Efficacy and Safety of Technosphere Inhaled Insulin Compared With Technosphere Powder Placebo in Insulin-Naive Type 2 Diabetes Suboptimally Controlled With Oral Agents

Julio Rosenstock, MD1
Richard Bergenstal, MD2
Ralph A. DeFronzo, MD3
Irl B. Hirsch, MD4
David Klonoff, MD5
Anders H. Boss, MD, MFPM6

David Kramer, PhD6
Richard Petrucci, MD6
Wen Yu, MD6
Brian Levy, MD, FACE6
FOR THE 0008 STUDY GROUP*

OBJECTIVE — This double-blind, placebo-controlled, randomized, multicenter, parallel-group study compared the efficacy, safety, and tolerability of Technosphere insulin with Technosphere powder as placebo in insulin-naive type 2 diabetic patients whose diabetes was suboptimally controlled with oral antidiabetic agents.

RESEARCH DESIGN AND METHODS — Patients (n = 126) were randomly assigned to 12 weeks of therapy with Technosphere insulin or Technosphere powder after lifestyle education on nutrition, exercise, and instructions on inhaler use. The primary efficacy outcome was change in A1C from baseline to study end, and the secondary efficacy outcome was area under the curve for postprandial glucose levels during a meal test at treatment weeks 4, 8, and 12.

RESULTS — A1C reduction from a mean baseline of 7.9% was greater with Technosphere insulin than with Technosphere powder (−0.72 vs. −0.30%; P = 0.003). Postprandial glucose excursions were reduced by 56% with Technosphere insulin compared with baseline, and maximal postprandial glucose levels were reduced by 43% compared with Technosphere powder. Incidences of hypoglycemia, hyperglycemia, cough, and other adverse events were low in both groups. Body weight was unchanged in both groups.

CONCLUSIONS — Technosphere insulin was well tolerated and demonstrated significant improvement in glycemic control with clinically meaningful reductions in A1C levels and postprandial glucose concentrations after 12 weeks of treatment.

Diabetes Care 31:2177–2182, 2008

Current standards of care for patients with type 2 diabetes focus on achieving and maintaining stringent glycemic goals. In an attempt to achieve these standards, the American Diabetes Association and the European Association for the Study of Diabetes issued a consensus algorithm for type 2 diabetes management that proposed the early use of insulin replacement as one therapeutic option (1). The algorithm was crafted to more effectively and rapidly reach and sustain A1C goals of <7%, attempting to overcome clinical inertia by using a target-driven strategy.

Early use of basal insulin therapy in combination with oral antidiabetic agents (OADs) in patients with type 2 diabetes failing to meet A1C goals has been demonstrated to achieve glycemic targets (1–3). The APOLLO study (A Parallel design comparing an Oral antidiabetic drug combination therapy with either Lantus once daily or Lispro at mealtime in type 2 diabetes patients failing Oral treatment) also demonstrated that a prandial short-acting insulin analog (insulin lispro) was similar to basal insulin analog therapy (insulin glargine) in reducing A1C to 7% (4). In addition, the use of prandial insulin added to oral agents has recently been shown to reduce A1C levels more than a basal insulin (insulin detemir) added to oral agents in individuals with type 2 diabetes, but the insulin titrations were not properly optimized (5).

Although insulin is the most effective therapy for reducing blood glucose levels (1), many patients are reluctant to initiate insulin therapy (6–8). Inhaled insulin is an alternative to subcutaneous administration and may help to overcome barriers to initiation of insulin therapy (9). Technosphere technology represents a drug delivery platform that allows pulmonary administration of therapeutic agents based on the intermolecular self-assembly of a fumaryl diketopiperazine molecule into microparticles called Technosphere particles. Technosphere insulin particles (human regular insulin loaded onto the diketopiperazine molecule) are prepared using this technology and are optimized for inhalation deep into the lung. They have a uniform size distribution in that >90% of the particles are in the respirable range with a mean particle diameter of 2.5 μm, they dissolve rapidly at physiological pH (10), and they are delivered with a
Technosphere insulin compared with powder placebo

handheld pocket-sized inhaler. Technosphere insulin is rapidly absorbed (within 15 min), has a fast onset of action (~25–30 min), and has a short duration of action (~2–3 h) (11–14), which closely mimics physiologic postprandial endogenous insulin responses.

As A1C levels improve toward the goal, the importance of therapies that reduce postprandial glucose (PPG) levels increases (15,16). Early use of prandial insulin may be increasingly common in type 2 diabetes because correction of PPG excursions is needed to achieve an optimal A1C level (16). Technosphere insulin is inhaled and has uniquely favorable pharmacokinetic properties that may enable more patients with type 2 diabetes to reach glycemic goals.

We report the first and only double-blind, placebo-controlled, randomized trial of any inhaled insulin therapy designed to evaluate the efficacy and safety of Technosphere insulin compared with Technosphere powder in type 2 diabetic patients whose diabetes is suboptimally controlled with OADs.

RESEARCH DESIGN AND METHODS — This double-blind, parallel-group, randomized study, conducted at 21 U.S. centers, directly compared efficacy and safety of 12 weeks of prandial treatment with Technosphere insulin or Technosphere powder added to OADs. The study complied with the Declaration of Helsinki for participation in human research and received appropriate institutional review board approvals before initiation. All participants gave written informed consent before entering into the study.

Insulin-naive patients (aged 18–80 years with diabetes duration of 2–12 years), treated with at least one OAD, were on a stable regimen for at least 3 months before enrollment. To participate, patients were required to have BMI <38 kg/m2, A1C of 6.6–10.5%, baseline forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) of 80–120% of predicted normal levels based on spirometric reference values developed from the National Health and Nutrition Examination Study III (17), and a baseline level single-breath carbon monoxide-diffusing capacity of the lung (DLCO) of 80–120% of predicted normal (18). Patients with severe diabetes complications, significant hepatic or renal disease, severe or multiple allergies, chronic pulmonary disease, AIDS, systemic autoimmune or collagen vascular disease, major psychiatric disorders, and myocardial infarction or stroke within the previous 6 months were excluded.

Study design and treatment

After screening, subjects received comprehensive nutrition and exercise education to reinforce American Diabetes Association recommendations (19). They were trained on the MedTone Inhaler, which uses cartridges containing Technosphere insulin formulated as a dry powder or as Technosphere powder. The hand-held, pocket-sized inhaler is a breath-powered, high-resistance, dry powder delivery device. At baseline, patients were randomly assigned to receive cartridges containing either Technosphere insulin or Technosphere powder. Technosphere insulin cartridges contained 6, 12, or 24 units of insulin as a nominal dose (equivalent to 1.56, 3.12, and 6.24 units of subcutaneous regular human insulin), based on an assumed bioavailability of 26% compared with subcutaneously administered human regular insulin (11). Subjects were instructed to use the inhaler just before the first mouthful of food at each main or substantive meal for three to four doses total each day. Subjects randomly assigned to Technosphere insulin were started at 6 nominal units of insulin before each meal at the baseline visit. At subsequent visits, doses in both groups were then adjusted concomitantly for each meal based on self-monitoring of PPG levels in 6- to 12-nominal unit increments with a maximum permitted dose of 48 nominal units per meal. Subjects were instructed to use the same amount of study drug at each meal after each adjustment, but study sites did not use a common structured titration algorithm. All subjects continued with their usual OAD regimen that was withheld on study visit days until any standardized meal or blood tests were performed. No changes in OAD regimens were allowed during the study.

At baseline, subjects underwent a meal challenge consisting of a mixed meal containing ~21 g fat, 16 g carbohydrates, and 14 g protein for a total of 310 kcal (Uncle Ben’s Breakfast Bowl) that was repeated at weeks 4, 8, and 12. Plasma glucose samples were collected at 0, 30, 60, and 120 min after the meal and were analyzed at a central laboratory for glucose metrics and A1C.

Study end points

The primary efficacy outcome was change in A1C from baseline to study end (12 weeks). The predetermined efficacy outcome was arbitrarily defined as a mean reduction in A1C of at least 0.6% in the Technosphere insulin group compared with the Technosphere powder group.

Secondary efficacy outcomes were the PPG concentrations after the meal at baseline and after 4, 8, and 12 weeks of treatment. These concentrations were used to calculate glucose area under the curve from 0 to 120 min (AUC0–120) after the start of a meal and maximum glucose concentration (Cmax).

Hypoglycemia, hyperglycemia, and cough were specifically evaluated to capture more detailed safety information. Hypoglycemia was defined as recognizable symptoms and/or a blood glucose concentration <63 mg/dl. Severe hypoglycemia was defined as an episode requiring glucagon injection, glucose administration, or help from another individual, as well as any episode that resulted in coma or seizures. Hyperglycemia was defined as a fasting plasma glucose concentration >280 mg/dl. Plasma glucose levels >400 mg/dl on more than one occasion, without adequate explanation, were designated as severe hyperglycemia. Any plasma glucose level >480 mg/dl resulted in automatic withdrawal of the patient from the study. Hypoglycemic or hyperglycemic episodes were not classified as adverse events unless they were severe or necessitated study withdrawal.

Monthly spirometry conducted at the study sites was used to measure FEV1 and FVC changes. DLCO changes were measured at the study sites by external pulmonologists at baseline and at study end and were corrected for carboxyhemoglobin and hemoglobin. Evaluations consistent with the American Thoracic Society recommendations for quality control were performed on all equipment before subject testing. An audit of the pulmonary function testing data was done after the study to confirm adherence to American Thoracic Society reporting standards.

Statistical analysis

Primary and secondary efficacy outcomes were baseline-adjusted. With use of a one-sided, one-sample t test, P < 0.05 was considered significant for within-group changes between baseline and subsequent visits. A one-sided, two-sample t test was used for between-
treatment comparisons. All other statistical tests of treatment effects used a two-sided, two-sample t test. Analysis of variance was performed for AUC_{0–120} and C_{max} using SAS (version 8.2, SAS Institute, Cary, NC). Continuous variables were summarized using descriptive statistics; categorical variables are presented as counts and percentages of totals. Results are expressed as means ± SD.

All randomly assigned subjects who took at least one dose of study medication were included in the safety population. The intent-to-treat (ITT) population comprised all randomly assigned subjects with baseline values and at least one post-baseline value for the primary efficacy outcome, A1C. Subjects were stratified into two subgroups of the ITT population for a predefined analysis as subgroup A, with screening A1C values of 6.6–7.9%, and subgroup B, with screening A1C values of 8.0–10.5%.

**RESULTS** — A total of 167 patients were screened for the study, with 126 subjects eligible for enrollment; 107 sub-

---

**Table 1—Baseline characteristics (randomized population) of subjects receiving Technosphere insulin and Technosphere placebo**

| Parameter                          | Technosphere insulin | Technosphere placebo |
|------------------------------------|----------------------|----------------------|
| **n**                              | 61                   | 62                   |
| **Sex**                            |                      |                      |
| Male                               | 39 (63.9)            | 43 (69.4)            |
| Female                             | 22 (36.1)            | 19 (30.6)            |
| **Ethnicity**                      |                      |                      |
| White                              | 40 (65.6)            | 39 (62.9)            |
| Black                              | 7 (11.5)             | 3 (4.8)              |
| Hispanic                           | 12 (19.7)            | 14 (22.6)            |
| Asian                              | 1 (1.6)              | 5 (8.1)              |
| Other                              | 1 (1.6)              | 1 (1.6)              |
| **Age (years)**                    | 55.9 ± 9.1 (34–75)   | 53.4 ± 10.0 (26–74)  |
| **Weight (kg)**                    | 86.9 ± 13.7 (50.3–122.9) | 94.1 ± 15.7 (55.6–135.2) |
| **BMI (kg/m^2)**                   | 29.7 ± 3.3 (22.0–38.1) | 31.4 ± 3.9 (21.0–39.3) |
| **A1C (%)**                        | 8.0 ± 1.2 (6.4–12.2)  | 7.8 ± 1.1 (6.2–10.7) |
| **Medications**                    |                      |                      |
| Sulfonylurea                       | 39 (63.9)            | 33 (53.2)            |
| Metformin                          | 43 (70.5)            | 37 (59.7)            |
| Sulfonylurea/metformin             | 9 (14.8)             | 10 (16.1)            |
| Thiazolidinediones                 | 17 (27.9)            | 22 (35.5)            |
| Other                              | 6 (9.8)              | 8 (12.9)             |
| **Number of medications**          |                      |                      |
| 1 OAD                              | 22 (36.1)            | 27 (43.6)            |
| ≥2 OADs                            | 39 (63.9)            | 35 (56.4)            |
| **Pulmonary function**             |                      |                      |
| FEV₁ (liters)                      | 2.97 ± 0.67 (1.88–4.72) | 3.17 ± 0.77 (2.00–4.60) |
| FVC (liters)                       | 3.79 ± 0.83 (2.19–5.74) | 4.08 ± 0.86 (2.47–5.97) |
| DLCO (ml·min⁻¹·mmHg⁻¹)             | 24.99 ± 4.70 (14.83–32.95) | 26.54 ± 5.57 (15.96–38.10) |

Data are n (%) or mean ± SD (range).
jects completed the study. Five subjects withdrew from the placebo group—four because of concerns about the demands of the study schedule and one because of cough. Subject disposition is summarized in Fig. 1. Subject baseline demographic characteristics were comparable between the two groups (Table 1); however, subjects receiving Technosphere powder had greater weight and BMI ($P = 0.008$ and $P = 0.014$, respectively). ITT population results are presented for efficacy, and the full randomized population results are presented for safety evaluation.

**Efficacy**

After 2 weeks of treatment, mean A1C decreased by $-0.7\%$ with Technosphere insulin and by $-0.3\%$ with Technosphere powder ($P = 0.003$) from baselines of 8.0 and 7.8\%, respectively. Mean decreases for ITT subgroup A (screening A1C 6.6–7.9\%) were $-0.5\%$ from a baseline of 7.2\% for Technosphere insulin ($n = 35$) and $-0.2\%$ from a baseline of 7.1\% for Technosphere powder ($n = 0.05$). For subgroup B (screening A1C 8.0–10.5\%), decreases were $-1.2\%$ for Technosphere insulin ($n = 20$) and $-0.4\%$ for Technosphere powder ($n = 18$) ($P = 0.05$) from baselines of 9.0 and 8.9\%, respectively (Fig. 2A).

During the study, the mean dose of Technosphere insulin increased from the initial baseline dose of 6 nominal units before each meal (18 nominal units/day). The mean dose at each meal was $20 \pm 9$ nominal units insulin at week 4, $30 \pm 13$ nominal units at week 8, and $31.6 \pm 12.9$ nominal units at week 12 (22 subjects received 6–24 nominal units and 32 subjects received 30–48 nominal units). Glucose AUC$_{0-120}$ in the Technosphere insulin group decreased from a baseline of 4,533 $\pm$ 2,647 to 1,977 $\pm$ 2,149 min $\cdot$ mg/dL ($P < 0.0001$) (Fig. 2B); the glucose $C_{\text{max}}$ was 43\% less with Technosphere insulin than with Technosphere powder: 34 vs. 60 mg/dL ($P < 0.0001$), respectively (data corrected by subtracting the baseline glucose value at 0 min).

**Safety**

As shown in Table 2, incidences of hypoglycemia and hyperglycemia were similar for both groups, with no significant between-group differences ($P = 0.321$ and $P = 0.871$, respectively). Technosphere insulin was associated with an incidence of hypoglycemic episodes per month similar to that with Technosphere powder (0.69 vs. 0.86, respectively; $P = 0.346$).

Coughing episodes were similar in both groups (Table 2). Eighteen of 61 (29.5\%) Technosphere insulin subjects and 17 of 62 (27.4\%) Technosphere powder subjects experienced ≥1 coughing episode. Most episodes of coughing were reported to occur within 10 min of study drug administration (41 of 63 episodes with Technosphere insulin and 89 of 113 with Technosphere powder). Three subjects in each group had sputum production. One subject in the Technosphere insulin group withdrew because of cough.

Mean changes from baseline in FEV$_1$ were $-0.04$ liter for Technosphere insulin ($P = 0.143$) and $-0.01$ liter for Technosphere powder ($P = 0.74$); mean changes from baseline in FVC were $-0.04$ liters ($P = 0.218$) and $-0.02$ liters ($P = 0.55$). Mean DL$_{CO}$ values decreased slightly in both groups (mean change = $0.02$ ml $\cdot$ min$^{-1}$ $\cdot$ mmHg$^{-1}$ with Technosphere insulin [$P = 0.943$] and 0.67 ml $\cdot$ min$^{-1}$ $\cdot$ mmHg$^{-1}$ with Technosphere powder [$P = 0.042$]). These changes were not considered clinically relevant (Table 2).

After 12 weeks of treatment with Technosphere insulin or Technosphere powder
CONCLUSIONS

This is the first double-blind, placebo-controlled, randomized inhaled insulin study (Technosphere insulin versus Technosphere powder) ever reported to assess the efficacy and safety/tolerability profile in insulin-naive type 2 diabetic patients suboptimally controlled withOADs alone. Technosphere insulin resulted in significant reductions in A1C compared with Technosphere powder over a 12-week treatment period, with greater reductions in subjects with higher baseline A1C values. Overall, the hypoglycemia rate was low and similar between Technosphere insulin and Technosphere powder.

The significant A1C reductions (0.7%) with Technosphere insulin were clinically meaningful, especially considering the mildly elevated A1C at baseline (8.0% for the Technosphere insulin group and 7.8% for the Technosphere powder group). This modestly elevated baseline A1C may explain why the arbitrary predetermined superiority limit of an A1C reduction $\geq 0.6\%$ (Technosphere insulin versus Technosphere powder) was not achieved over a 12-week treatment period. Additional factors that may have contributed to not achieving the 0.6% A1C difference between groups include the relatively short treatment period (12 weeks), the A1C reduction in the placebo group due to the study effect and dietary/diabetes education (20), the unfamiliarity of the investigators with adjusting the dose of inhaled pulmonary Technosphere insulin, and the lack of a common structured insulin titration algorithm for all sites. Of note, Technosphere insulin doses were not increased to the maximum permitted level of 48 nominal units per meal in $>40\%$ of subjects. This lack of maximal dosing may have been due to the investigators’ caution with the apparent higher numerical Technosphere insulin doses.

Previous studies have demonstrated that Technosphere insulin has a much more rapid absorption with a shorter time to $C_{\text{max}}$ than subcutaneous human regular insulin (21,22). This pharmacokinetic profile, which more closely approximates early-phase insulin release, has the potential to result in significant improvement in PPG excursions. Indeed, this study demonstrated that the PPG excursions with Technosphere insulin after meals were less than half of those with Technosphere powder. This reduction in PPG exposure would be expected to contribute to significant A1C reductions, especially when the A1C level is mildly elevated, as was demonstrated in this study.

Both Technosphere insulin and Technosphere powder were well tolerated in this study. Technosphere insulin and Technosphere powder were associated with mild, transient cough (29.5 and 27.4% of subjects, respectively), but there was only one discontinuation in the Technosphere insulin group. Technosphere insulin and Technosphere powder had no clinically meaningful effects on short-term pulmonary function, as measured by either spirometry or diffusion capacity, after 12 weeks of exposure. The incidence of hypoglycemia was comparable between groups despite greater A1C reductions with Technosphere insulin, and no clinically severe hypoglycemia was reported in either group. No other clinically relevant adverse events occurred during the study. Despite improvement in glycemic control, subjects in the Technosphere insulin group did not gain weight compared with those in the Technosphere powder group.

Technosphere insulin is a new insulin delivery system with a unique pharmacokinetic profile compared with all currently available insulins. Patients with type 2 diabetes could potentially benefit from initiation of prandial insulin therapy with an insulin that mimics the peripheral insulin level that reflects early insulin secretion. Such an insulin would be an important addition to the armamentarium of diabetes therapies. Injected prandial insulin added to oral agents has been shown to potentially reduce A1C levels in patients with type 2 diabetes more effectively than basal insulin but has resulted in more hypoglycemia and weight gain (5). It remains to be determined whether Technosphere insulin, with its unique pharmacologic profile, might result in less hypoglycemia and weight gain while still effectively lowering the A1C in patients with type 2 diabetes.

This first proof-of-concept trial demonstrated that Technosphere insulin is well tolerated and substantially reduced A1C levels and meal-related glucose excursions in type 2 diabetic patients. Technosphere insulin may become an important treatment option in type 2 diabetes. Larger, long-term clinical trials are in progress to further evaluate the efficacy and safety of Technosphere insulin reported in this study.
Acknowledgments—This study was sponsored by MannKind Corporation. Technical editorial support for this article was provided by MannKind Corporation.

Parts of this study were presented in abstract form at the 65th annual meeting of the American Diabetes Association, San Diego, California, 10–14 June 2005.

APPENDIX

Additional 0008 Study Group Investigators are the following: O.J. Bizzozero Jr., L. Blonde, A. Drexler, S. Engel, V. Fonseca, R. Henry, D. Lorber, J. Marks, J. McGill, W. Petit, P. Raskin, S. Schwartz, G. Uwaifo, M. Warren, D. Weiss, and H. Zisser.

References

1. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B: Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 29:1963–1972, 2006
2. Riddle MC, Rosenstock J, Gerich J: The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 26:3080–3086, 2003
3. Yki-Jarvinen H: Combination therapies with insulin in type 2 diabetes. Diabetes Care 24:758–767, 2001
4. Bretzel RG, Nuber U, Landgraf W, Owens DR, Bradley C, Linn T: Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. Lancet 371:1073–1084, 2008
5. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, Levy JC: Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med 357:1716–1730, 2007
6. Hunt LM, Valenzuela MA, Pugh JA: NIDDM patients’ fears and hopes about insulin therapy: the basis of patient reluctance. Diabetes Care 20:292–298, 1997
7. Korytkowski M: When oral agents fail: practical barriers to starting insulin. Int J Obes Relat Metab Disord 26 (Suppl. 3):S18–S24, 2002
8. Peyrot M, Reiner RR, Lauritzen T, Skovlund SE, Snock EJ, Matthews DR, Landgraf R, Kleinebrel L: Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes Care 28:2673–2679, 2005
9. Rosenstock J, Cappellen JC, Bolinder B, Gerber RA: Patient satisfaction and glycemic control after 1 year with inhaled insulin (Exubera) in patients with type 1 or type 2 diabetes. Diabetes Care 27:1318–1323, 2004
10. Leone-Bay A, Grant M: Technosphere® insulin: mimicking endogenous insulin release. In Modified-Release Drug Delivery Technology. Vol. 2, 2nd ed. Rathbone M, Hadgraft J, Roberts M, Lane M, Eds. New York, Informa Healthcare USA, 2008
11. Steiner S, Pfützner A, Wilson BR, Harzer O, Heinemann L: Results of a dose-response study with a new insulin formulation for pulmonary delivery. Exp Clin Endocrinol Diabetes 110:17–21, 2002
12. Pfützner A, Forst T: Pulmonary insulin delivery by means of the Technosphere drug carrier mechanism. Expert Opin Drug Deliv 2:1097–1106, 2005
13. Rave K, Heise T, Pfützner A, Boss AH: Coverage of postprandial blood glucose excursions with inhaled Technosphere insulin in comparison to subcutaneously injected regular human insulin in subjects with type 2 diabetes. Diabetes Care 30:2307–2308, 2007
14. Boss AH, Rave K, Cheatham WW, Heise T: Inhaled Technosphere/Insulin: glucose elimination at the right time (abstract 443–P). Diabetes 54 (Suppl. 1):A109, 2005
15. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group, European Diabetes Epidemiology Group, Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe. Lancet 354:617–621, 1999
16. Monnier L, Lapinski H, Colette C: Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA1c. Diabetes Care 26:881–885, 2003
17. Hankinson JL, Odencrantz JR, Fedan KB: Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 159:179–187, 1999
18. Miller A, Thornton JC, Warshaw R, Anderson H, Teirstein AS, Selikoff IJ: Single breath diffusing capacity in a representative sample of the population of Michigan, a large industrial state: predicted values, lower limits of normal, and frequencies of abnormality by smoking history. Am Rev Respir Dis 127:270–277, 1983
19. American Diabetes Association: Standards of medical care in diabetes—2007. Diabetes Care 30 (Suppl. 1):S4–S41, 2007
20. Gale EA, Beattie S, Hu J, Kovisto V, Tan M: Recruitment to a clinical trial improves glycemic control in patients with diabetes. Diabetes Care 30:2989–2992, 2007
21. Heinemann L, Heise T: Current status of the development of inhaled insulin. Br J Diabetes Vasc Dis 4:295–301, 2004
22. Rave KM, Heise T, Pfützner A, Steiner S, Heinemann L: Results of a dose-response study with a new pulmonary insulin formulation and inhaler (Abstract 305–PP). Diabetes 49 (Suppl. 1):A75, 2000