 (13.87)	0.867
Source: M5, v 1.41, sec 5.3.5.1, pp 43-49			

The causes of death, as assigned by the investigators, among all randomized patients are summarized in Table 87.

Reviewer's Comment: ***A pertinent negative in the results is that renal and sepsis deaths were no different in this study, in contract to KL4-IRDS-06. Indeed, for sepsis a difference appears in the opposite direction, favoring Surfaxin.***

Table 87: Causes of Death: KL4-IRDS-02

Cause of Death	Surfaxin (N=124)	Curosurf (N=128)
	N (%)	

Cause of Death	Surfaxin (N=124)	Curosurf (N=128)
Air leak	3 (2.4)[a]	2 (1.6)
IVH	5 (4.0)	8 (6.3)
NEC	3 (2.4)	1 (0.8)[a]
Pulmonary hemorrhage	0	0
Renal failure	0	0
Sepsis	5 (4.0)	9 (7.0)
RDS	1 (0.8)	1 (0.8)
Cardiac failure	2 (1.6)	0
Congenital anomaly	2 (1.6)[a]	1 (0.8)[a]
Other	0	3 (2.3)
[a] One patient randomized but not treated		
Source: M5, v 1.41, sec 5.3.5.1, p 67		

The next Table summarizes the results for the concurrent diagnoses. There were no differences except for a higher rate of periventricular leukomalacia in Curosurf patients, a paradoxical result considering the rate of IVH was not different.

Table 88: Concurrent Diagnoses: KL4-IRDS-02

Concurrent Diagnosis	Stage/ Grade	Surfaxin (N=119)	Curosurf (N=124)	p-value Surfaxin vs. Curosurf
		N (%)		
IVH				0.332
	None	73 (61.3)	76 (61.3)	
	I	14 (11.8)	20 (16.1)	
	II	16 (13.4)	17 (13.7)	
	III	7 (5.9)	5 (4.0)	
	IV	9 (7.6)	5 (4.0)	
	Overall	46 (38.7)	47 (37.9)	0.924
NEC				0.933
	None	103 (86.6)	105 (84.7)	
	I	7 (5.9)	8 (6.5)	
	IIa	1 (0.8)	4 (32.)	
	IIb	0	2 (1.6)	
	IIIa	2 (1.7)	2 (1.6)	
	IIIb	6 (5.0)	3 (2.4)	
	Overall	16 (13.4)	19 (15.3)	0.626
Periventricular leukomalacia	Yes	5 (4.2)	12 (9.7)	0.097
Apnea	Yes	78 (65.5)	93 (75.0)	0.131
PDA	Yes	51 (42.9)	54 (43.5)	0.807
ROP				0.796
	None	80 67.2)	83 (66.9)	
	1	18 (15.1)	17 (13.7)	
	2	14 (11.8)	12 (9.7)	
	3	6 (5.0)	9 (7.3)	
	4	0	1 (0.8)	
	Overall	38 (31.9)	39 (31.5)	0.934
Pulmonary hemorrhage	Yes	7 (5.9)	10 (8.1)	0.495
Acquired Sepsis	Yes	54 (45.4)	64 (51.6)	0.119
Source: M5, v 1.41, sec 5.3.5.1, p 51				

10.2.3.5 Safety outcomes

Safety analyses included all patients who received at least one dose.

10.2.3.5.1 Exposure

The number of patients who received each possible number of doses of the surfactants is shown in Table 89.

Table 89: Number of Doses of Surfactant: KL4-IRDS-02

Number of Doses	Surfaxin (N=124)	Curosurf (N=128)	p-value Surfaxin vs. Curosurf
	N (%)		
0	5 (4.0)	4 (3.1)	0.522
1	80 (64.5)	92 (71.9)	
2	23 (18.5)	28 (21.9)	
3	16 (12.9)	4 (3.1)	

Source: M5, v 1.41, sec 5.3.5.1, p 55

10.2.3.5.2 Adverse events

As with study KL4-IRDS-06, the Applicant included in summary tables only those AEs occurring in ≥10% of patients. For this review, however, as with KL4-IRDS-06, the summary Table below, in two parts, includes AEs occurring in ≥1% of patients and more frequently in Surfaxin patients as well as all AEs occurring in ≥10% of patients. Every patient in this study experienced at least one AE. The most common events were neonatal jaundice, anemia neonatal, neonatal apnea, BPD, RDS, and PDA. These same events were also among the most common in KL4-IRDS-06. The rates of the events in Surfaxin-treated patients were similar in the two studies for anemia neonatal and RDS, and about 10% higher in this study for jaundice, BPD, apnea, and PDA, but the rates were not different from Curosurf in this study. Higher rates occurred in KL4-IRDS-06 for IVH and comparable rates occurred for neonatal sepsis.

Table 90: Adverse Events in At Least 1% of Patients and More Frequent in Surfaxin Patients (Part 1): KL4-IRDS-02

MedDRA Organ Class/ MedDRA Preferred Term	Surfaxin (N=119)	Curosurf (N=124)	p-value Surfaxin vs. Curosurf
	N (%)		
ANY EVENT	119 (100)	124 (100)	
Blood and lymphatic system	94 (79.0)	93 (75.0)	0.543
Anemia neonatal	92 (77.3)	92 (74.2)	0.654
Leukocytosis NOS	2 (1.7)	0	0.239
Thrombocytopenia neonatal	8 (6.7)	3 (2.4)	0.130
Cardiac disorders	43 (36.1)	46 (37.1)	0.895
Bradycardia NOS	22 (18.5)	26 (21.0)	0.633
Cardiac murmur NOS	13 (10.9)	18 (14.5)	0.446
Neonatal cardiac failure	5 (4.2)	4 (3.2)	0.745
Pericardial effusion	2 (1.7)	0	0.239
Congenital, familial, genetic disorders	52 (43.7)	55 (44.4)	1.000
Patent ductus arteriosus	51 (42.9)	53 (42.7)	1.000
Ear and labyrinth disorders	4 (3.4)	2 (1.6)	0.439
Hearing impaired	3 (2.5)	2 (1.6)	0.679
Endocrine disorders	3 (2.5)	5 (4.0)	0.722
Eye disorders	39 (32.8)	39 (31.5)	0.891
Retrolental fibroplasia[a]	37 (31.1)	38 (30.6)	1.000
Retinal vascular disorder NOS	2 (1.7)	0	0.239
Gastrointestinal disorders	60 (50.4)	57 (46.0)	0.522
Abdominal distention	12 (10.1)	15 (12.1)	0.686
Anal fissure	2 (1.7)	0	0.239

MedDRA Organ Class/ MedDRA Preferred Term	Surfaxin (N=119)	Curosurf (N=124)	p-value Surfaxin vs. Curosurf
	N (%)		
Constipation	4 (3.4)	4 (3.2)	1.000
Gastric hemorrhage	3 (2.5)	1 (0.8)	0.362
Gastro-esophageal reflux disease	14 (11.8)	13 (10.5)	0.839
Gastrointestinal hemorrhage NOS	4 (3.4)	4 (3.2)	1.000
Gastrointestinal motility disorder	3 (2.5)	2 (1.6)	0.679
Inguinal hernia NOS	10 (8.4)	8 (6.5)	0.629
Intestinal perforation	4 (3.4)	1 (0.8)	0.206
Necrotizing enterocolitis	16 (13.4)	16 (12.9)	1.000
Umbilical hernia NOS	11 (9.2)	8 (6.5)	0.479
Vomiting neonatal	7 (5.9)	3 (2.4)	0.209
General disorders	36 (30.3)	36 (29.0)	0.889
Edema NOS	25 (21.0)	24 (19.4)	0.752
Edema lower limb	2 (1.7)	2 (1.6)	1.000
Pyrexia	3 (2.5)	1 (0.8)	0.362
Temperature regulation disorder NOS	2 (1.7)	1 (0.8)	0.616
Hepato-biliary disorders	95 (79.8)	96 (77.4)	0.755
Jaundice neonatal	93 (78.2)	94 (75.8)	0.761
Infections and infestations	87 (73.1)	98 (79.0)	0.295
Bacterial infection NOS	4 (3.4)	4 (3.2)	1.000
Fungal infection NOS	6 (5.0)	3 (2.4)	0.326
Neonatal conjunctivitis NOS	17 (14.3)	18 (14.5)	1.000
Nosocomial infection	3 (2.5)	1 (0.8)	0.362
Omphalitis	13 (10.9)	15 (12.1)	0.842
Pneumonia NOS	19 (16.0)	22 (17.7)	0.735
Respiratory tract infection NOS	2 (1.7)	2 (1.6)	1.000
Sepsis neonatal	45 (37.8)	51 (41.1)	0.603
Septic shock	4 (3.4)	4 (3.2)	1.000
Injury and poisoning	5 (4.2)	12 (9.7)	0.131
Source: M5, v 1.48, sec 5.3.5.1, p 2718ff			

Table 91: Adverse Events in At Least 1% of Patients and More Frequent in Surfaxin Patients (Part 2): KL4-IRDS-02

MedDRA Organ Class/ MedDRA Preferred Term	Surfaxin (N=119)	Curosurf (N=124)	p-value Surfaxin vs. Exosurf
	N (%)		
Investigations	40 (33.6)	36 (29.0)	0.490
Oxygen saturation decreased	30 (25.2)	27 (21.8)	0.548
PO_2 increased	2 (1.7)	1 (0.8)	0.616
Metabolism and nutrition disorders	79 (66.4)	82 (66.1)	1.000
Acidosis NOS	12 (10.1)	11 (8.9)	0.828
Dehydration	3 (2.5)	2 (2.4)	1.000
Feeding disorder NOS	15 (12.6)	11 (8.9)	0.409
Food intolerance NOS	7 (5.9)	5 (4.0)	0.565
Hyperglycemia NOS	27 (22.7)	26 (21.0)	0.758
Hyperkalemia	12 (10.1)	13 (10.5)	1.000
Hypermagnesemia	7 (5.9)	5 (4.0)	0.565
Hypernatremia	9 (7.6)	3 (2.4)	0.079
Hypokalemia	9 (7.6)	9 (7.3)	1.000
Hyponatremia	28 (23.5)	31 (25.0)	0.881
Hypovolemia	2 (1.7)	0	0.239
Musculoskeletal, connective tissue, bone	1 (0.8)	0	0.490
Nervous system disorders	25 (21.0)	33 (26.6)	0.367
Convulsion neonatal	11 (9.2)	11 (8.9)	1.000
Hydrocephalus NOS	2 (1.7)	2 (1.6)	1.000

MedDRA Organ Class/ MedDRA Preferred Term	Surfaxin (N=119)	Curosurf (N=124)	p-value Surfaxin vs. Exosurf
	N (%)		
Hypotonia neonatal	2 (1.7)	0	0.239
Pregnancy and perinatal conditions	1 (0.8)	0	0.490
Psychiatric disorders	2 (1.7)	1 (0.8)	0.616
Renal and urinary	15 (12.6)	21 (16.9)	0.371
Oliguria	3 (2.5)	3 (2.4)	1.000
Renal failure NOS	2 (1.7)	0	0.239
Urinary tract infection NOS	2 (1.7)	1 (0.8)	0.616
Reproductive system	3 (2.5)	1 (0.8)	0.362
Respiratory, thoracic, mediastinal	111 (93.3)	118 (95.2)	0.590
Airway obstruction NOS	2 (1.7)	1 (0.8)	0.616
BPD	58 (48.7)	57 (46.0)	0.701
Bronchospasm NOS	2 (1.7)	1 (0.8)	0.616
Dyspnea NOS	6 (5.0)	3 (2.4)	0.326
Hypercapnia	8 (6.7)	8 (6.5)	1.000
Hypocapnia	6 (5.0)	2 (1.6)	0.165
Intercostal retraction	5 (4.2)	5 (4.0)	1.000
Neonatal apneic attack	72 (60.5)	87 (70.2)	0.138
Neonatal respiratory acidosis	16 (13.4)	20 (16.1)	0.592
Neonatal RDS	58 (48.7)	54 (43.5)	0.442
Neonatal respiratory failure	2 (1.7)	1 (0.8)	0.616
Pneumothorax NOS	11 (9.2)	3 (2.4)	0.027
Rhinitis NOS	7 (5.9)	6 (4.8)	0.781
Rhinorrhea	7 (5.9)	4 (3.2)	0.368
Tachypnea	4 (3.4)	3 (2.4)	0.718
Skin and subcutaneous tissue	23 (19.3)	14 (11.3)	0.107
Contusion	7 (5.9)	1 (0.8)	0.033
Dermatitis NOS	5 (4.2)	2 (1.6)	0.273
Dermatitis contact	3 (2.5)	1 (0.8)	0.362
Hemangioma NOS	5 (4.2)	0	0.027
Skin discoloration	2 (1.7)	1 (0.8)	0.616
Surgical and medical procedures	4 (3.4)	3 (2.4)	0.718
Vascular disorders	67 (56.3)	71 (57.3)	0.898
Hematoma NOS	2 (1.7)	2 (1.6)	1.000
Intracranial hemorrhage NOS	2 (1.7)	0	0.239
IVH NOS	2 (1.7)	1 (0.8)	0.616
IVH neonatal	42 (35.3)	44 (35.5)	1.000
Neonatal hypotension	25 (21.0)	24 (19.4)	0.752
Pulmonary hypertension NOS	2 (1.7)	2 (1.6)	1.000
Source: M5, v 1.8, sec 5.3.5.1, p 2718ff			

10.2.3.5.2.1 Deaths and serious adverse events

Deaths are considered as efficacy measures in this study and reviewed in that section.

The serious AEs occurring more commonly in Surfaxin patients or in ≥10% of patients are shown in the next Table.

Table 92: Serious Adverse Events: KL4-IRDS-02

MedDRA Organ Class/ MedDRA Preferred Term	Surfaxin (N=119)	Curosurf (N=124)	p-value Surfaxin vs. Curosurf
	N (%)		
ANY EVENT	76 (63.9	79 (63.7)	1.000

MedDRA Organ Class/ MedDRA Preferred Term	Surfaxin (N=119)	Curosurf (N=124)	p-value Surfaxin vs. Curosurf
	N (%)		
Blood and lymphatic system	1 (0.8)	0	0.490
Cardiac disorders	5 (4.2)	2 (1.6)	0.273
Bradycardia NOS	1 (0.8)	0	0.490
Cardiac failure NOS	2 (1.7)	0	0.239
Pericardial effusion	1 (0.8)	0	0.239
Pulmonary edema NOS	1 (0.8)	0	0.490
Congenital, familial, genetic disorders	15 (12.6)	12 (9.7)	0.542
Congenital pulmonary artery anomaly NOS	1 (0.8)	0	0.490
Tetralogy of Fallot	1 (0.8)	0	0.490
Patent ductus arteriosus	14 (11.8)	11 (8.9)	0.529
Eye disorders	7 (5.9)	8 (6.5)	1.000
Retrolental fibroplasia	7 (5.9)	8 (6.5)	1.000
Gastrointestinal disorders	11 (9.2)	10 (8.1)	0.821
Ileal perforation	1 (0.8)	0	0.490
Inguinal hernia NOS	2 (1.7)	1 (0.8)	0.616
Intestinal perforation NOS	4 (3.4)	1 (0.8)	0.206
Necrotizing enterocolitis	8 (6.7)	6 (4.8)	0.590
Infections and infestations	19 (16.0)	29 (23.4)	0.152
Respiratory tract infection NOS	1 (0.8)	0	0.490
Sepsis neonatal	11 (9.2)	13 (10.5)	0.831
Septic shock	4 (3.4)	4 (3.2)	1.000
Metabolism and nutrition disorders	3 (2.5)	3 (2.4)	1.000
Acidosis NOS	2 (1.7)	0	0.239
Fatty acid deficiency	1 (0.8)	0	0.490
Nervous system disorders	1 (0.8)	7 (5.6)	0.066
Renal and urinary	0	1 (0.8)	1.000
Respiratory, thoracic, mediastinal disorders	59 (49.6)	53 (42.7)	0.305
BPD	16 (13.4)	8 (6.5)	0.085
Bronchospasm NOS	1 (0.8)	0	0.490
Dyspnea NOS	1 (0.8)	0	0.490
Neonatal RDS	37 (31.1)	32 (25.8)	0.395
Neonatal respiratory failure	1 (0.8)	0	0.490
Pneumothorax NOS	9 (7.6)	2 (1.6)	0.031
Surgical and medical	0	1 (0.8)	1.000
Vascular disorders	16 (13.4)	14 (11.3)	0.698
Intracranial hemorrhage NOS	1 (0.8)	0	0.490
IVH neonatal	12 (10.1)	9 (7.3)	0.498
Neonatal hypotension	4 (3.4)	2 (1.6)	0.439
Source: M5, v 1.41, sec 5.3.5.1, p 68			

Two serious events were reported more frequently in Surfaxin patients, at the 10% level of significance, in this study: BPD and pneumothorax. As noted, the overall rates of those events were not different when considered as efficacy measures.

10.2.3.5.2.2 Discontinuations due to adverse events

No patients discontinued from this study because of AEs.

10.2.3.5.3 Negative reactions to dose administration

Reaction to dosing was evaluated in exactly the same way in this study as in KL4-IRDS-06. The results are shown in Table 93. As in KL4-IRDS-06, more frequent reactions were seen with Surfaxin administration, although there were fewer differences in this study in comparison to

Curosurf than in comparison to Exosurf in the other study. The predominant reaction in this study was obstruction and the Applicant notes that 9 of the 27 (33%) obstruction events occurred at a single center, which enrolled 7% of all patients in the study. From the data available, it is impossible to know if this heavy reporting at one center was due to some common administration technique at the center, different reporting, higher acuity of illness, or some other factor.

Table 93: Negative Reactions to Dose Administration: KL4-IRDS-02

	Surfaxin	Curosurf	p-value Surfaxin vs. Curosurf
	N (%)		
Dose 1	**N=119**	**N=124**	
Interruption	5 (4.2)	1 (0.8)	0.114
Pallor	13 (11.0)	4 (3.2)	0.023
Apnea	7 (5.9)	2 (1.6)	0.096
ETT reflux	32 (27.1)	27 (21.8)	0.370
ETT obstruction	16 (13.6)	1 (0.8)	<0.001
Dose 2	**N=39**	**N=32**	
Interruption	1 (2.6)	1 (3.1)	1.000
Pallor	4 (10.5)	3 (9.4)	1.000
Apnea	5 (13.5)	2 (6.3)	0.437
ETT reflux	8 (21.1)	3 (9.4)	0.208
ETT obstruction	6 (15.8)	0	0.028
Dose 3	**N=16**	**N=4**	
Interruption	1 (6.3)	0	1.000
Pallor	1 (6.7)	0	1.000
Apnea	1 (6.7)	0	1.000
ETT reflux	7 (46.7)	1 (25.0)	0.603
ETT obstruction	5 (33.3)	0	0.530
Source: M5, v 1.41, sec 5.3.5.1, p 60			

10.2.3.5.4 Concomitant medications

The next Table summarizes in a manner similar to KL4-IRDS-06 the medications used in this study. Unlike in the previous study, more Surfaxin patients were given sedatives as a group in this study. That difference was accounted for by the only difference for an individual medication, midazolam (47.9% Surfaxin vs. 34.7% Curosurf, p=0.038).

Table 94: Concomitant Medications: KL4-IRDS-02

Drug Class	Surfaxin (N=119)	Curosurf (N=124)	p-value Surfaxin vs. Curosurf
Vasopressors	63 (52.9)	71 (57.3)	0.521
Sedatives	107 (89.9)	98 (79.0)	0.022
Steroids	52 (43.7)	49 (39.5)	0.518
Bronchodilators	69 (58.0)	65 (52.4)	0.439
Antibiotics	117 (98.3)	122 (98.4)	1.000
Diuretics	69 (58.0)	82 (66.1)	0.234
Source: M5, v 1.41, sec 5.3.5.1, p 61			

10.2.3.5.5 Vital signs and physical examinations [M5, v 1.41, sec 5.3.5.1, pp 70-74]

The results of these evaluations were very similar to those in KL4-IRDS-02, with spotty statistical differences at several time points, but all differences were small and generally not clinically significant.

10.2.4 Study Summary and Discussion

Like its companion study KL4-IRDS-06, KL4-IRDS-02 was an international, multicenter, randomized, masked, active comparator-controlled study in the prevention strategy. Neonates of the same birth weights and prematurity were enrolled in the two studies. Despite these important similarities, however, KL4-IRDS-02 contributes relatively little to the evidence for efficacy of Surfaxin because of critical differences between the studies that override the similarities, as follows.

- Although KL4-IRDS-02 used a prevention strategy, its design and sample size determination were based on a published study using the rescue strategy. That invalidates use of the study to establish non-inferiority margins and everything that derives from the margins; i.e., sample size and estimates of efficacy. A rescue strategy would overestimate the expected rate of the primary efficacy variable relative to a prevention strategy and consequently establish an inappropriate non-inferiority margin.

- The comparator surfactant used in this study is not approved in the U.S. for the prevention strategy, only for the rescue strategy.

- The primary efficacy variable was different from study KL4-IRDS-06. Although the co-primary endpoints in KL4-IRDS-06 were included as secondaries in this study, they were evaluated in a critically different way; i.e., an independent Adjudication Committee vs. the investigators' clinical interpretations.

- A different dosing regimen for Surfaxin was used in this study than in KL4-IRDS-06 (fewer total doses) and the regimen for Curosurf was not the regimen approved in the U.S. (smaller first dose, shorter interval between doses). These differences weaken the contribution of this study's results to the safety evaluations.

- The study was terminated early at about half the planned enrollment.

The study's contribution to the demonstration of effectiveness is tempered by these factors. It was relied upon for this review for evidence of *consistency* with KL4-IRDS-06, and the results in fact provided that consistency. There were no differences in incidence of RDS or RDS-related deaths, but the study was not designed or powered to detect them. The rates of those events, however, were generally similar to those in the other study, as were the results for the secondary endpoints.

The study also provided a source for additional safety evidence and was valuable in that regard. First, the higher rate of negative reactions to dosing was replicated in this study. On the other hand, no differences were noted in this study for renal or infectious AEs.

10.3 Line-by-Line Labeling Review

Refer to section 9.4.

11 REFERENCES

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/s/

John Gunkel
1/14/05 01:34:45 PM
MEDICAL OFFICER

Peter Starke
1/14/05 02:58:47 PM
MEDICAL OFFICER
I concur with this review.

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-746	**TRADE NAME:**	Surfaxin
APPLICANT/SPONSOR:	Discovery Laboratories, Inc.	**USAN NAME:**	Lucinactant
MEDICAL OFFICER:	J. Harry Gunkel, M.D.		
TEAM LEADER:	Peter Starke, M.D.	**CATEGORY:**	Lung surfactant
DATE OF REVIEW:	May 21, 2004	**ROUTE:**	Intratracheal instillation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
April 13, 2004	April 13, 2004	NDA 21-746	Paper in CTD format

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW SUMMARY: This is a paper NDA for Surfaxin, a synthetic lung surfactant for "the prevention of respiratory distress syndrome (RDS) in premature infants". The application follows the CTD format with 148 volumes in clinical/statistical Module 5. Reports of nine clinical studies, complete and ongoing, are included in the application. Four studies are for the neonatal RDS indication and five are for two other indications. One of the neonatal RDS studies is considered pivotal.

The pivotal study, conducted in Europe and Latin America, was a superiority trial comparing Surfaxin to Exosurf, an approved synthetic surfactant. The co-primary outcomes were incidence of RDS at 24 hours and RDS-related deaths at 14 days. Surfaxin was superior to Exosurf in both these outcomes and in most of the secondary outcomes as well. A third arm was included in the study where about half the number of patients received a reference surfactant, Survanta. Survanta is also approved and is a naturally-based product. Comparisons were performed between Surfaxin and Survanta "for informational purposes". There was no difference in incidence of RDS or all-cause death at 14 days. There was a difference in RDS-deaths at 14 days.

The Sponsor requested Priority Review of the application. The request is denied for two reasons. First, the data offered in the application do not convincingly demonstrate an improvement over the other marketed surfactant products. Second, the application does not include 6- or 12-month follow-up data for evaluation of long-term safety. Including the 6-month data in the application was specifically requested by the Division at the pre-NDA meeting of June, 2003. The 6-month follow-up evaluations will not be complete in time to accommodate a priority review timetable.

All required elements are present and the application is fileable.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	X	**FILEABLE**		**NOT FILEABLE**		
		APPROVAL		**APPROVABLE**		**NOT APPROVABLE**
OTHER ACTION:						

1. GENERAL INFORMATION

This is the Medical Officer Filing and Planning review for NDA 21-746. The application was filed by Discovery Laboratories, Inc., Doylestown, PA, and the subject of the application is Surfaxin® (lucinactant) Intratracheal Suspension, a synthetic lung surfactant. The proposed indication is "the prevention of respiratory distress syndrome (RDS) in premature infants".

The CDER stamp date is April 13, 2004. The application is on paper in Common Technical Document format with electronic case report forms. The CRF's are filed in the Electronic Document Room and are accessible and legible. Module 1 of the application is one volume, Module 2 is 49 volumes, and Module 5 is 148 volumes.

Surfaxin was granted Orphan Drug Designation in 1995. The Sponsor requests priority review of this NDA, on grounds that Surfaxin provides a significant improvement compared to existing marketed products in the treatment of RDS.

2. BACKGROUND AND RATIONALE

2.1 RDS

Neonatal RDS occurs primarily in premature neonates, born before pulmonary surfactant is available in sufficient quantity for normal lung function. Lung surfactant is a complex of proteins and lipids that forms a mono-layer lining of the alveolar wall. Its unique biophysical properties reduce surface tension within the alveolus such that alveolar collapse does not occur at the end of normal exhalation. When there is inadequate surfactant, surface-tension-lowering does not occur and the alveolus collapses when transpulmonary pressure increases. Widespread alveolar collapse, or atelectasis, results in reduced air exchange, ventilation-perfusion inequalities, pulmonary blood flow shunting, and increased work of breathing. The clinical consequences are respiratory distress, hypoxia and acidosis, and respiratory failure. In premature neonates, respiratory failure and its complications and treatment can result in significant morbidity and mortality.

2.2 Surfactant Replacement

After the observation that RDS is caused by surfactant deficiency and the recognition that all mammalian surfactants are remarkably similar, surfactant replacement products were developed for RDS. Bovine-and porcine-based products were developed and marketed. Investigations were also carried out to develop synthetic surfactants. There were two main challenges in the development of synthetic surfactant: which are the essential and critical components among the many proteins and lipids found in natural surfactant; and if proteins are essential, which peptide sequences or properties are most important? Experiments indicated that the low molecular-weight, hydrophobic surfactant-associated protein SP-B is necessary for optimal activity because of its critical role in ordering of the lipid mono-layer of surfactant. Several phospholipids have abundant surface activity, but the one most active in lung surfactant and most associated with lung surfactant preparations is colfosceril palmitate (formerly named dipalmitoylphosphatidylcholine [DPPC]).

Two approaches have been used in surfactant replacement therapy. The first is a prevention or prophylactic approach. In this strategy, surfactant is administered within minutes of birth or as soon as feasible to prevent the development of RDS. Because this is a preventive approach, it has been used only in those neonates whose risk for RDS is greatest; i.e., at least 50%. Generally, these are patients born before about 32 weeks gestational age. The other approach is for neonates

who did not receive prophylaxis and have developed RDS requiring mechanically assisted ventilation. This is the "rescue" or treatment strategy.

Four surfactant products have been approved in the U.S. and are shown in the table below. The first surfactant approved in the U.S., Exosurf, is no longer marketed here. Surfaxin is included in the table to illustrate its differences and similarities to the approved products.

Table 1: Surfactant Replacement Products

Drug (approval date)	Product Information	Indication
Exosurf (1990) ***No longer marketed in U.S.***	Synthetic: Colfosceril palmitate 67.5 mg/mL; tyloxapol; cetyl alcohol	Prevention and treatment of RDS
Survanta (1991)	Bovine: 25 mg PL/mL < 1 mg SP-B/mL	Prevention and treatment of RDS
Infasurf (1998)	Bovine: 35 mg PL/mL 0.26 mg SP-B/mL	Prevention and treatment of RDS
Curosurf (1999)	Porcine: 80 mg PL/mL 0.3 mg SP-B/mL	Treatment of RDS
Surfaxin	Synthetic: 30 mg PL/mL. 0.8 mg SP-B/mL	Proposed: Prevention of RDS

PL=phospholipid

Reviewer's Comment: Note that only the prevention indication is being sought for Surfaxin. The submission contains no information about use in a rescue strategy.

2.3 Surfaxin

Surfaxin contains several surface-active lipids and sinapultide, a 21-residue peptide of lysine (K) and leucine (L) residues in a KL-4 sequence (KLLLLKLLLL…etc) synthesized specifically to mimic the properties of SP-B. The composition of Surfaxin is:

Sinapultide	0.8 mg/mL
Palmitic acid	4.05 mg/mL
Colfosceril palmitate (DPPC)	22.5 mg/mL
1-Palmitoyl-2-Oleoyl-3-[Phospho-rac-(1-Glycerol)] POPG	7.5 mg/mL

The proposed dose for Surfaxin is 175 mg phospholipids/kg or 5.8 mL/kg/dose for up to four doses.

Reviewer's Comment: The differences in composition should be noted between Surfaxin and its comparator products in the pivotal study, Exosurf and Survanta. Although the concentration of phospholipids is similar, the volume dose of Surfaxin is higher resulting in delivery of considerably more phospholipids and SP-B or peptide.

3. REGULATORY AND FOREIGN MARKETING HISTORY

3.1 Regulatory History

IND 40,287 was filed for Surfaxin as "KL-4 Surfactant" in August, 1992, by Dr. Charles Cochrane of the Scripps Research Institute. (b) (4) [redacted]. This section will focus on the regulatory history of the neonatal drug development, the subject of this application.

Clinical study plans proceeded for neonatal RDS and an End-of-Phase 2 meeting was held in September, 1995. At that time, the Division communicated concerns about the clinical development plans that had been pursued. (b) (4) [redacted] The Division suggested a superiority trial to Exosurf, another synthetic surfactant that was marketed in the U.S. at the time.

Sponsorship of the IND changed hands in December, 1996, when Acute Therapeutics, Inc., acquired it. (Acute Therapeutics, Inc. subsequently became known as Discovery Laboratories, Inc.) Discussions about the design of pivotal studies for neonatal RDS continued with the new Sponsor over the next several years. In the interim, the Sponsor began to investigate Surfaxin in meconium aspiration syndrome (b) (4) [redacted]

Agreement between the Sponsor and the Division on design of a pivotal study was reached in March-April, 2001. That agreement was for a single prophylaxis strategy, superiority study with three treatment groups: Surfaxin, Exosurf as the primary comparator, and a natural surfactant as a reference. Co-primary endpoints were agreed upon: incidence of RDS at 24 hours and the composite endpoint, RDS-related deaths and/or air leak at 14 days. Subsequently, the Division acquiesced to a change in the primary endpoints proposed by the Sponsor. The Division stated that they would accept alternatives: removing the air leak component from the composite co-primary endpoint, or making the composite endpoint RDS-related deaths or air leaks instead of "and/or". The Sponsor chose the former.

On numerous occasions, the Division stated its position that long-term follow-up data would be necessary for complete evaluation of the drug. The pivotal study was to include assessments of patients at six and 12-months adjusted age. The Division stated that the 6-month data should be included in the NDA with 12-month data to follow as they became available. At the pre-NDA meeting of June 13, 2003, the Division stated, "Your NDA submission must contain complete data for the 36 week PCA [post-conceptional age] and the 6 month corrected age time points. If your NDA contains complete data for these two time points, submission of one year follow-up data as periodic amendments is acceptable to the Division." Later, in a facsimile correspondence, the Division wrote, "We reiterate our position that complete 6-month data will be necessary in order for the Division to make a determination of safety and efficacy. Therefore, we recommend that you not submit the application until the 6-month data have been analyzed. Although the Agency may file the application with less than complete 6-month data, it is most likely that the incomplete database would not be sufficient to allow a confident determination of safety and efficacy."

3.2 Foreign Marketing History

No information is included in the application about whether foreign marketing approvals have been or are being sought for Surfaxin.

4. ITEMS REQUIRED FOR FILING

4.1 Items Included in Submission

All required components of the application (21 CFR 314.50) are present as detailed in Table 2.

Table 2: NDA Required Elements

Item	Status	Location
Application Form (FDA 356h)	Present	Module 1, Section 1 (1.1)
Index / Table of Contents	Present	1.1
Format	CTD	
Samples and Labeling		
Proposed Package Insert	Present	1.7
Proposed Label	Present	1.7
Summary	Present	Module 2
Quality Overall Summary	Present	2.3
Nonclinical Summary	Present	2.6
Clinical	Present	2.7
Benefits vs. Risks	Present	2.5.6
CMC	Present	Module 3
Environmental Impact statement	Request for Categorical Exclusion under 21 CFR 25.31(a)	1 2.8 (Request for categorical exclusion)
Non-clinical Pharmacology and Toxicology	Present	Module 4
Human Pharmacokinetics and Bioavailability	N/A	
Clinical	Present	Module 5
Integrated Summary of Effectiveness (subsets for age, gender, and race)	Present	5.3.5.3
Integrated Summary of Safety	Present	5.3.5.3
Potential for Abuse	Present	
Benefits vs. Risks	Present	2.5.6
Statements of Good Clinical Practice and that all clinical studies were conducted in accordance with IRB and Informed Consent procedures	Present	Within Individual Study Reports
Safety Updates	Present	Summary 2.7.4; AERS/ADR search CDROM
Statistics	Combined with Clinical	5.3
Case Report Forms (for patients who died or did not complete studies due to AEs)	Present	Submitted Electronically to the Electronic Document Room
Patent Information	Present	1.2.1
Patent Certification	Present	1.2.2
Investigator Debarment Certification	Present	1.2.3
Field copy certification (if applicable)	Present	1.2.4
User Fee Cover Sheet	Present	1.2.5
Financial Disclosure	Present	1.2.6

Item	Status	Location
Pediatric Use	Not present	

4.2 Items Not Included in Submission

The application does not include the 6-month follow-up data that were requested by the Division (see Section 3.1 above). The absence of this information will not affect fileability of the application but is a factor in determining review status (see Section 9 below).

5. CLINICAL STUDIES

The application includes information about nine clinical studies performed in support of three indications: neonatal RDS, meconium aspiration syndrome (MAS), and adult RDS (ARDS). Four neonatal RDS studies, one designated as Pivotal by the Sponsor, comprise the basis of efficacy and safety for the NDA review for the proposed indication. The five studies for other indications will provide additional safety information about the product but will not be used to establish efficacy. All the studies are summarized in the table below.

Table 3: Surfaxin Clinical Studies

Study	Centers	Design	Test Products/ Therapies	N	Endpoints	Status
Studies for Neonatal RDS						
KL4-IRDS-06 – Pivotal Study	54 US, Europe, Latin America	•Prevention •Neonates 600-1250g •Randomized, double-blind, event-driven, active-controlled	Surfaxin 175 mg/kg Exosurf 67.5 mg/kg (Comparator) Survanta 100 mg/kg (Reference)	527 509 258	•Co-Primary: RDS at 24 hr RDS-deaths at 14 days •Numerous secondary	Complete
KL4-IRDS-02	35 US, N America, Europe	•Prevention •Neonates 600-1250g •Randomized, double-blind, active-controlled	Surfaxin 175 mg/kg Curosurf 175 mg/kg	124 128	•Primary: Alive without BPD at 28 days •Numerous secondary	Complete
KL4-IRDS-05	1 Ecuador	•Prevention •Neonates 600-1250g •Open-label, uncontrolled •Evaluate two ½-doses vs. four ¼-doses	Surfaxin 175 mg/kg	11	Numerous	Complete
KL4-IRDS-01	6 US	•Rescue •Neonates 750-1750 g •Open-label, uncontrolled	Surfaxin 133 mg/kg or 200 mg/kg	47	Efficacy endpoints not defined. Info collected about ventilation requirements, RDS, BPD, death	Complete
Studies for Meconium Aspiration Syndrome						
KL4-MAS-01	15 US	•Neonates ≥ 35 wks •Multicenter, randomized, controlled	Surfaxin 48 mL/kg by lavage over 1-2 hrs Standard of care	22		Complete
KL4-MAS-03	55 US	•Neonates ≥ 37 wks •Multicenter, randomized, open-label, controlled	Surfaxin 32 mL/kg by lavage over 1-2 hrs	55		Ongoing

Study	Centers	Design	Test Products/ Therapies	N	Endpoints	Status
Studies for Adult RDS						
KL4-ARDS-02	7 US	•Adults with ARDS •Open-label, uncontrolled, Phase 2	Surfaxin in various doses by lavage	12	Safety and tolerability	Complete
KL4-ARDS-03	34 US	•Adults with ARDS •Multicenter, randomized, open-label, controlled, Phase 3	Surfaxin in 2 lavage regimens Standard of care	14		Complete
KL4-ARDS-04	16 US	•Adults with ARDS •Multicenter, open-label, uncontrolled, two-part, Phase 2	Surfaxin in various dosage lavage regimens	56		Ongoing

5.2 Pivotal Study

Study KL4-IRDS-06, as the pivotal study for the application, is briefly summarized here.

Title: "A Multinational, Multicenter, Randomized, Masked, Controlled, Prophylaxis Superiority Trial of the Safety and Effectiveness of SURFAXIN® (lucinactant) Compared to Exosurf® (Colfosceril Palmitate) in the Prevention of Respiratory Distress Syndrome (RDS) in Premature Neonates"

The study was conducted in 54 study centers in Chile, Ecuador, Russia, Uruguay, Panama, Mexico, Brazil, Hungary, and Poland. An international trial was required because the active comparator product, Exosurf, is not marketed in the U.S. The study was conducted from July, 2001 through December, 2003. The objectives were:

1) To determine the difference in efficacy between Surfaxin and Exosurf in the prevention of RDS in premature neonates, and
2) To assess the safety profile of Surfaxin compared to that of Exosurf and Survanta.

Neonates between 600-1250 grams birth weight and gestational ages up to 32 weeks were randomized to receive Surfaxin, Exosurf, or Survanta between 15 and 30 minutes after birth. Randomization occurred in a 2:2:1 Surfaxin:Exosurf:Survanta ratio. Survanta was a reference product. The doses administered were:

Surfaxin 175 mg phospholipids/kg/dose
Exosurf 67.5 mg/kg/dose
Survanta 100 mg/kg/dose

Patients could receive additional doses if they met specified retreatment criteria that indicated ongoing respiratory distress. Three additional doses of Surfaxin or Survanta could be given at minimum 6 hour intervals and two retreatments of Exosurf could be given at 12 hour intervals. The different regimen for Exosurf adhered to the product labeling.

Patients were evaluated for efficacy and safety endpoints at several time points: 24 hours, 7 days, 14 days, 28 days, hospital discharge, 36 weeks post-conceptional age (36 weeks after the estimated date of conception, regardless of gestational age at delivery), and death. Six- and 12-month adjusted age follow-up assessments are in progress. The submission includes non-audited summaries of overall well-being for 94 patients at 6 months and 27 at 12 months. The last patient enrolled should reach 6 months adjusted age in July, 2004.

Co-primary efficacy variables for the study were: incidence of RDS at 24 hours of age, and incidence of RDS-related mortality at 14 days of age. Both assessments were based on determinations by a 7-member Adjudication Committee. This committee determined the presence of RDS based on x-ray review and clinical data provided in the Case Report Forms. A cause of death was determined based on Case Report Form data and autopsy data when available. The Adjudication Committee also determined the presence and type of pulmonary air leak, a secondary endpoint.

There were numerous secondary efficacy endpoints including all-cause mortality, pulmonary air leaks, severity of RDS, bronchopulmonary dysplasia, and days of ventilation and hospitalization. In addition, the incidences of several common complications of prematurity and RDS were determined: necrotizing enterocolitis, intracranial hemorrhage, retinopathy of prematurity, apnea, pulmonary hemorrhage, and patent ductus arteriosus. Finally, some of these endpoints were combined to form several composite endpoints (e.g., incidence of RDS and air leak). Safety assessment depended mainly on adverse experiences and negative reactions to dosing.

The basis for efficacy and safety in the study rests on superiority comparisons between Surfaxin and Exosurf. The definitions of superiority used to determine sample size were an expected incidence of RDS of 30% in the Surfaxin group vs. 40% in the Exosurf group. The estimate for RDS-deaths at 14 days was 3.5% for Surfaxin and 7.5% for Exosurf. An event-driven design was employed, and 420 RDS events and 66 deaths would detect the differences with 94% and 83% power, respectively, using 2-sided testing with α=0.05. The total sample size was planned to be 1500 patients. No adjustments were made for multiple comparisons.

Survanta was included in the study to provide reference to a naturally-derived surfactant as well as a surfactant commonly used in the U.S. The Sponsor performed statistical comparisons between Surfaxin and Survanta (see Section 9 below).

6. DSI REVIEW AND AUDIT

A DSI review will be requested. Because no U.S. centers participated in the pivotal study, auditing will be requested of heavy-enrolling centers and/or centers with disproportionate adverse experiences, deaths, or protocol violations.

7. TRADE NAME REVIEW

A review of the trade name Surfaxin was requested by the Sponsor and will be performed.

8. FILING DECISION

The application is fileable.

9. PRIORITY REVIEW DECISION

CDER MAPP 6020.3, Priority Review Policy, states that priority review may be designated for a drug product that "if approved, would be a significant improvement compared to marketed products…in the treatment, diagnosis, or prevention of a disease." Evidence is presented in the application that Surfaxin would constitute an improvement over Exosurf, an approved but no longer marketed product. However, three other surfactants are available on the market, including Survanta, which was included in the pivotal study as a reference. The Sponsor performed statistical comparisons between Surfaxin and Survanta for several outcomes in this study, and

they are tabulated below. It should be noted that the study was not designed for these comparisons and only half as many patients were randomized to Survanta as Surfaxin.

Table 4: Study KL4-IRDS-06, Summary of Primary Efficacy Endpoints

	Exosurf (509)	Surfaxin (527)	Survanta (258)
Incidence of RDS at 24 h	240 (47.2%)	206 (39.1%)	86 (33.3%)
Comparison (OR, CI)	0.679 (0.519-0.888); p=0.005	1.319 (0.941-1.849); p=0.108	
RDS-deaths at 14 days	49 (9.6%)	25 (4.7%)	27 (10.5%)
Comparison (OR, CI)	0.417 (0.246-0.707); p=0.001	0.347 (0.183-0.658); p=0.001	
All-cause deaths at 14 days	86 (16.9%)	84 (15.9%)	48 (18.6%)
Comparison (OR, CI)	0.869 (0.603-1.251); p=0.450	0.782 (0.500-1.225); p=0.284*	

OR=Odds ratio; CI=confidence interval

There was no difference between Surfaxin and Survanta in the co-primary outcome, incidence of RDS, but RDS-deaths at 14 days in the Surfaxin group were significantly fewer than in the Survanta group. However, the difference in all-cause deaths was not significant.

For perspective, the rates of comparable events in patients receiving Survanta reported in the Survanta package insert are shown below. The incidences of RDS are comparable to those in the Survanta patients in the Surfaxin study above, but the mortality rates are quite different, demonstrating the variability in these outcomes in premature neonates. For this reason, results of this single study do not constitute convincing clinical superiority of Surfaxin over the marketed product.

Table 5: Survanta Package Insert, Efficacy Endpoints

	Study 1 N=119	Study 2 N=91
Incidence of RDS	27.6%	28.6%
RDS-death at 28 d	2.5%	1.1%
All-cause death at 28 d	7.6%	16.5%

In addition, in contradistinction to specific requests from the Division, the Sponsor failed to provide long-term follow-up data with the application. A designation of priority review would require those data. Since the last patient enrolled would reach six months adjusted age in July of 2004, it would be logistically impossible for the applicant to provide six-month follow-up data to the NDA in time for priority review.

Priority Review is not recommended.

10. SUMMARY

This is a paper NDA for Surfaxin, a synthetic lung surfactant for "the prevention of respiratory distress syndrome (RDS) in premature infants". The application follows the CTD format with 148 volumes in clinical/statistical Module 5. Reports of nine clinical studies, complete and ongoing, are included in the application. Four studies are for the neonatal RDS indication and five are for two other indications. One of the neonatal RDS studies is considered pivotal.

The pivotal study, conducted in Europe and Latin America, was a superiority trial comparing Surfaxin to Exosurf, an approved synthetic surfactant. The co-primary outcomes were incidence of RDS at 24 hours and RDS-related deaths at 14 days. Surfaxin was superior to Exosurf in both these outcomes and in most of the secondary outcomes as well. A third arm was included in the study where about half the number of patients received a reference surfactant, Survanta. Survanta is also approved and is a naturally-based product. Comparisons were performed between Surfaxin and Survanta "for informational purposes". There was no difference in incidence of RDS or all-cause death at 14 days. There was a difference in RDS-deaths at 14 days.

The Sponsor requested Priority Review of the application. The request is denied for two reasons. First, the data offered in the application do not convincingly demonstrate an improvement over the other marketed surfactant products. Second, the application does not include 6- or 12-month follow-up data for evaluation of long-term safety. Including the 6-month data in the application was specifically requested by the Division at the pre-NDA meeting of June, 2003. The 6-month follow-up evaluations will not be complete in time to accommodate a priority review timetable.

All required elements are present and the application is fileable.

11. TIMELINE FOR REVIEW

An estimated timeline for completion of the review is as follows.

Table 6: NDA 21-746 Review Timeline

Milestone	Estimated Date of Completion
Stamp Date	April 13, 2004
60-Day Review	June 13, 2004
Pivotal Study Review	August 6, 2004
Other Studies	September 24, 2004
ISE	October 29, 2004
ISS	December 3, 2004
Complete Review	December 31, 2004
Division Goal Date	January 14, 2005
PDUFA Date	February 13, 2005

12. COMMENTS TO SPONSOR

The following comments will be provided to the Sponsor.

1. [redacted] (b) (4)

meeting on June 13, 2003. Therefore, we have concluded that this application should receive a standard review.

2. Submit 6-month follow-up data, as requested by the Agency during the pre-NDA meeting on June 13, 2003.
3. Provide a list of countries, if any, in which application for marketing is pending or has been approved.

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/s/

John Gunkel
5/24/04 12:13:42 PM
MEDICAL OFFICER

Peter Starke
5/25/04 09:31:12 AM
MEDICAL OFFICER
I concur with this review.