Exogenous Natural Surfactant for Treatment of Acute Lung Injury and the Acute Respiratory Distress Syndrome

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***Rationale*: Compositional changes in surfactant and/or decreased surfactant content of the lungs are common features in patients with acute respiratory failure. Instillation of exogenous surfactant into the lungs of neonates with respiratory distress syndrome or pediatric patients with acute respiratory distress syndrome (ARDS) has resulted in improved survival.**

***Objectives*: We conducted this trial to determine whether the instillation of exogenous surfactant would improve the Day 28 outcome of adult patients with acute lung injury (ALI) or ARDS.**

***Methods*: A total of 418 patients with ALI and ARDS were included in an international, multicenter, stratified, randomized, controlled, open, parallel-group study. We randomly assigned 418 patients to receive usual care either with or without instillation of exogenous natural porcine surfactant HL 10 as large boluses.**

***Measurements and Main Results*: The primary endpoint was death rate before or on Day 28. Secondary endpoints were adverse event and death rate on day 180. The 28-day death rate in the usual care group was 24.5% compared with 28.8% in the HL 10 group. The estimated odds ratio for death at Day 28 in the usual care group versus the HL 10 group was 0.75 (95% CI, 0.48–1.18; $P = 0.22$). The most common adverse events related to HL 10 administration were temporary hypoxemia defined as oxygen saturation less than 88% (51.9% in HL 10 group vs. 25.2% in usual care) and hypotension defined as mean arterial blood pressure less than 60 mm Hg (34.1% in HL 10 group vs. 17.1% in usual care).**

***Conclusions*: In this study, instillation of a large bolus of exogenous natural porcine surfactant HL 10 into patients with acute lung injury and ARDS did not improve outcome and showed a trend toward increased mortality and adverse effects.**

Clinical trial registered with www.clinicaltrials.gov (NCT 00742482).

Keywords: intensive care units; pulmonary ventilation; acute respiratory distress syndrome; acute lung injury

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Compositional changes in surfactant and/or decreased surfactant content of the lungs are common features in patients with acute respiratory failure. Beneficial effects of exogenous surfactant instillation into the lungs have been shown in neonates with respiratory distress syndrome and pediatric patients with acute respiratory distress syndrome (ARDS).

What This Study Adds to the Field

In patients with acute lung injury and ARDS, a large bolus of exogenous natural porcine surfactant HL 10 did not improve outcome and showed a trend toward increased mortality and adverse effects.

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (1) represent common clinical syndromes that can occur after diverse pulmonary or systemic insults (2). The primary feature is acute onset of severe hypoxemia associated with diffuse, noncardiogenic pulmonary infiltrates. Although necessary for supporting the patient, mechanical ventilation has been implicated in the associated high morbidity and mortality (3); new therapies have thus been attempted to improve oxygenation and ventilation while providing lung protective ventilatory support (4).

Several studies in patients with ARDS have demonstrated compositional changes in surfactant and/or decreased surfactant content of the lungs (5). Moreover, Gregory and coworkers (6) showed that these alterations occur early, even appearing in patients at risk of developing ARDS. Although a different condition, the mortality of premature infants with respiratory distress syndrome appears to have decreased with exogenous surfactant therapy (7) and more recently a phase III pediatric study demonstrated improvement of oxygenation and survival (8). Despite this, intratracheal surfactant has not proved to be beneficial for adult patients with ALI/ARDS. Two large, randomized, controlled studies have been performed in adults using two different synthetic surfactant preparations (9, 10). Neither study showed an improvement in survival. On the other hand, several small clinical trials using natural surfactant (bovine or porcine) have shown reduced mortality (11–13). Some of the results of these studies have been previously reported in the form of abstracts (12, 13).

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Supported by LEO Pharma A/S. The sponsor designed the trial and interpreted the results in cooperation with the Advisory Committee. The database was held at LEO Pharma A/S. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

A list of members of the HL 10 INT Study Group can be found at the end of this article.

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Against this background, we set out to determine if in adult patients with ALI/ARDS, the instillation of a large bolus of exogenous natural (porcine) surfactant within a period of 36 hours of the onset of the syndrome could improve 28-day survival.

METHODS

Study Design and Enrollment

This was an international, multicenter, stratified, randomized, controlled, open, parallel-group study conducted between January 2003 and May 2004. Intubated and mechanically ventilated patients with a diagnosis of ALI/ARDS (14) in 67 medical centers in Austria, Belgium, Canada, Denmark, Finland, France, Germany, the Netherlands, Norway, Spain, Sweden, and the United Kingdom were randomized either to the surfactant group (three doses of surfactant planned at times 0, 12, and 36 hours in addition to usual care) or a control group who received usual care only. The study could not be performed as a double-blind trial because control patients could not safely have a placebo instilled. The institutional review board of each center approved the study protocol. The trial was monitored by a Data Monitoring Committee (DMC). Informed consent was obtained from each patient, their next of kin, or their legal representative. Other inclusion criteria included: fewer than 60 hours from the start of mechanical ventilation to the first large bolus of surfactant, an expected requirement for mechanical ventilation of more than 24 hours, and 18 years of age or older. The complete list of exclusion criteria is available in the online supplement.

Randomization

All eligible patients received usual care and were randomly assigned to either treatment with surfactant or usual care alone group (control subjects) in a 1:1 ratio, stratified according to the cause of ALI/ARDS as follows: (*1*) sepsis; (*2*) pneumonia, shock, other; (*3*) aspiration pneumonia, trauma. To avoid allocation bias a central telephone randomization procedure was used.

The recommendations regarding mechanical ventilation and daily weaning for both groups were according to the ARDSnet protocol (4). Educational sessions were organized to ensure compliance with usual care and the correct intratracheal administration of surfactant.

Surfactant

The surfactant (HL 10; LEO Pharmaceutical Products, Ballerup, Denmark; Halas Pharma GmbH, Oldenburg, Germany) used in this trial is a freeze-dried natural surfactant isolated from pig lungs. It consists of approximately 90 to 95% phospholipids and 1 to 2% hydrophobic proteins (surfactant proteins SP-B and SP-C), the remainder being other lipids. The product was delivered in 100-ml vials containing 3 g of HL 10 to be dispersed in 60 ml warm (37–40°C) saline (50 mg/ml after dispersion).

The large bolus regimen was as follows: Day 1, time 0 hours was defined as the time after randomization at which the blood gas values were obtained, which was immediately before the first large bolus of surfactant, which could occur up to a maximum of 8 hours from the patient meeting the blood gas inclusion values. Up to three doses of HL 10, totaling a maximum cumulative amount of 600 mg/kg, were instilled at 0 hours and approximately 12 and 36 hours thereafter. The 12-hour and 36-hour doses were given to the patients if they continued to be expected to be on mechanical ventilation for an additional 24 hours. Before each large bolus patients were assessed and treated for hypovolemia as necessary, sedated, and at least 10 minutes before given a neuromuscular blocking agent to prevent coughing. HL 10 was then placed in two 300-ml syringes, with half of the total dose in each. The mechanical ventilator was set on volume control with a tidal volume of 6 to 8 ml/kg predicted body weight (PBW) and $F_{I_{O_2}}$ of 1.0, with the positive end-expiratory pressure (PEEP) left unchanged. The patient was turned to one side, the endotracheal tube was clamped at expiratory hold, the mechanical ventilator was disconnected from the patient, and the HL 10 was injected into the endotracheal tube as fast as possible. The patient was reconnected to the ventilator, the tube was unclamped, and the tidal volume was temporarily increased to 10 to 12 ml/kg PBW with PEEP reduced to 5 cm H_2O to allow the distribution of HL 10. After five breaths the PEEP was put 5 cm H_2O above pre–HL 10 administration values for 30 minutes, to avoid transient hypoxemia. After all the HL 10 had disappeared from the tube the patient was turned back to the supine position and the tidal volume was put back to 6 to 8 ml/kg PBW. Once the stability of the patient was ensured, the patient was turned to the opposite side and the administration process was repeated to the other lung. This procedure was derived from prior preclinical and clinical experience (12, 13). In addition, the DMC made some suggestions concerning amendments to the administration procedure after some cases of (transient) hypoxemia, which involved increasing the $F_{I_{O_2}}$ to 1.0 during the procedure. For the first 3 hours after large bolus HL 10 ventilatory settings and patient position were not changed unless there were clinical indications.

Baseline and Outcome Measurements

Ventilator and cardiovascular parameters, arterial blood gas data, and standard laboratory variables were measured at baseline and during the study. Acute Physiology and Chronic Health Evaluation and Simplified Acute Physiology Score were recorded. Sequential Organ-Failure Assessment (SOFA) was calculated on Days 1, 4, and 8. The day of the first HL10 administration was considered as Day 1. The primary outcome was the impact of three doses of HL 10 given at time intervals compared with usual care on 28-day mortality, measured at Day 29. Secondary objectives were days alive and out of intensive care unit (ICU) at Day 28, days alive and out of ICU at Day 28 for patients alive at the end of Day 28, changes in the $Pa_{O_2}/F_{I_{O_2}}$ ratio and other relevant lung parameters, change in SOFA score, and 180-day mortality. Adverse events were categorized according to the MedDRA (Medical Dictionary for Regulatory Activities) System, version 6.1 and reported for both groups. The DMC reviewed all serious adverse events on an ongoing basis.

Statistical Analysis

The anticipated 28-day mortality for the study population was 40% and the study was powered to detect a 10 percentage point absolute reduction in mortality to 30%. The sample size of 1,000 patients was needed and there were preplanned interim analyses at every 200 patients. The prespecified primary efficacy analysis was a binary (28-day mortality) logistic regression with stratum of ALI/ARDS, $Pa_{O_2}/F_{I_{O_2}}$ ratio group, and age group as explanatory variables, and a standard asymptotic method with Wald confidence intervals was used. Supplementary 28-day and 180-day mortality were analyzed by Kaplan-Meier plots and the corresponding log-rank test. All binary variables were analyzed by Pearson chi-square test with corresponding 95% confidence intervals. Other variables were analyzed by Wilcoxon two-sample rank-sum test. *Post hoc* analysis concerning 28-day and 180-day mortality for patients with direct and indirect ARDS was performed by log-rank test.

RESULTS

The study was prematurely terminated because a 300-patient safety analysis showed a trend toward higher mortality in the treatment group. The DMC reviewed the data after 200 patients reached the 28-day follow-up period and noted that there was a trend to increased mortality in 60-day and 90-day mortality in the HL 10 arm and asked for an unplanned review of data after 300 patients. The DMC recommended that the trial be stopped after looking at the data on 300 patients even though the increased mortality signal was largely in the 60- to 90-day follow-up, but not at the 28-day time point. On study closure a total of 418 (210 usual care and 208 treatment) patients had been randomized (Figure 1). The number of patients studied per site ranged from 1 to 23. There was no center effect or practice effect (i.e., better effects after multiple patients treated) identified by the DMC. The groups were well matched at baseline (Tables 1 and 2). Sepsis was the most common predisposing event followed by pneumonia. A total of 327 patients (78.2%) had ARDS at baseline. Three patients randomized for HL 10 did not receive treatment, but were analyzed as per the intent-to-treat approach. The time interval between onset of mechanical ventilation and initiation of treatment in HL 10 group was median 35.04 hours with a range 2.4 to 73.92 hours.

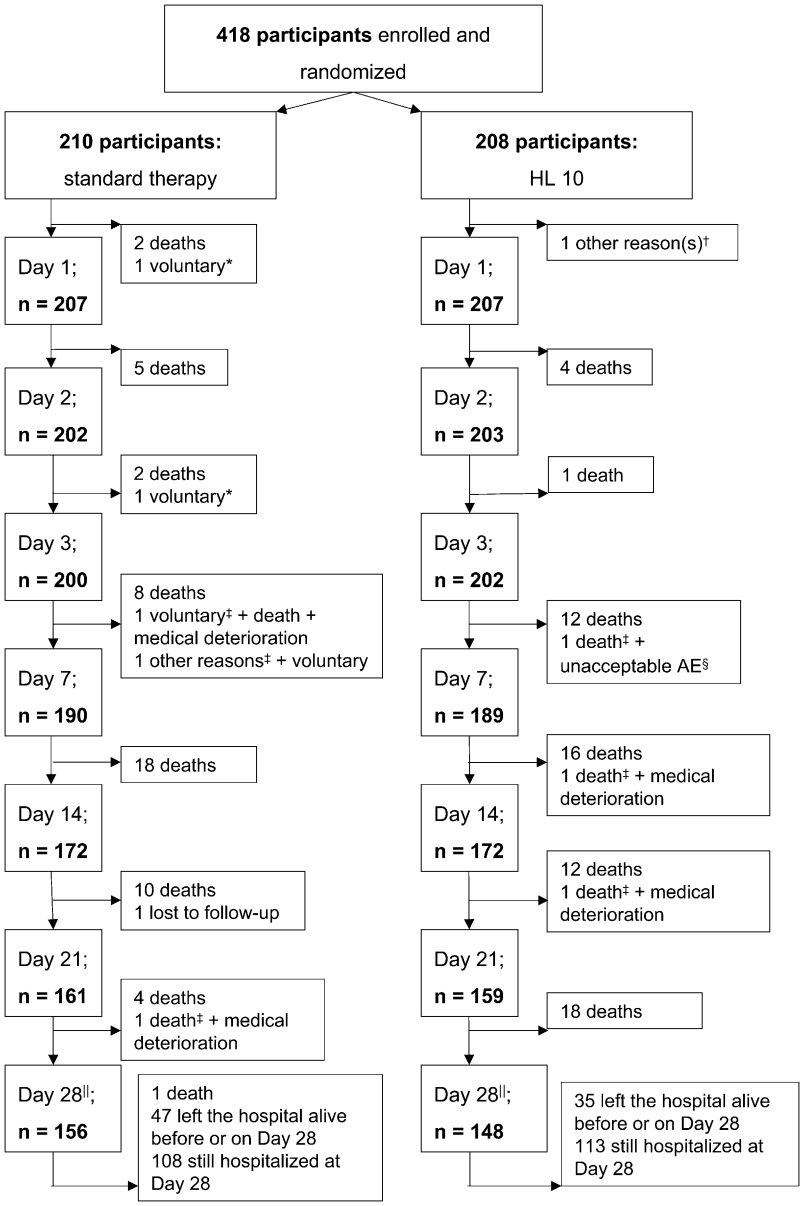

Figure 1. Participant flow through the study. *The patient was withdrawn from the study by the family. †The patient was withdrawn from the study by the family on Day 1. The patient died, however, on Day 14. ‡Primary reason for withdrawal. §Adverse event. ‖Patients shown as withdrawn after Day 28 were withdrawn on Day 28.

Data Analyses

In the usual care group 51 patients (24.5%) died before or on Day 28, as compared with 60 patients (28.8%) in the HL 10 group. The estimated odds ratio for death at Day 28 in the usual care group versus the HL 10 group was 0.75 (95% CI, 0.48–1.8; $P = 0.22$). A Kaplan-Meier survival plot for the 28-day mortality is shown in Figure 2 ($P = 0.34$ by log-rank test). The 180-day mortality in the surfactant and usual care groups was 49.0 and 39.6%, respectively (Figure 3; $P = 0.069$ by log-rank test). The 28-day mortalities by various strata and 180-day mortality are depicted in Table 3. A statistical significance was observed between the groups in the evaluation of the last two parameters ($P = 0.005$). As expected, patients older than 70 years had a higher mortality. The 28-day and 180-day mortality data analyzed separately for patients with ALI and ARDS receiving HL 10 or usual care are available in the online supplement.

Post hoc analysis of 28-day and 180-day mortality in the patients with direct lung injury (aspiration, pneumonia) receiving HL 10 was 30 and 52%, respectively. In the same group receiving usual care the mortality was 27 and 39%, respectively. When patients with indirect lung injury were analyzed, the HL 10 group had 28-day and 180-day mortality of 27 and 41%, respectively. This was 21 and 36%, respectively, for the usual care group. No statistical significance was observed between the groups (28-d mortality, $P = 0.6$; 180-d mortality, $P = 0.13$ by log-rank test). *Post hoc* analysis of changes in oxygenation between the groups receiving HL 10 or usual care showed a significant decrease in Pa_{O_2}/FI_{O_2} ratios up to 4 hours after each large bolus surfactant. Data concerning changes in Pa_{O_2}/FI_{O_2} in the whole group and the *post hoc* analysis of patients with either direct or indirect ALI/ARDS are available in the online supplement.

The SOFA scores (mean ± SD) at Days 1, 4, and 8 in the groups receiving usual care versus HL 10 were 10.8 ± 3.7 and 10.7 ± 3.6; 8.5 ± 3.9 and 8.5 ± 3.9; 7.6 ± 4.0 and 7.2 ± 3.6, respectively, decreasing equally over time in both treatment groups.

A total of 249 serious adverse events were reported in 116 patients (55.2%) in the usual care group and 438 serious adverse events were reported in 157 patients (76.6%) in the HL 10 group. The percentages of patients in the usual care group and the HL 10 group with one or more serious adverse events were statisti-

TABLE 1. BASELINE CHARACTERISTICS OF THE PATIENTS

Characteristic	Usual Care (*N = 210*)	HL 10 (*N = 208*)
Age, years	57.4 ± 15.7	57.2 ± 15.9
Age, %		
18–69 yr	73.3	76.9
>70 yr	26.7	23.1
Sex, male, %	65.7	63.0
Ethnic origin, white, %	93.8	90.4
Height, cm	170.0 ± 10.8	170.0 ± 9.8
Weight, kg	78.4 ± 18.0	75.8 ± 17.0
Primary cause of ALI/ARDS, %		
Sepsis	41.9	36.5
Pneumonia	29.0	30.8
Shock	6.2	7.2
Other	10.0	11.1
Aspiration pneumonia	8.6	10.6
Trauma	4.3	3.8
Strata based on CRF books, %		
Sepsis	34.3	35.1
Pneumonia, shock, other	52.9	51.4
Aspiration pneumonia, trauma	12.9	13.5

Definition of abbreviations: ALI = acute lung injury; ARDS = acute respiratory distress syndrome; CRF = case report form.

Data expressed as mean ± SD unless otherwise noted.

TABLE 2. BASELINE VENTILATORY, CARDIOVASCULAR CHARACTERISTICS, AND SURVIVAL SCORES OF PATIENTS

Characteristic	Usual Care (*N = 210*)	HL 10 (*N = 208*)
Ventilatory parameters		
$F_{I_{O_2}}$	0.64 ± 0.20	0.62 ± 0.18
PEEP, cm H_2O	10.5 ± 3.5	10.7 ± 3.3
RF, per min	20.8 ± 5.7	20.7 ± 6.1
Expiration V_T, ml/kg PBW	8.4 ± 2.1	8.4 ± 2.0
Peak inspiration pressure, cm H_2O	30.8 ± 7.2	29.6 ± 6.3
Plateau pressure, cm H_2O	24.4 ± 6.7	25.3 ± 6.6
Mean airway pressure, cm H_2O	17.5 ± 5.2	16.6 ± 4.0
Arterial blood gas values		
pH	7.35 ± 0.1	7.36 ± 0.09
Pa_{CO_2}, mm Hg	42.8 ± 9.5	42.4 ± 9.3
Std bicarbonate, mmol/L	22.9 ± 4.5	23.4 ± 4.4
Pa_{O_2}, mm Hg	96.9 ± 32.5	92.8 ± 33.1
$Pa_{O_2}/F_{I_{O_2}}$, mm Hg	161.4 ± 55.2	156.7 ± 54.8
$Pa_{O_2}/F_{I_{O_2}}$ categorization, %		
ALI	22.4	21.2
ARDS	77.6	78.8
Cardiovascular parameters		
Heart rate, bpm	101.5 ± 23.0	100.5 ± 21.5
Central temperature, °C	37.4 ± 1.1	37.4 ± 1.0
Systolic blood pressure, mm Hg	117.7 ± 18.5	119.3 ± 21.2
Diastolic blood pressure, mm Hg	59.2 ± 11.3	58.7 ± 11.5
Mean blood pressure, mm Hg	78.1 ± 12.4	78.5 ± 13.3
Sp_{O_2}, %	96.4 ± 2.8	96.0 ± 3.1
APACHE II*	25.2 ± 7.3	25.7 ± 8.2
Risk of hospital death, %	53.6 ± 23.7	54.8 ± 23.7
SAPS II*	51.3 ± 15.5	51.7 ± 15.8
Risk of hospital death, %	47.9 ± 26.2	48.0 ± 26.4
SOFA score*	10.8 ± 3.7	10.7 ± 3.6
LODS*	8.0 ± 3.2	7.8 ± 2.9
Risk of hospital death, %	47.9 ± 24.7	46.0 ± 23.9
MPM_0*	10 (1-92)	9 (1-93)
MPM_{24}*	26 (2-89)	29 (2-99)

Definition of abbreviations: ALI = acute lung injury; ARDS = acute respiratory distress syndrome; APACHE II = Acute Physiology and Chronic Health Evaluation II; LODS = Logistic Organ Dysfunction Score; MPM = Mortality Prediction Model at 0 (admission) and 24 (randomization) hours expressed as median (range); PBW = predicted body weight; PEEP = positive end-expiratory pressure; RF = respiratory frequency; SAPS II = Simplified Acute Physiologic Score II; SOFA = Sepsis-related Organ Failure Assessment; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.

Data expressed as mean ± SD unless otherwise noted.

* N = 209 in standard therapy patient group.

cally significantly different ($P < 0.001$, chi-square test). The most common adverse events related to large bolus HL 10 were temporary hypoxemia defined as oxygen saturation less than 88%, and hypotension defined as mean arterial blood pressure less than 60 mm Hg. Episodes of hypoxemia have been reported for 108 (51.9%) of the 208 patients receiving HL 10 and 53 (25.2%) of the 210 patients receiving usual care only. Episodes of hypotension have been reported for 70 (34.1%) of the 208 HL 10 group patients and 36 (17.1%) of the 210 patients receiving usual care only. All patients experiencing hypoxemia and hypotension recovered from their episodes and the events were not specifically linked to the first, second, or third large bolus.

DISCUSSION

The results of our study showed that a large bolus of exogenous porcine surfactant for the treatment of ALI/ARDS, as performed in this study, did not improve survival and was associated with a concerning trend to increased mortality as well as increased serious adverse events when compared with the usual care. The excess mortality in the HL10 arm appeared to occur late, well after the large bolus of the surfactant.

Although the study was designed for the inclusion of 1,000 patients, recruitment was stopped because a 300-patient safety analysis requested by the independent DMC showed a trend toward higher mortality in the treatment group. By that time 418 patients had been randomized, although no patients received further surfactant after the decision to stop the study. It is less than ideal to stop any randomized trial early, because a positive benefit of the intervention may have been missed (15). However, given the trends in morbidity and mortality, this is highly unlikely and would at best indicate futility and at worst an adverse effect.

Mortality after 28 days was selected as the primary endpoint. Anticipated 28-day mortality of patients with ARDS was 40%, based on recently published studies (16–22), and the study was powered to detect a 10 percentage point reduction in mortality to 30%. In the study, the HL 10 group mortality was actually slightly lower at 28.8%; however, the mortality from usual care alone was even lower at 24.5%. The lower than anticipated 28-day mortality in the usual care group could have been partly due to the continuous improvement in the management of patients in intensive care. An example could be revised ventilation strategy in ALI/ARDS, by using low tidal volumes. Consistent with this, our overall mortality rate was in accordance with the recent findings of ARDSnet (23).

No improvement related to HL 10 was observed either in the secondary study objective (mortality at Day 180) or after the *post hoc* analysis of 28-day and 180-day mortality in the direct and indirect lung injury groups. Days alive and out of ICU and days alive and out of ICU for the subgroup of patients alive at Day 28 were significantly worse for patients receiving HL 10. Analyses of secondary objectives support the conclusion of the primary objective, that patients receiving HL 10 have a trend toward an inferior outcome. There was also a concerning higher incidence of adverse events noted in the surfactant group. The extent to which these adverse outcomes are directly related to the surfactant itself versus the installation procedure and/or the associated ventilation practice is not clear.

Our results are disappointing considering the two previous smaller studies that have demonstrated benefit with the same surfactant preparation (12, 13). In the first study performed on 36 patients with ALI/ARDS, the mortality at Day 28 in the

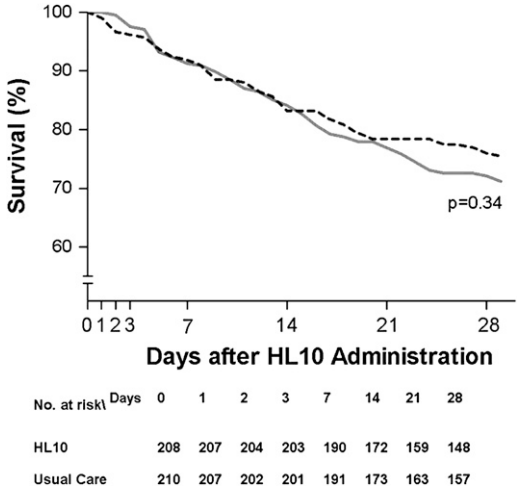

Figure 2. Kaplan-Meier estimates of survival among 418 patients with acute lung injury/acute respiratory distress syndrome treated with usual care (n = 210) or HL 10 (n = 208). Treatment with HL10 (*solid line*) was not significantly different from usual care (*dashed line*).

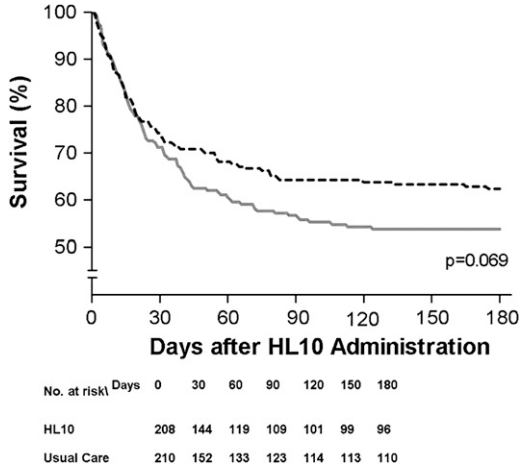

Figure 3. Kaplan-Meier estimates of survival among 418 patients with acute lung injury/acute respiratory distress syndrome treated with usual care (n = 210) or HL 10 (n = 208). Treatment with HL10 (*solid line*) was not statistically significantly different from usual care (*dashed line*).

surfactant group was 9.1% and in the usual care group 42.9%. In the second study performed on 23 patients, 28-day mortality was 33.1% with a single dose and 14.3% with three doses. The difference in outcome between the three studies is probably due to the small number of patients included in the two phase II studies. Similar situations were observed in two previous reports on exogenous surfactant replacement, which were performed after promising results obtained in phase II studies (9, 10). Our results confirm the findings of Anzueto and colleagues (9) who could not show an improvement in oxygenation and mortality related to aerosolized synthetic surfactant. A possible reason for this was the technique used in their study. It was speculated that only a fraction of the aerosolized surfactant could reach the lungs. Hence we decided to use a large bolus technique. In addition the tidal volume and PEEP were temporarily increased after large bolus for promoting optimal distribution. Once again, the extent to which the changes in tidal volume and PEEP affected negatively on morbidity and mortality is unclear, although we believe it is unlikely, given the brief time period involved. Another recent study performed by Spragg and coworkers (10) reported an improvement of oxygenation related to recombinant surfactant protein C–based instillation in ALI/ARDS. However, similar to the findings of Anzueto, 28-day mortality was not improved.

Different results obtained in various studies can have several explanations, such as the type of surfactant used or technique and time of instillation. In addition, the age of the patient seems to be an important factor. Contrary to the adults with ALI/ARDS, premature neonates born with surfactant deficiency or pediatric patients with ARDS have improved survival from exogenous surfactant instillation (7, 8). Notably, neonatal or pediatric patients who die often do so as a result of respiratory failure, whereas adults with ALI/ARDS mostly die as a result of multiorgan failure. Hence, it may not be surprising that surfactant is more effective on mortality in the young. The mortality between the large bolus HL 10 and the usual care group started to diverge approximately 3 weeks after beginning the trial. This divergence was consistent up to Day 180, showing a trend to worse outcome in the HL 10 group. We do not have data to explain this finding. It could be speculated that the outcomes at Days 28 and 180 were related to factors other than HL 10 or ALI/ARDS. Another important factor is the heterogeneous nature of the ALI/ARDS population. As in previous studies, patients with ALI (Pa_{O_2}/FI_{O_2} <300 mm Hg) were enrolled in our study (4, 23). However, their overall mortality was much lower than reported previously (38.5%) by Rubenfeld and coworkers (24). Furthermore, the definition of ALI/ARDS has several limitations. For example the current definition considers neither the ventilatory settings nor the duration of hypoxemia. Recent publications have shown that this can have a dramatic impact on patient selection and associated outcome (25). A combination of these factors mentioned might explain why exogenous surfactant large bolus failed to improve survival in patients with ALI/ARDS.

In conclusion, three doses of exogenous porcine surfactant administered as large bolus did not improve survival and showed a trend toward increased mortality and adverse events in patients with ALI/ARDS. At this stage exogenous surfactant

TABLE 3. 28-DAY MORTALITIES BY VARIOUS STRATA AND 180-DAY MORTALITY

Characteristic	Usual Care (*N = 210*)	HL 10 (*N = 208*)	*P* Value
Age			
18–69 yr	27 (17.8)	36 (22.5)	NS
>70 yr	24 (42.9)	24 (50)	NS
Pa_{O_2}/FI_{O_2}			
ALI (201–300 mm Hg)	6 (13)	11 (25)	NS
ARDS (≤ 200 mm Hg)	45 (27.8)	49 (29.9)	NS
Stratum ALI/ARDS			
Sepsis	16 (22.2)	25 (34.2)	NS
Pneumonia, shock, other	31 (27.9)	30 (28.0)	NS
Aspiration pneumonia, trauma	4 (16.0)	5 (17.9)	NS
Sex			
Female	18 (25)	23 (29.9)	NS
Male	33 (24.3)	37 (28.2)	NS
Days alive and out of ICU (Day 28)	8.8 ± 9.5	6.1 ± 8.6	0.005
Days alive and out of ICU for patients alive at the end of Day 28	11.5 ± 9.4	8.3 ± 9.3	0.005
180-d mortality	76 (39.6)	96 (49)	0.063

Definition of abbreviations: ALI = acute lung injury; ARDS = acute respiratory distress syndrome; ICU = intensive care unit; NS = not significant.

Data expressed as number of patients (% of total), except for days alive and out of ICU (day 28 and at the end of day 28), which are expressed as mean ± SD.

cannot be recommended for routine use in patients with ALI/ARDS. It is possible that exogenous surfactant in a different preparation or delivered an alternate way has a place in the treatment of ALI/ARDS.

Conflict of Interest Statement: J.K. received €10,000 per year for a total of three years from LEO Pharma Ballerup Copenhagen during the design and conduct of the study, between 2002 and 2004, as international coordinating investigator. R.B. served on an advisory board for this study and received patient enrollment fees to the institution for participation in this study, approximately $120,000 from LEO Pharma Ballerup Copenhagen. T.E.S. was country primary investigator and received remuneration from the sponsoring company, LEO Pharma Ballerup Copenhagen, in the range of $5,001–$10,000 during the conduct of this study. G.P.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J-J.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. L.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. P.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.J.S. received more than $100,001 employed as the Head of Medical Department at LEO Pharma A/S. O.K.J. is an employee of LEO Pharma. B.L. has been reimbursed by Draeger for giving talks at scientific meetings and received a research grant from Lyomark Pharma GmbH, Germany (€10,000) in 2009.

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