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## AEROSOLIZED SURFACTANT IN ADULTS WITH SEPSIS-INDUCED ACUTE RESPIRATORY DISTRESS SYNDROME

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**Abstract Background.** Patients with acute respiratory distress syndrome (ARDS) have a deficiency of surfactant. Surfactant replacement improves physiologic function in such patients, and preliminary data suggest that it may improve survival.

**Methods.** We conducted a prospective, multicenter, double-blind, randomized, placebo-controlled trial involving 725 patients with sepsis-induced ARDS. Patients were stratified according to the risk of death at base line (indicated by their score on the Acute Physiologic and Chronic Health Evaluation [APACHE III] index) and randomly assigned to receive either continuously administered synthetic surfactant (13.5 mg of dipalmitoylphosphatidylcholine per milliliter; 364 patients) or placebo (0.45 percent saline; 361 patients) in aerosolized form for up to five days.

**Results.** The demographic and physiologic characteristics of the two treatment groups were similar at base line. The mean ( $\pm$ SD) age was  $50\pm 17$  years in the surfactant group and  $53\pm 18$  years in the placebo group, and the mean APACHE III scores at randomization were

$70.4\pm 25$  and  $70.5\pm 25$ , respectively. Hemodynamic measures, measures of oxygenation, duration of mechanical ventilation, and length of stay in the intensive care unit did not differ significantly in the two groups. Survival at 30 days was 60 percent for both groups. Survival was similar in the groups when analyzed according to APACHE III score, cause of death, time of onset and severity of ARDS, presence or absence of documented sepsis, underlying disease, whether or not there was a do-not-resuscitate order, and medical center. Increased secretions were significantly more frequent in the surfactant group; the rates of other complications were similar in the two groups.

**Conclusions.** The continuous administration of aerosolized synthetic surfactant to patients with sepsis-induced ARDS had no significant effect on 30-day survival, length of stay in the intensive care unit, duration of mechanical ventilation, or physiologic function. (N Engl J Med 1996;334:1417-21.)

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WHEN Ashbaugh et al.<sup>1</sup> described the acute respiratory distress syndrome (ARDS) in 1967, they suggested that the clinical and pathological findings in patients with this condition were in part due to abnormalities in the alveolar wall. Petty et al.<sup>2,3</sup> later reported both qualitative and quantitative abnormalities in lung surfactant in patients with ARDS. Hallman et al.<sup>4</sup> confirmed that surfactant not only is decreased in quantity but also is functionally abnormal in patients with ARDS. These studies offer evidence that ARDS is a condition of surfactant deficiency.<sup>5</sup>

Recent data suggest that mechanical ventilation may

induce lung damage. Dreyfuss et al.<sup>6,7</sup> demonstrated that the use of high tidal volumes, but not high pressures, results in lung injury. It seems reasonable to assume that if surfactant replacement results in a more equitable distribution of tidal volume among the alveoli, it might reduce the damage caused by mechanical ventilation. It might also help reinflate collapsed areas of the lung, improve lung compliance, and reduce intrapulmonary shunting, thus leading to reductions in morbidity and mortality.

On the basis of these observations and the similarities between ARDS and the neonatal respiratory distress syndrome, surfactant-replacement therapy has been used and described in case reports<sup>8-10</sup> and phase 2 studies of patients with ARDS.<sup>11-14</sup> Although their results were encouraging, these studies were small and were designed primarily to address issues of safety, rather than efficacy.

We evaluated the efficacy of surfactant replacement in a prospective, multicenter, randomized, double-blind, placebo-controlled study of patients with sepsis-induced ARDS. The primary objective was to test the hypothesis that treatment with exogenous surfactant would reduce mortality at 30 days. Surfactant treatment was

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also evaluated for its effects on hemodynamic, ventilatory, and oxygenation-related variables; the duration of mechanical ventilation, the length of stay in the intensive care unit, and the duration of oxygen supplementation; and measures of safety.

## METHODS

### Study Design

The study was conducted between March 1992 and September 1993 in the medical-surgical intensive care units of 63 hospitals in nine countries. The study protocol was approved by each institutional review board, and a signed consent form was obtained from each patient before enrollment, if possible; otherwise, consent was obtained from the patient's next of kin or a legal representative. Patients were randomly assigned to receive either aerosolized surfactant (13.5 mg of dipalmitoylphosphatidylcholine [DPPC] per milliliter; Exosurf, Glaxo Wellcome, Research Triangle Park, N.C.) or placebo (0.45 percent saline) continuously for up to five days. Patients were stratified at randomization according to their risk of death, as indicated by their scores on the Acute Physiologic and Chronic Health Evaluation (APACHE III) index.<sup>15</sup> Group assignment was balanced within and among all centers and strata by means of an adaptive computerized randomization program applied at an independent central facility. The study consisted of a screening period during which the diagnosis of sepsis or sepsis syndrome and ARDS was established, a treatment period during which the study drug was administered for up to 5 days, a post-treatment period of 24 hours after the discontinuation of the drug, and a follow-up period consisting of the 30 days after randomization. Two interim analyses were conducted by a safety monitoring board.

### Patients

Because the cause of ARDS may affect its outcome, we evaluated only patients with ARDS caused by sepsis; ARDS caused by other conditions was evaluated separately. ARDS was considered present if the patient had diffuse infiltrates visible on the chest radiograph, a ratio of the partial pressure of arterial oxygen ( $\text{PaO}_2$ ) to the fraction of inspired oxygen ( $\text{FiO}_2$ ) indicating hypoxemia ( $<250$ ), and no evidence of left ventricular failure.<sup>16,17</sup> For patients to be included, ARDS had to have begun within 48 hours, the patients had to be receiving mechanical ventilation with a tidal volume of 150 ml or more, and ARDS had to be associated with sepsis or sepsis syndrome (within 96 hours), with or without hypotension (as previously defined).<sup>18</sup> Patients were excluded if they were enrolled in another randomized study or if they had left ventricular failure, chronic pulmonary disease requiring the use of supplementary oxygen, acute renal failure or worsening chronic renal failure, acute hepatic failure, disseminated intravascular coagulation, suspected inhalation injury, infection with the human immunodeficiency virus and *Pneumocystis carinii* pneumonia, or a terminal illness with a life expectancy of less than three months. Renal or hepatic failure and disseminated intravascular coagulation were defined according to preset laboratory criteria.

### Base-Line and Follow-up Assessments

The base-line evaluation consisted of a medical history taking and physical examination; 12-lead electrocardiography; standard hematologic and blood-chemistry measurements and urinalysis; chest radiography; and blood cultures. During treatment, during the 24-hour post-treatment period, and at the follow-up examinations we measured hemodynamic variables and arterial-blood gas values and obtained ventilatory data. The number of days of mechanical ventilation, the length of stay in the intensive care unit and in the hospital, and the number of days of supplemental oxygen during the 30 days after randomization were also recorded. Survival was evaluated after 30 days, and causes of death were determined. Information on adverse events was collected throughout the study.

### Administration of Surfactant

In this study we used a synthetic surfactant, Exosurf (Glaxo Wellcome), invented by J.A. Clements.<sup>19</sup> This preparation is a mixture of DPPC, cetyl alcohol, tyloxapol, and sodium chloride in a ratio of 13.5:1.5:1.0:5.8, respectively; the preparation contained 13.5 mg of DPPC per milliliter after dilution with 0.45 percent saline.

After each patient underwent randomization, 240 ml of surfactant

or 0.45 percent saline was placed in an opaque canister (Tri-NEB 400; Vortran Medical Technologies, Sacramento, Calif.) and administered as an aerosol through a Visan-9 nebulizer (Vortran Medical Technologies). The study drug was aerosolized into the inspiratory limb of the ventilator circuit during the expiratory phase and was delivered to the patient during the next assisted breath.<sup>20</sup> The weights of the canister before and after nebulization were used to determine the amount of study drug aerosolized.

### Statistical Analysis

Data are presented as means  $\pm$ SD. The target sample size was based on the number of deaths anticipated in the study population. A sample in which there were 306 deaths among the patients would provide the study with 90 percent power to detect a 25 percent relative improvement in survival with surfactant treatment. Assuming 50 percent mortality in the placebo group, we calculated that 700 patients should be enrolled. Two interim analyses were conducted, after 102 and 204 deaths had occurred. No further patients were enrolled after the second interim analysis indicated it was futile to continue this study of efficacy. The final sample size was 725 patients, 288 of whom died. All patients randomly assigned to study groups were included in analyses of efficacy and safety. Patients were assigned to low-, intermediate-, and high-risk categories on the basis of their APACHE III scores (0 to 45, 46 to 89, and 90 to 299, respectively). Survival at 30 days was assessed by means of a Cochran-Mantel-Haenszel test with adjustment for the patient's risk category.<sup>21</sup> Analyses of mortality were performed in subgroups of patients defined by the following variables: entry within one day of the onset of ARDS or later, the  $\text{PaO}_2$ : $\text{FiO}_2$  ratio, the medical center where the patient was enrolled, the mortality rate in the placebo group at that medical center, the presence or absence of a positive blood culture at randomization, the presence or absence of a do-not-resuscitate order, the cause of ARDS (pneumonia vs. other conditions), method of mechanical ventilation, and geographic area. Exploratory logistic-regression analyses were also performed to assess the effects of age, ventilatory measures, and concomitant therapies on mortality at 30 days and the amount of drug aerosolized (dose). Kaplan-Meier step-function plots were used to display survival in the treatment groups over time.<sup>22</sup> The degree of improvement in continuous physiologic variables was compared in the two groups by means of an analysis of the average area under the curve. The incidence of adverse events and expected medical complications of ARDS was calculated, and the two groups were compared with the use of 95 percent confidence intervals.

## RESULTS

The study population consisted of 725 patients (424 men and 301 women) with a mean age of  $51 \pm 17$  years (range, 16 to 90); 361 patients (49.8 percent) received placebo and 364 (50.2 percent) received surfactant. The groups were similar at base line with respect to age, sex, race, APACHE III score, mean arterial pressure, alveolar-arterial oxygen gradient, the ratio of  $\text{PaO}_2$  to  $\text{FiO}_2$ ,  $\text{PaO}_2$ , the partial pressure of arterial carbon dioxide, and  $\text{FiO}_2$  (Table 1). In addition, the distribution of underlying medical conditions and variables indicating the medical history was similar in the two groups. The primary diagnoses leading to admission to the intensive care unit were medical conditions (i.e., not requiring surgery) for 75 percent of the placebo group and 69 percent of the surfactant group. The source of sepsis was similar in both groups (pulmonary, 39 percent; nonpulmonary, 61 percent), and pneumonia was the most common condition precipitating sepsis (in 18 percent in the placebo group and 19 percent in the surfactant group). Blood cultures were positive before randomization for 28 percent of the patients in the placebo group and 32 percent in the surfactant group. Gram-positive organisms were isolated from blood from 72 percent of the patients in the placebo group and 68 percent of those in the surfactant group.

**Table 1. Base-Line Demographic and Clinical Characteristics of the 725 Patients, According to Study Group.\***

CHARACTERISTIC	PLACEBO (N = 361)	SURFACTANT (N = 364)
Sex — no. (%)		
Male	211 (58)	214 (59)
Female	150 (42)	150 (41)
Race — no. (%)		
White	265 (73)	259 (71)
Black	48 (13)	62 (17)
Other	48 (13)	43 (12)
Age — yr	53±18	50±17
Mean APACHE III score	70.5±25	70.4±25
APACHE III score — %		
<46	15	15
46–90	67	67
>90	18	19
Mean arterial pressure — mm Hg	82±15	82±15
Alveolar–arterial oxygen gradient — mm Hg	338±133	329±140
PaO <sub>2</sub> :FiO <sub>2</sub>	140±64	145±82
PaO <sub>2</sub> — mm Hg	86±33	88±43
PaCO <sub>2</sub> — mm Hg	38±9	39±19
FiO <sub>2</sub> — %	66±19	65±19

\*Plus–minus values are means ±SD. APACHE denotes the Acute Physiology and Chronic Health Evaluation scale, PaO<sub>2</sub> the partial pressure of arterial oxygen, FiO<sub>2</sub> the fraction of inspired oxygen, and PaCO<sub>2</sub> the partial pressure of arterial carbon dioxide. Because of rounding, percentages may not total 100.

A total of 257 patients in the placebo group (71 percent) and 268 in the surfactant group (74 percent) completed five days of aerosolized treatment. The reasons for the early termination of treatment were similar in the two groups and included death, extubation, and a change to a method of assisted ventilation that was incompatible with the use of the nebulizer. Both groups received similar volumes of the study preparations. The surfactant group received an estimated 112 mg of aerosolized DPPC per kilogram of body weight per day; this amount is based on the mean weight of the canister before and after the drug was delivered. The response of both groups to treatment was similar in terms of the alveolar–arterial oxygen gradient (Fig. 1A) and the ratio of PaO<sub>2</sub> to FiO<sub>2</sub> (Fig. 1B). The characteristics of ventilation and the results of the analysis of the area under the curve for other physiologic variables did not differ significantly between the study groups.

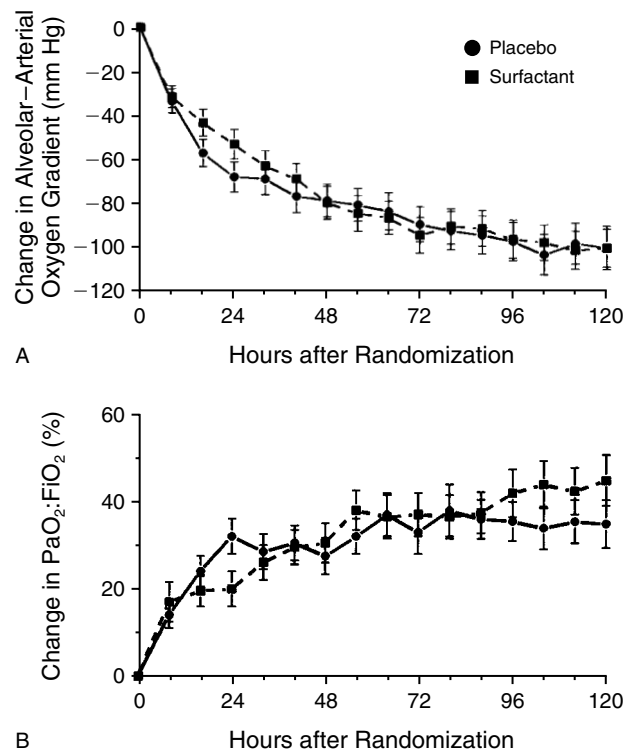
In both groups, there was a 60 percent survival rate 30 days after randomization (Fig. 2). The primary causes of death were respiratory disease and multiple-organ failure (Table 2). Both treatment groups had similar mortality rates in subgroups defined according to the severity of ARDS at base line, APACHE III score, duration of ARDS, the ratio of PaO<sub>2</sub> to FiO<sub>2</sub>, resuscitation status, and the number of patients enrolled at the medical center. There were no significant differences in mortality rates between the groups according to initial diagnosis, medical center, country, or method of mechanical ventilation. The placebo and surfactant groups were similar in terms of the mean number of days of mechanical ventilation required (16.4±0.9 and 16.0±1.0, respectively), the length of stay in the intensive care unit (16.7±0.8 vs. 18.1±1.1 days), the number of days of

supplemental oxygen therapy (19.8±1.2 vs. 19.3±1.2), and the number of days until death for patients who died (20.5±2.2 vs. 21.4±2.1).

Serious adverse events occurred in 8 of the 725 patients and were associated with the administration of the study preparations. These events included hypotension in three patients (two in the placebo group and one in the surfactant group), barotrauma (one patient in each group), worsening hypoxemia (one in the surfactant group), respiratory arrest (one in the surfactant group), and increased peak inspiratory pressure (one in the surfactant group). Most of these events were probably due to unrecognized air trapping (intrinsic [“auto”] positive end-expiratory pressure), occlusion of the expiratory filter, or mucous plugging. Table 3 shows the frequency of the ARDS-associated complications defined in the protocol. Increased secretions were more frequent in the patients given surfactant, but other complications were similar in frequency in the two groups.

## DISCUSSION

In this study, we determined the demographic characteristics of a large group of patients with ARDS and evaluated the results of treatment with placebo or aerosolized synthetic surfactant. We found that among patients with sepsis-induced ARDS, aerosolized exogenous surfactant did not improve oxygenation, peak airway pres-



**Figure 1. Mean (±SD) Changes in Indexes of Oxygenation in the Surfactant and Placebo Groups.**

Panel A shows the decreases (indicated by negative numbers) in the alveolar–arterial oxygen gradient during the administration of placebo or surfactant. There were no significant differences between the groups. Panel B shows the percent change in the ratio of PaO<sub>2</sub> to FiO<sub>2</sub> from base line. The surfactant group and the placebo group had similar changes during the five-day treatment period.

sure, or overall survival at 30 days, nor did it reduce the amount of time patients required mechanical ventilation, the need for oxygen supplementation, or the length of the stay in the intensive care unit or the hospital.

Previous studies suggested the potential efficacy of aerosolized surfactant in patients with ARDS.<sup>11-14</sup> Given every 12 hours or continuously for five days, aerosolized surfactant was well tolerated and its use was associated with a trend toward improvement in survival and physiologic indicators.<sup>11</sup> More dramatic improvement was seen when higher concentrations of aerosolized surfactant were compared with placebo.<sup>14</sup> Our study differs from these previous studies in several ways. We studied 725 patients, as compared with 51<sup>11</sup> and 49<sup>14</sup>; the patients we studied were enrolled within 48 hours after the diagnosis of ARDS, instead of 72 hours; the ratio of PaO<sub>2</sub> to FiO<sub>2</sub> was less than 250, rather than less than 299; and an updated delivery system and a liquid formulation of surfactant were used. Despite these differences in the protocols, patients in our study and those of Weg et al.<sup>11</sup> and Reines et al.<sup>14</sup> had similar base-line characteristics, including age, FiO<sub>2</sub>, ratio of PaO<sub>2</sub> to FiO<sub>2</sub>, positive end-expiratory pressure, peak inspiratory pressure, and duration of ARDS at study entry. Thus, it is likely that the larger number of patients in this study accounts for the differences in outcome. Other pilot studies<sup>8,12,13</sup> are difficult to compare with ours both because they were small and because they did not provide detailed descriptions of the study groups.

There are several possible explanations for the lack of effect of exogenous surfactant in the patients with sepsis-induced ARDS in our study. First, although ARDS is a state of surfactant deficiency, the mechanisms involved are complex. ARDS associated with sepsis is caused by an increase in endothelial and epithelial permeability in the lung, with an associated inflammatory response.<sup>23</sup> Surfactant replacement may simply not be sufficient to affect the symptoms of ARDS. Furthermore, many of our patients died from multiple-organ failure, which was a sequela of sepsis and was unrelated to the initial pulmonary insult.

Another explanation could be our inability to deliver enough aerosolized surfactant to the patients' lungs. Only 4.5 percent of radiolabeled surfactant reached the

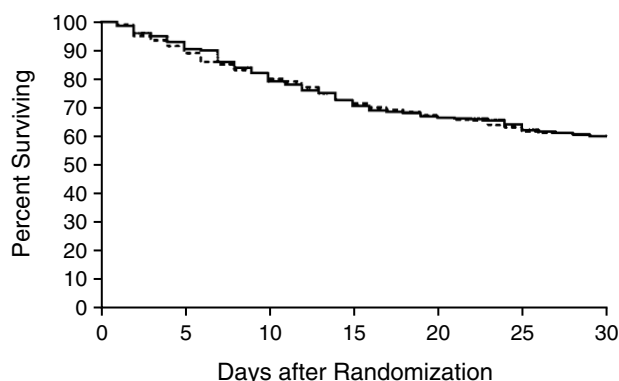


Figure 2. Kaplan-Meier Curves Showing the Percentage of Patients Surviving in the Placebo Group (Solid Line) and Surfactant Group (Dashed Line).

Table 2. Causes of Death, According to Study Group.

CAUSE	PLACEBO	SURFACTANT
	(N = 143)	(N = 145)
	no. (%)	
Respiratory disease*	46 (32)	44 (30)
Multiple-organ failure	37 (26)	38 (26)
Sepsis or septic shock	27 (19)	38 (26)
Cardiac arrest	13 (9)	15 (10)
Other	20 (14)	10 (7)

\*Includes initial pneumonia that did not resolve, nosocomial pneumonia, and respiratory failure.

Table 3. Complications of ARDS, According to Study Group.

COMPLICATION*	PLACEBO	SURFACTANT
	(N = 361)	(N = 364)
	percent	
Increased secretions	11	25†
Hypotension	36	36
Tachycardia	28	28
Other arrhythmias	18	16
Renal failure	11	10
Barotrauma	10	11‡
Hypertension	9	11
Bradycardia	8	9
Pneumonia	5	7
Worsened mental status	9	9
Hepatic failure	7	4
Gastrointestinal bleeding	4	4
Accidental extubation	3	2

\*Only complications with an incidence greater than 1 percent are listed.

†P < 0.05 for the comparison with the placebo group.

‡Includes pneumothorax, pneumomediastinum, pneumopericardium, and pneumatocele.

lungs in studies using the same delivery system.<sup>24</sup> Although no direct data on the amount of surfactant delivered to the lungs were obtained in this study, we estimate that less than 5 mg of the dose of 112 mg of aerosolized DPPC per kilogram per day was actually delivered to the lungs. Although aerosolized surfactant may be deposited in less severely injured areas,<sup>25</sup> administration by nebulizer has been shown to be superior to tracheal instillation in some models.<sup>26</sup> Recent data on rabbits indicate that other factors, including the ventilatory method<sup>27</sup> and the level of positive end-expiratory pressure,<sup>28</sup> may also influence the delivery of surfactant. Considering that no physiologic effect was seen in our patients, an insufficient dose of surfactant is a likely explanation for our results.

The synthetic surfactant preparation we used may also have influenced the results. This preparation lacked a protein component, a fact that may have affected its onset of action and the susceptibility of the surfactant to inhibition by serum proteins. However, this preparation is similar in efficacy to other surfactants that contain protein and that are used in the treatment of neonatal respiratory distress syndrome.<sup>10</sup> Furthermore, like other surfactants,<sup>29</sup> the surfactant we used has anti-inflammatory effects, including the inhibition of the production of tumor necrosis factor  $\alpha$ ,<sup>30</sup> suppression of in-

terleukin-1 and interleukin-2,<sup>31</sup> and inhibition of the endotoxin-stimulated secretion of cytokines by alveolar macrophages.<sup>32</sup>

Since the description of ARDS in 1967,<sup>1</sup> the rate of survival among patients with this syndrome has been about 20 to 40 percent. However, Suchyta et al.<sup>33</sup> recently reported increased survival in a subgroup of patients with ARDS who met criteria for extracorporeal membrane oxygenation. In analysis of data from a multicenter registry, Sloane et al.<sup>34</sup> reported a survival rate of 46 percent. Mitchell et al.<sup>35</sup> reported an improvement in survival, to 62 percent, at a single institution from 1983 to 1992. Milberg et al.<sup>36</sup> reported survival rates that increased from 33 percent in 1990 to 60 percent in 1993, with most of the improvement accounted for by patients with sepsis-induced ARDS. We found a survival rate of 60 percent for sepsis-induced ARDS, similar to the rates in these recent reports.<sup>35,36</sup>

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#### APPENDIX

The members of the Exosurf Acute Respiratory Distress Syndrome Sepsis Study Group were as follows: R.S. Tharratt (Sacramento, Calif.); E. Caldwell (Portland, Me.); R. Balk (Chicago); H. Paz (Philadelphia); N. MacIntyre (Durham, N.C.); S.M. Fakhry (Chapel Hill, N.C.); L. Napolitano (Worcester, Mass.); J. Warren (Pittsburgh); J. Messick and R. Corbin (Charlotte, N.C.); S. Koerner (Los Angeles); H. Silverman and J. Britten (Baltimore); P. Lanken (Philadelphia); D. Schuster (St. Louis); J. Hurst (Tampa, Fla.); J. Williams (Orange, Calif.); B. DeBoisblanc (New Orleans); L. Rotello (Syracuse, N.Y.); S. Peters (Rochester, Minn.); D. Scholten (Grand Rapids, Mich.); B. Soifer (Portland, Oreg.); K. Davis (Cincinnati); J. Shah, E. de Maria, and C. Sessler (Richmond, Va.); R. Treat (Birmingham, Ala.); D. Dries (Maywood, Ill.); S. Jenkinson (San Antonio, Tex.); M. Tweeddale (Vancouver, B.C.); W.D.N. Chin, R. Johnston, and D. Stollery (Edmonton, Alta.); P. Boiteau and S. Viner (Calgary, Alta.); D. Johnson (Saskatoon, Sask.); P. Gray (Winnipeg, Man.); G. Darling, D. Jones, R. Grossman, R. Byrick, and W. DeMajo (Toronto); R. Hodder (Ottawa, Ont.); J. Malo, Y. Berthiaume, and P. Goldberg (Montreal); A. MacNeil (Halifax, N.S.); H.A. Bruining (Rotterdam, the Netherlands); F. Brunet and C. Gibert (Paris); W. Tullett (Glasgow, United Kingdom); P. Damas (Liege, Belgium); R. Hopkinson (Birmingham, United Kingdom); G. Lavery (Belfast, United Kingdom); P. Lehmkühl (Hannover, Germany); W. Schaffartzik (Berlin, Germany); R. Wenstone (Liverpool, United Kingdom); T. Evans and D. Bihari (London); L. Heslet (Copenhagen, Denmark); and R. Kishen (Salford, United Kingdom).

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