

AIR<sup>®</sup> Inhaled Insulin in Subjects with Chronic Obstructive Pulmonary Disease:  
Pharmacokinetics, Glucodynamics, Safety, and Tolerability

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Klaus Rave, MD<sup>1</sup>, Amparo de la Peña, PhD<sup>2</sup>, Fabián S. Tibaldi, PhD<sup>3</sup>,  
Liping Zhang, PhD<sup>2</sup>, Bernard Silverman, MD<sup>4</sup>, Michaela Hausmann, MD<sup>1</sup>,  
Lutz Heinemann, PhD<sup>1</sup>, Douglas B. Muchmore, MD<sup>2</sup>

<sup>1</sup>Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany

<sup>2</sup>Eli Lilly and Co, Indianapolis, IN

<sup>3</sup>Eli Lilly Services SA, Mont-Saint-Guibert, Belgium

<sup>4</sup>Alkermes Inc., Cambridge, MA

Correspondence:

Dr. Klaus Rave

Profil Institut für Stoffwechselforschung GmbH,

Hellersbergstr. 9, 41460 Neuss, Germany.

Email: Klaus.Rave@profil-research.de

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## **Abstract**

**OBJECTIVE**—In this open-label, randomized, crossover study, pharmacokinetic and glucodynamic responses were compared in healthy subjects versus subjects with moderate COPD, following administration of 12 units-equivalent AIR<sup>®</sup> Inhaled Insulin versus 12 units subcutaneous (SC) insulin lispro.

**RESEARCH DESIGN AND METHODS**—Three nonsmoking groups ( $n=15$  each)—healthy subjects (baseline mean  $\pm$  SD: aged  $38\pm 13$  years, FEV<sub>1</sub>  $4.06\pm 1.04$  L), subjects with chronic bronchitis (aged  $53\pm 9$  years, FEV<sub>1</sub>  $2.14\pm 0.60$  L), and subjects with pulmonary emphysema (aged  $58\pm 6$  years, FEV<sub>1</sub>  $1.67\pm 0.61$  L)—were randomly assigned to one of three treatment sequences. Three euglycemic glucose clamp procedures were performed.

**RESULTS**—In subjects with chronic bronchitis and emphysema, AIR Inhaled Insulin administration resulted in reduced insulin exposure ( $AUC_{0-t}$ ) (55.7%,  $P = 0.13$  and 78.5%,  $P < 0.001$ , respectively) and reduced total insulin effect ( $GIR_{tot}$ ) (60.4%,  $P < 0.01$  and 67.1%,  $P < 0.01$ , respectively) relative to healthy subjects. SC insulin lispro administration resulted in similar responses across study groups for insulin exposure and metabolic effect. Intra-subject pharmacokinetic and glucodynamic variability ranged from 17–52% across groups. No significant differences were shown for pre- and post-clamp pulmonary function tests. During clamps, FEV<sub>1</sub> and FVC declined modestly in both COPD groups with no difference between AIR Insulin and SC insulin lispro.

**CONCLUSIONS**—Short-time exposure with AIR Inhaled Insulin was well tolerated by COPD subjects, showing similar time-exposure and time-action profiles, but with reduced insulin absorption and metabolic effect compared with healthy subjects. Further clinical evaluation is warranted in patients with comorbid diabetes and COPD.

Inhaled insulin has been approved recently in both Europe and the United States as an alternative to subcutaneous (SC) insulin injection in the treatment of patients with diabetes. A number of clinical trials in subjects with diabetes have demonstrated the feasibility and patient acceptance of administering insulin by the pulmonary route (1–6); however, there is little or no information on the acute or chronic effects of inhaled insulin exposure in patients with concomitant lung disease. Similarly, there is little data about how lung disease itself might alter pharmacokinetic (PK) and glucodynamic (GD) responses to inhaled insulin.

AIR<sup>®</sup> Inhaled Insulin (AIR Insulin; AIR<sup>®</sup> is a registered trademark of Alkermes Inc., Cambridge, MA) is a newly developed inhaled insulin formulation that uses a novel technology to deliver a dry-powder aerosol composed of large, low-density particles (2-5  $\mu\text{m}$  in aerodynamic diameter) of spray-dried human insulin in an excipient matrix (7). This type of formulation results in a high dispersibility of respirable particles (8) and allows for the use of an inhaler that employs only the energy of a modest inhalation effort to aerosolize the powder. The primary purpose of this study was to compare PK and GD responses in nonsmoking healthy subjects and nonsmoking subjects with moderate chronic obstructive pulmonary disease (COPD), following the administration of either AIR Insulin or SC insulin lispro. Secondary objectives included an evaluation of intra-subject variability and pulmonary function before and after insulin dosing.

## RESEARCH DESIGN AND METHODS

### Subjects

A total of 45 subjects, comprised of both healthy subjects and subjects diagnosed with moderate COPD Class II (forced expiratory volumes [FEV<sub>1</sub>]: 30 to 79% of predicted value, respectively) (9), were enrolled in this

study. Subjects between 18 and 65 years of age, recruited from a number of nearby pulmonology practices, were considered eligible for the screening phase if they presented without a history of diabetes, a BMI  $\leq 35 \text{ kg/m}^2$ , fasting blood glucose (FBG)  $\leq 117 \text{ mg/dL}$  (6.5 mmol/L), and the ability to perform spirometry according to American Thoracic Society criteria (10). Subjects with COPD were subcategorized to either a “chronic bronchitis” group if they had a history of chronic productive cough (productive cough for at least 3 months in each of the preceding 2 years) or to a “pulmonary emphysema” group if they lacked such cough history. Exclusion criteria included active smoking during the previous 6 months or serum cotinine levels  $\geq 20 \text{ ng/mL}$  at the screening visit; history of asthma, recent upper respiratory or lower respiratory tract infection; or acute exacerbation of COPD within the last 2 months. Individuals using beta-blockers, thiazides, or systemic corticosteroids within the past 3 months were also excluded.

A local ethics committee approved the protocol. This phase I trial was conducted in agreement with the principles outlined in the Declaration of Helsinki and the International Conference on Harmonization Guideline to Good Clinical Practice. All subjects were given a full explanation of study procedures at the screening visit, and written informed consent was obtained prior to participation in the study.

### Study design

This phase I, open-label, randomized, three-way crossover study was conducted at a single investigative site (Profil Institut für Stoffwechselforschung, Neuss, Germany). Eligible subjects entered a screening phase, which included clinical laboratory tests and an evaluation of a subject’s ability to achieve suitable inhalation flow and volume targets

(30 L/min for 3 to 5 seconds), using the AIR Insulin inhaler connected in series with a spirometer.

Qualified participants were randomly assigned to one of three possible treatment sequences, wherein each subject was administered insulin: twice as AIR Insulin and once as SC insulin lispro. AIR Insulin was supplied as 6 units-equivalent capsules (2.6 mg insulin/capsule) packaged in foil blister cards. The capsule contents were aerosolized for deep lung delivery by means of a hand-held, breath-actuated, mechanical inhaler device. Insulin lispro (Humalog, Eli Lilly and Company, Indianapolis, IN) was supplied in 10 mL vials (100 unit/mL).

Euglycemic clamp procedures were separated by an interval of 5 to 18 days. At each clamp visit, subjects were administered (approximately 90 min after the start of the baseline clamp procedure) either a 12 units dose (two inhalations of 6 units-equivalent capsule strength) of AIR Insulin or a 12 units dose of SC insulin injected into the abdominal region, according to the treatment sequence. The dose equivalence of AIR Insulin relative to SC insulin lispro was determined in a previous study in healthy volunteers (11). Blood samples were collected at multiple time points (up to 10 h) for free serum immunoreactive insulin (IRI) determination. Routine physical examinations, vital signs, electrocardiograms, and pulmonary function tests (PFTs) were performed at screening and at final visit. Observational data regarding adverse reactions were collected throughout the study.

### **Pulmonary function tests**

Complete PFTs, which included flow volume spirometry (FEV<sub>1</sub> and forced vital capacity [FVC]), carbon monoxide diffusion capacity (DL<sub>CO</sub>), total lung capacity (TLC), and residual volume (RV) measurements, were performed before and after (within 48 h) each clamp procedure.

Additionally, bedside spirometry (FEV<sub>1</sub> and FVC) was performed at predose, approximately 30 min postdose, halfway through the clamp, and immediately at the end of the clamp with the subject in a semi-recumbent position. The protocol specified that any subject who experienced a  $\geq 20\%$  decline in FEV<sub>1</sub> during the clamp, following AIR Insulin exposure, (confirmed by laboratory PFT) would be excluded from further exposure to inhaled insulin.

### **Pharmacokinetic analyses**

Following administration of AIR Insulin and SC insulin lispro, IRI concentrations were measured using a conventional, competitive radioimmunoassay method validated over the range of 20 – 2500 pmol/L, with 100% cross-reactivity for regular human insulin and insulin lispro (MDS Pharma Services, St. Laurent QC, Canada).

WinNonlin software (Professional Edition 4.1; Mountain View, CA) was used to compute noncompartmental PK parameters, including maximum IRI concentration ( $C_{max}$ ), time of maximum IRI concentration ( $t_{max}$ ), and area under the IRI concentration versus time curve ( $AUC_{0-t}$ ; from time zero until the IRI concentrations returned to the predose baseline value). The relative bioavailability (F) of AIR Insulin to that of SC insulin lispro was calculated according to the equation

$$F = D_{SC} \cdot AUC_{(0-t)AIR} / D_{AIR} \cdot AUC_{(0-t)SC}$$

where D is the dose of insulin (in mg) for each route of administration (11).

### **Glucodynamic analyses**

Glucodynamic parameters were derived from the glucose clamp data. Glucose infusion rates (GIR) data were individually fitted using a LOcally weighted linear regrESSion (LOESS) smoothing function (12). Parameters determined from the individual LOESS prediction included the maximum GIR ( $R_{max}$ ) and the time of maximum GIR ( $tR_{max}$ ). The total amount of glucose infused

from time 0 to 10 h ( $G_{tot}$ ) was calculated from the observed GIR. The biopotency for AIR Insulin relative to SC insulin lispro ( $F'$ , analogous to bioavailability) was individually assessed, based on the GD parameter  $GIR_{tot}$ , as previously described (11).

### Statistical analyses

All statistical analyses were performed using SAS<sup>®</sup> Version 8.2 (SAS Institute, Cary, NC). Data from all subjects with stage IIA and IIB severity were pooled in the chronic bronchitis and emphysema groups, respectively, for all analyses. The PK parameters ( $AUC_{0-t}$  and  $C_{max}$ ) were log-transformed. A linear mixed-effect model was applied using the subject group (healthy, chronic bronchitis, and emphysema), visit, and treatment sequence as fixed effects, and subject nested within group sequence as a random effect. The log-transformed results were transformed to the original scale by exponentiation to obtain geometric least squares means and treatment ratios. Glucodynamic parameters were analyzed similarly.

The effect of PFT parameters on PK and GD parameters was explored using a linear mixed regression model that included all available observations. The model was fitted for each PFT parameter with treatment, group, PK or GD parameter, and interactions between the terms, if deemed appropriate. Parameters were log-transformed prior to the analysis. The model considered random variations due to subject.

### Pulmonary function analyses

Pulmonary function test variables ( $FEV_1$ , FVC, TLC, RV, and  $DL_{CO}$ ) and their change from baseline and at visits were analyzed to detect group and treatment differences. Each pre- and post-clamp observation was analyzed separately. A linear mixed-effects model was fitted with group, treatment, group-by-treatment, visit, baseline, and sequence as fixed effects and subject (group sequence) as

a random effect. Group and treatment differences in pulmonary function response variables were examined.

**RESULTS**—Of the 45 subjects who were assigned to treatment and received at least one dose of the study drugs, 42 completed the study. One subject in the emphysema group discontinued the study because of an adverse event (malaise, nausea, dry and productive cough). Two other subjects (both from the chronic bronchitis group) were discontinued for safety reasons after experiencing a >20% decrease in  $FEV_1$  following AIR Insulin administration. Neither of the subjects experienced symptoms associated with the decline in pulmonary function.

At baseline, bodyweight means were  $82.8 \text{ kg} \pm 18.8$ ,  $88.9 \pm 19.4$ , and  $75.8 \pm 14.1$  for healthy subjects, subjects with chronic bronchitis, and emphysema, respectively. The mean age of healthy subjects was  $38.3 \pm 12.7$  years, a lower mean age than for subjects with chronic bronchitis and emphysema ( $53.4 \pm 9.3$  years and  $57.5 \pm 5.6$  years, respectively). Baseline mean  $FEV_1$  was  $4.06 \pm 1.04$  L/second in the healthy group,  $2.14 \pm 0.60$  L/second in the chronic bronchitis group, and  $1.67 \pm 0.61$  L/second in the emphysema group. Neither pulmonary nor demographic characteristics differed significantly between both COPD groups.

### Pharmacokinetics

Subcutaneous insulin lispro administration resulted in time-exposure profiles (Fig. 1A) and total insulin exposures (Table 1) that were indistinguishable among groups. Following the inhalation of AIR Insulin, subjects with chronic bronchitis demonstrated significantly reduced maximal insulin levels ( $C_{max}$ ), 59.3% of those found in healthy subjects ( $P = 0.002$ ), with a total exposure ( $AUC_{0-t}$ ) 55.7% of that of healthy subjects ( $P = 0.001$ ) (Fig. 1B). Subjects with pulmonary emphysema had reduced maximal insulin levels ( $C_{max}$ ) and

reduced total exposure ( $AUC_{0-t}$ ) (respectively, 75.8 and 78.5% of the levels in healthy subjects; not significantly different at  $\alpha = 0.05$ ). AIR Insulin bioavailability compared with SC insulin lispro was 6.2% in healthy subjects, 3.4% in subjects with bronchitis, and 4.9% in subjects with pulmonary emphysema. Intra-subject variability (CV %) for  $AUC_{0-t}$  ranged from 28.0% (subjects with emphysema and healthy subjects) to 52% (subjects with chronic bronchitis).

### Glucodynamics

Glucodynamic response to AIR Insulin administration in subjects with COPD was 35% lower than in healthy subjects, whereas all three groups had comparable GD responses to SC insulin lispro (Fig. 1C, D). Subjects with chronic bronchitis exhibited a total insulin effect ( $GIR_{tot}$ ) that was 60.4% of that seen in healthy subjects ( $P < 0.01$ ). Similarly, subjects with pulmonary emphysema exhibited a total insulin effect of 67.1% as that seen in healthy subjects ( $P < 0.01$ ). Healthy subjects had a higher relative biopotency (Table 1) of 9.3% compared with subjects with COPD (chronic bronchitis 5.2%; pulmonary emphysema 6.3%). Intra-subject variability estimates (CV%) ranged from 16.8–43.0% for the different GD parameters (Table 1).

### Analyses of pharmacokinetic and glucodynamic parameters versus pulmonary function tests

A statistically significant relationship was found between  $DL_{CO}$  and PK responses to AIR Insulin, including  $AUC_{0-t}$  (Fig. 2A) and  $C_{max}$  ( $P < 0.01$ ). However, the correlation coefficient associated with this relationship was low ( $r = 0.00148$ ). No other significant relationships were observed between any of the PK or GD variables and PFT parameters ( $P > 0.2$ ) using the described models (Fig. 2B, C, D).

### Safety

Review of the laboratory, vital signs, and electrocardiogram data found no safety issues of clinical relevance (data not shown). Pulmonary function tests did not generally suggest any safety concerns, although bedside spirometry showed clinically minor but consistent declines (pre-clamp to end-clamp) in subjects with COPD that were statistically significant ( $P < 0.001$ ), regardless of the treatment administered. In subjects with chronic bronchitis, bedside  $FEV_1$  declined –0.24 L with AIR Insulin administration, and –0.33 L with SC insulin lispro. In subjects with pulmonary emphysema,  $FEV_1$  reductions were –0.24 L and –0.16 L, respectively. At the end of the clamp, no significant between-treatment differences in  $FEV_1$  were observed. No clinically relevant changes in  $FEV_1$  were noted in healthy subjects.

Following AIR Insulin administration, 27 subjects reported a total of 15 adverse events considered by the investigator to be related to the study drug. Events were mild-to-moderate in intensity and included headache, cough, abdominal pain, rhinitis, and palmar erythema. One subject in the pulmonary emphysema group discontinued the study because of adverse events (malaise, cough, and nausea). Two subjects in the chronic bronchitis group were discontinued from the study by investigator decision. According to protocol-specified procedures, subjects who experienced a >20% decline in  $FEV_1$  (following AIR Insulin dosing) were to be discontinued from further exposure if this decline was confirmed at the next scheduled laboratory PFT. One subject experienced a 31% decline in  $FEV_1$  (with no pulmonary symptoms) during an AIR Insulin clamp, but follow-up PFT showed only an 18% decline compared with the pre-clamp laboratory-based PFT. Another subject experienced a 38% decline in  $FEV_1$  (also without symptoms) during an AIR Insulin clamp. However, it was not possible to accurately

assess this subjects' pre- to post-clamp FEV<sub>1</sub> change, since the pre-clamp PFT was given an "unacceptable" quality score of "F." Although neither subject completely fulfilled protocol-defined criteria for study discontinuation, both were withdrawn by investigator decision based on these PFT results.

**CONCLUSIONS**—This study is the first published clinical trial to report the impact of COPD on PK and GD responses to inhaled insulin versus SC insulin. Based on its panoply of physiologic and anatomic abnormalities (13, 14), COPD might be expected to affect the size of the absorptive surface available and/or the distribution and deposition of inhaled particles in the lung, potentially reducing the amount of insulin available for systemic absorption. The results in this study support this hypothesis in that although PK and GD responses to SC insulin lispro were comparable in healthy subjects and in COPD, the administration of AIR Insulin resulted in a significant reduction in insulin exposure and metabolic effects in subjects with emphysema and chronic bronchitis compared with healthy subjects. Similar bioavailability and biopotency values for AIR Insulin (relative to insulin lispro) in healthy subjects have been reported previously (11) and have been corroborated by clinical experience in patients with diabetes (15). Further, the intra-subject variability values that were observed for AIR Insulin—an important consideration in the context of an insulin's clinically reproducible metabolic effect (16, 17)—are compatible with the potential use of this product in the treatment of diabetes.

In contrast with our results, studies in active smokers have shown that the absorption of pulmonary insulin of various formulations is actually increased (18–21), although this is partially reversible upon smoking cessation. Since the subjects in this

study were only included if they had ceased smoking for at least 6 months, acute increased PK and GD responses would have been expected to abate. Thus, we hypothesize that the reduced PK and GD responses observed in our study are likely attributable to lung tissue damage associated with COPD.

The significant relationship observed between DL<sub>CO</sub> and PK parameters could provide a partial explanation for the reduced bioavailability of inhaled insulin observed in the COPD groups. Carbon monoxide diffusion capacity (DL<sub>CO</sub>) is an index of a key aspect of lung function and may be altered by a variety of pathophysiologic and anatomic processes, including effective diffusion barrier thickness, pulmonary capillary blood flow, and size of the total absorptive surface available. Chronic obstructive pulmonary disease (COPD) may affect any of these parameters. Our results are the first demonstration of a relationship between a pulmonary function variable and PK parameters for a systemically delivered inhaled drug. Although there is certainly a significant difference in FEV<sub>1</sub> across the study groups and a comparable difference is seen between study groups in both PK and GD responses, the lack of a significant relationship between FEV<sub>1</sub> and the PK/GD parameters suggests that the mechanisms responsible for airflow obstruction are not responsible for these observed PK and GD differences. In other words, breathing mechanics seem to be less important than factors related to gas transfer mechanisms in modulating the absorption of inhaled insulin among patients with COPD.

No serious adverse events and no clinically significant changes in safety-related laboratory parameters, vital signs, or electrocardiograms were reported in this study. Adverse events reported as possibly related to AIR Insulin were mild or moderate in intensity and consistent with previous AIR Insulin studies in nonsmoking, healthy

subjects or insulin studies involving glucose clamp procedures (11, 20). Inhaled insulin formulations have also demonstrated safety profiles similar to the comparator regimens (22–24).

In our study, a decline in bedside spirometric pulmonary function was demonstrated in subjects with COPD during the prolonged bed rest of the clamp procedure, following both AIR Insulin and SC insulin lispro treatments. However, there was no difference between laboratory PFTs performed on the days before and after clamps. Healthy subjects did not demonstrate a decline in FEV<sub>1</sub> during clamps with either insulin treatment. It thus appears that the decline in FEV<sub>1</sub> during the clamps in most of the COPD subjects was probably not therapy related but rather a function of the disease state and study procedures. However, two subjects with chronic bronchitis were withdrawn from further inhaled insulin exposure after experiencing >20% reductions in FEV<sub>1</sub> following AIR Insulin administration. Neither of these cases definitely fulfilled protocol-based PFT criteria for discontinuation from study, and neither subject had any symptoms associated with the acute declines in FEV<sub>1</sub>. Pulmonary function tests (PFTs) are intrinsically more variable in subjects with COPD compared with healthy subjects, making it more difficult to identify changes in PFTs in the subject population. Given these constraints, the two subjects were discontinued from further study based on investigator decision.

Single doses of AIR Insulin (12 units-equivalent or 5.2 mg) were well tolerated in both healthy subjects and in subjects with moderate COPD. AIR Insulin was absorbed as rapidly as SC insulin lispro, irrespective of the disease state. For healthy subjects, the bioavailability and biopotency of AIR Insulin relative to SC insulin lispro, as well as the overall PK and PD profiles, appear to be consistent with a previous study (11). This

profile has been shown to be suitable for treatment of patients with diabetes (15).

In summary, this clinical experimental study suggests that AIR Insulin bioavailability and biopotency are reduced in subjects with moderate COPD, relative to healthy subjects. Because of the reduced pulmonary absorption, an individual adaptation of insulin doses (as usual in diabetes care) is essential. In the case of patients with chronic bronchitis, the observation of increased intrasubject variability may also be clinically important because this may lead to greater fluctuations in glycemic control. Overall, AIR Insulin was generally well tolerated. The results of this study do not, however, provide a basis for dosing guidance of AIR Insulin in patients with COPD since longer-term experience will be required in order to more fully characterize both the effects of COPD on inhaled insulin dosing and the effects of inhaled insulin on the COPD disease process. Such experience will provide the basis for recommendations regarding inhaled insulin dosing and pulmonary safety monitoring that may be specific to patients with COPD. The results do, however, support the conduct of long-term studies with AIR Insulin in patients with COPD and diabetes to evaluate these questions. Until such data are available it would be advisable for patients with concomitant diabetes and COPD to use conventional approaches to diabetes management.

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**Table 1—Pharmacokinetic and glucodynamic results (mean and CV%) for the groups studied, following administration of 12 units AIR Insulin or 12 units SC insulin lispro**

	Healthy		Chronic Bronchitis		Pulmonary Emphysema	
	AIR <sup>®</sup>	SC lispro	AIR <sup>®</sup>	SC lispro	AIR <sup>®</sup>	SC lispro
	n=30	n=15	n=28	n=14	n=29	n=14
<b>Pharmacokinetic</b>						
AUC <sub>(0-t')</sub> (nmol • min/L)	61.9	80.4	35.6	82.9	48.3	77.3
	(38.7)	(32.8)	(64.6)	(20.0)	(50.4)	(24.6)
C <sub>max</sub> (pmol/l)	303.3	415.4	183.8	376.8	228.7	383.5
	(49.1)	(51.6)	(47.4)	(46.0)	(45.8)	(44.0)
t <sub>max</sub> (min) *	45	45	45	60	45	58
	(20.0–180)	(20.0–90.0)	(20.0–90.0)	(45.0–120)	(20.0–60.0)	(45.0–90.0)
F (%)	6.20		3.41		4.9	
	(50.0)		(61.8)		(44.7)	
<b>Glucodynamic</b>						
GIR <sub>tot</sub> (g)	118.0	102.0	71.3	110.0	79.2	101.0
	(32.7)	(40.4)	(45.2)	(31.3)	(41.6)	(22.9)

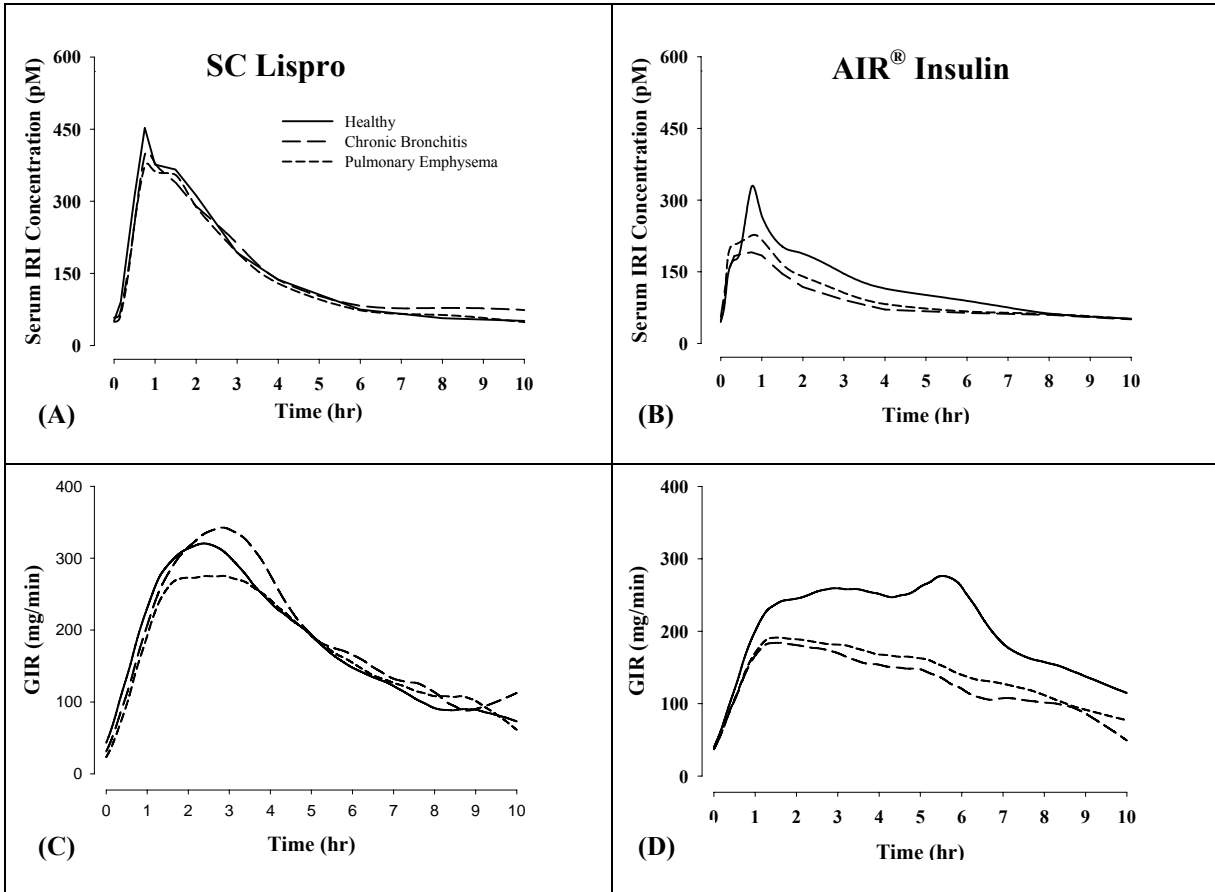
$R_{\max}$ (mg/min)	313	332	214	351	214	314
	(32)	(31.9)	(37.9)	(38.5)	(36.8)	(18.3)
$t_{R\max}$ (min) *	261	153	184	177	188	178
	(60–600)	(81–280)	(71–536)	(117–600)	(72–600)	(79–403)
$F'$ (%)	9.30		5.18		6.26	
	(50.2)		(44.9)		(53.7)	

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Results are expressed in terms of geometric means (except where indicated), with coefficients of variation (%) enclosed in parentheses below. Abbreviations: AIR<sup>®</sup>=AIR<sup>®</sup> Inhaled Insulin (Alkermes Inc., Cambridge, MA), AUC<sub>(0-t')</sub>=area under the serum insulin concentration curve from time 0 until time of return to baseline, C<sub>max</sub>=maximum serum insulin concentration, F=relative bioavailability, F'=relative biopotency, GIR<sub>tot</sub>=amount of glucose infused, N=number of experiments performed, R<sub>max</sub>=maximum glucose infusion rate, SC=subcutaneous, t<sub>max</sub>=time to maximum insulin concentration, t<sub>Rmax</sub>=time to maximum glucose infusion rate, \* Median (range)

**Figure 1.** Pharmacokinetic and glucodynamic responses to administration of SC Lispro (A,C) or AIR<sup>®</sup> Insulin (B,D) in healthy subjects, subjects with chronic bronchitis, and subjects with emphysema.

Abbreviations: AIR<sup>®</sup>=AIR<sup>®</sup> Inhaled Insulin (Alkermes Inc., Cambridge, MA), GIR=amount of glucose infused, IRI=immunoreactive insulin, SC=subcutaneous.



**Figure 2**—Analyses of pharmacokinetic and glucodynamic responses to AIR<sup>®</sup> Insulin administration versus PFTs for each study group. A linear model was fitted for each PFT parameter with treatment, group, exposure parameter, and interaction terms. A significant relationship was found between DLco and AUC<sub>0-t</sub> ( $P < 0.01$ ) (Panel A). No other significant relationships were observed between any of the PK or GD variables and PFT parameters ( $P > 0.2$ ) using the described models (Panels B, C, D). Black triangles (▲) = healthy group; white circles (○) = chronic bronchitis group; black squares (■) = pulmonary emphysema group. Abbreviations: AIR<sup>®</sup> = AIR<sup>®</sup> Inhaled Insulin (Alkermes Inc., Cambridge, MA), AUC<sub>0-t</sub> = area under the IRI concentration versus time curve, DLco = carbon monoxide diffusion capacity, FEV<sub>1</sub> = forced expiratory volumes, GD = glucodynamic, G<sub>tot</sub> = total amount of glucose infused, PFT = pulmonary function test, PK = pharmacokinetic.

