An Open, Randomized, Parallel-Group Study to Compare the Efficacy and Safety Profile of Inhaled Human Insulin (Exubera) With Glibenclamide as Adjunctive Therapy in Patients With Type 2 Diabetes Poorly Controlled on Metformin

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OBJECTIVE — To compare the efficacy and safety profile of adding inhaled human insulin (INH) (Exubera) or glibenclamide to metformin monotherapy in patients with poorly controlled type 2 diabetes.

RESEARCH DESIGN AND METHODS — We conducted an open-label, parallel, 24-week multicenter trial. Patients uncontrolled on metformin were randomized to adjunctive INH ($n = 243$) or glibenclamide ($n = 233$). Before randomization, patients were divided into two HbA_{1c} (A1C) arms: ≥8 to ≤9.5% (moderately high) and >9.5 to ≤12% (very high). The primary efficacy end point was A1C change from baseline.

RESULTS — Mean adjusted A1C changes from baseline were −2.03 and −1.88% in the INH and glibenclamide groups, respectively; between-treatment difference −0.17% (95% CI −0.34 to 0.01; $P = 0.058$), consistent with the noninferiority criterion. In the A1C >9.5% arm, inhaled insulin demonstrated a significantly greater reduction in A1C than glibenclamide, between-treatment difference −0.37% (−0.62 to −0.12; $P = 0.004$). In the A1C ≤9.5% arm, between-treatment difference was 0.04% (−0.19 to 0.27; $P = 0.733$). Hypoglycemia (events per subject-month) was greater with INH (0.18) than glibenclamide (0.08), risk ratio 2.24 (1.58–3.16), but there were no associated discontinuations. Other adverse events, except increased cough in the INH group, were similar. At week 24, changes from baseline in pulmonary function parameters were small. Insulin antibody binding increased more with INH but did not have any associated clinical manifestations.

CONCLUSIONS — In patients with type 2 diabetes poorly controlled on metformin, adding INH or glibenclamide was similarly effective in improving glycemic control, and both were well tolerated. A predefined subgroup with very high A1C (>9.5%) was more effectively treated with the addition of INH.

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Abbreviations: ADA, American Diabetes Association; DL_{co}, carbon monoxide transfer factor; FEV_1, forced expiratory volume in 1 s; INH, inhaled human insulin.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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The goal of therapy in type 2 diabetes management is to reach and sustain near-normal glycemic levels (HbA_{1c} [A1C] of ≤7%) (1,2). Since the American Diabetes Association (ADA) dropped the 8% "action threshold" in 2004 in favor of a general recommendation to treat most patients to A1C <7% (3), levels above this goal have signaled the need to intensify therapy. Oral antidiabetic agent monotherapy is associated with a high secondary failure rate (4,5). The usual next step is progression to oral agent combination therapy; the most extensively studied and widely used combination being a sulfonylurea plus metformin (6). Despite poor glycemic control on average in the general population of patients with type 2 diabetes (7), there is often a reluctance to initiate insulin therapy because of concerns from both physicians (8,9) and patients (10,11).

Improvements in insulin formulation may overcome some of these concerns (12). Inhaled human insulin (INH; Exubera [insulin human {rDNA origin} Inhalation Powder]), which has recently been approved in both the U.S. and European Union for the treatment of type 1 and type 2 diabetes in adults, has proven effective in patients failing to obtain adequate glycemic control with diet and exercise (13) and with multiple oral agents (14,15) and has demonstrated comparable glycemic control to subcutaneously injected insulin (16). The objective of this study was to compare the glycemic control achieved with INH as adjunctive therapy versus a second oral agent (glibenclamide [glyburide]) in patients with type 2 diabetes poorly controlled with metformin monotherapy.

RESEARCH DESIGN AND METHODS

— This was an open-label, multicenter, parallel-group, comparator study conducted and led by academic in-

vestigators and managed by Pfizer Global Research and Development (the sponsor). The study protocol was approved by the independent local institutional review boards of all participating centers, and all patients provided written informed consent. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki.

Inclusion criteria were: *1*) age 35–80 years; *2*) type 2 diabetes diagnosed at least 6 months before screening visit (some subjects with a shorter duration were included and were not excluded from the analyses); *3*) poorly controlled outpatients (A1C 8–12%) failing maximal doses of metformin (>1.5 g/day) for a minimum of 2 months before screening; *4*) pulmonary function tests within the following ranges: carbon monoxide transfer factor (DL_{co}) ≥75%, total lung capacity 80–120% inclusive, and forced expiratory volume in 1 s (FEV_1) ≥70% of predicted; and *5*) written informed consent.

Exclusion criteria included moderate or severe asthma or chronic obstructive pulmonary disease, clinically significant abnormalities on chest X-ray, smoking within 6 months before randomization, concomitant therapy with hypoglycemic agents or agents affecting glycemic control (e.g., oral steroids), fasting C-peptide ≤0.2 nmol/l, major organ system disease, laboratory values >1.5 times upper limit of normal for renal and hepatic function tests (other abnormalities on laboratory screening were at investigators' discretion), known drug or alcohol dependence, and pregnancy, lactation, or planned pregnancy.

After screening, patients entered a 4-week run-in period and all received 1 g metformin twice daily, regardless of prior exact dose of metformin; this treatment was continued throughout the study. Before randomization, patients were divided into two arms based on their A1C value at week −1: A1C ≥8 to ≤9.5% (moderately high) and A1C >9.5 to ≤12% (very high).

The cutoff of 9.5% was based on the median baseline A1C in an earlier study of similar design (14).

Randomization was concealed and used an interactive telephone system. The investigator dialed a central database and answered a series of prompts (protocol number and patient identification). The interactive system then randomized the patient to INH or glibenclamide. Dietary advice and exercise instructions were in line with ADA recommendations (17,18).

The INH (Exubera) dry powder formulation and inhaler system, developed by Pfizer in collaboration with Nektar Therapeutics (San Carlos, CA), was administered within 10 min before meals. Before beginning the study, patients were trained in the inhalation procedure. INH was available in 1- and 3-mg dose blister packs (1 mg equivalent to ~2.5–3.0 units of subcutaneously injected insulin) (19).

Patients were instructed in self-monitoring of blood glucose (MediSense Precision QID blood glucose sensor). All patients performed glucose monitoring a minimum of three (preferably four) times daily. As with conventional insulin therapy, dosing of INH involved an empirical, ongoing process of individualized dose titration based upon each subject's glucose response. Initial recommended INH doses were based on factors including the patient's weight and degree of glycemic control. Administration was preceded by a blood glucose test, and the dose was adjusted weekly at the discretion of the investigator, based on self-monitored blood glucose results, to achieve a mean fasting glycemic target of 4.4–7.8 mmol/l (80–140 mg/dl). If preprandial glucose values fell outside this target range, the investigator would recommend a new insulin dose for the preceding dosing period. The subject was to use the recommended dose when the self-measured premeal glucose value was in the range 4.4–10.0 mmol/l (80–180 mg/dl). In the event of lower (<4.4 mmol/l) or higher (>10 mmol/l) glucose values at the time of dosing, the subject could adjust the dose down or up by one inhalation of the 1-mg strength of INH. Patients could also adjust doses in anticipation of a smaller- or larger-than-usual meal or on an "as-needed" basis. Subjects randomized to adjunctive glibenclamide underwent a period of dose titration during which the dose was increased from 2.5 mg once daily to 5 mg twice daily.

The primary objective was to test the hypothesis that INH is noninferior to glibenclamide in patients in the combined A1C arm and achieves better glycemic control at 24 weeks compared with glibenclamide in patients with baseline A1C >9.5%. Noninferiority in the moderately high A1C arm (≤9.5%) was assessed secondarily. The primary efficacy end point was change in A1C from baseline to week 24. Secondary efficacy end points included percentage of patients achieving A1C <7 and <8% at week 24 (the A1C criterion of 8% was chosen as it was the ADA action level at the time of the study [3]), incidence and severity of hypoglycemic events, change in fasting plasma glucose and 2-h postprandial glucose, change in fasting lipid profile, body weight, and discontinuation rate. Efficacy analyses were based on patients randomized.

Safety analyses were based on actual treatment received. Evaluations included full pulmonary function tests, physical examination, 12-lead electrocardiogram, chest X-ray, clinical laboratory safety tests, and insulin antibodies. Observed and volunteered adverse events were recorded.

Patients were instructed to check blood glucose if they experienced symptoms of hypoglycemia. Hypoglycemia was defined as one of the following: characteristic symptoms of hypoglycemia with no blood glucose check but prompt resolution with food intake, subcutaneous glucagon, or intravenous glucose; characteristic symptoms of hypoglycemia with blood glucose ≤3.3 mmol/l (59 mg/dl); or any blood glucose measurement ≤2.7 mmol/l (49 mg/dl). Severe hypoglycemia was based on the Diabetes Control and Complications Trial criteria (20).

Statistical methods

Statistical analyses were performed by the sponsors in accordance with a predetermined statistical analysis plan. A sample size of 90 patients in each of the two baseline A1C arms (180 patients per treatment group) was planned to provide 80–94% power to detect a 0.7% difference in change from baseline A1C between the groups and 81–95% power to ensure that the change from baseline A1C with adjunctive INH is "at least as good as" that with adjunctive glibenclamide. To account for a possible 20% drop-out rate, a total of 450 patients (225 per group) were to be recruited for the study.

The primary analysis population was the intent-to-treat set, defined a priori in the protocol as all randomized patients with a baseline A1C and at least one post-baseline A1C value. The primary model was an ANCOVA with baseline A1C as a continuous covariate and indicator variables for country and a four-level term for A1C arm by treatment group: A1C ≤9.5% (INH), A1C ≤9.5% (glibenclamide), A1C >9.5% (INH), and A1C >9.5% (glibenclamide). A1C arm-specific (A1C ≤9.5 vs. >9.5%) and combined A1C arm comparisons between the

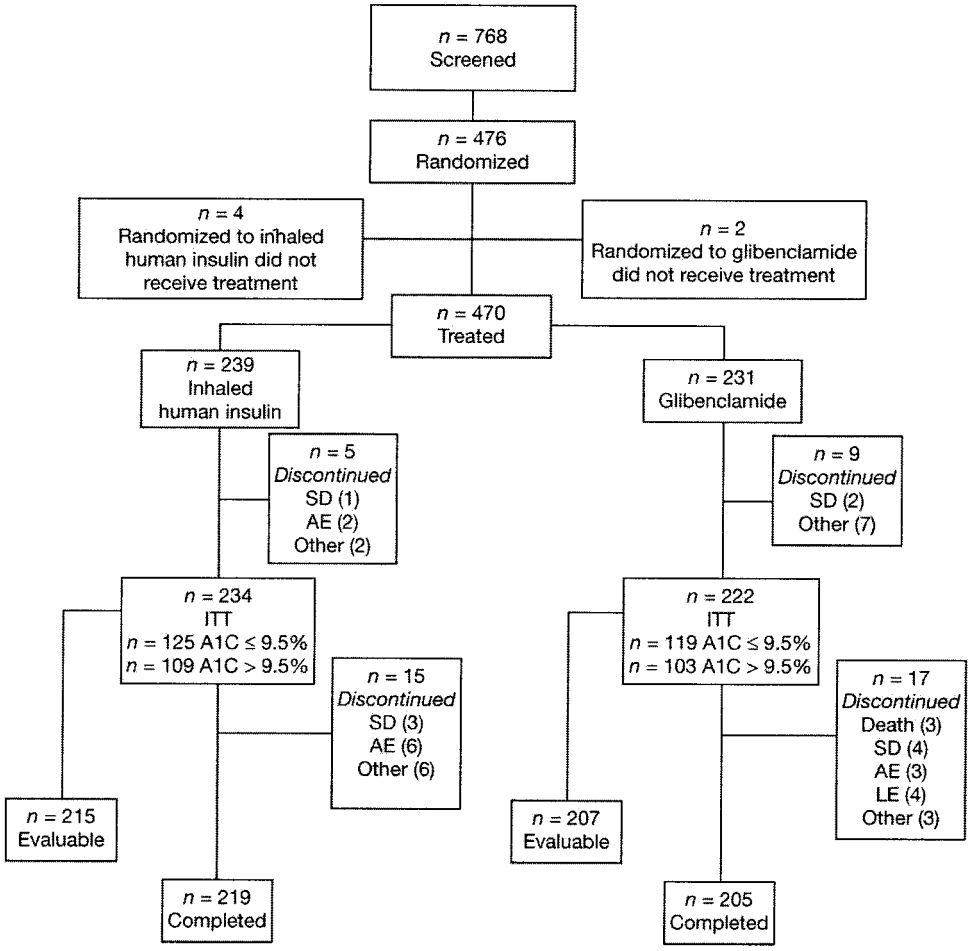

Figure 1—*Patient disposition for patients with type 2 diabetes failing metformin therapy randomized to adjunctive INH or glibenclamide. Other: does not meet entrance criteria, protocol violation, or other (subject did not take prescribed dose of metformin, subject could no longer attend clinic visits for professional reasons, low compliance, did not meet lung function criteria, or subject emigrating). AE, adverse event; ITT, intent to treat; LE, lack of efficacy; SD, subject defaulted.*

INH and glibenclamide groups were made. Due to the multiplicity of testing, a significance level of 0.025 was used to test the hypothesis of superiority. The supplemental claim for noninferiority (combined A1C arm) was met if the upper bound of the two-sided 95% CI of the difference in change from baseline A1C did not exceed 0.5%. If the week 24 observation was not available, the last observation was carried forward. Secondary end points were assessed similarly. The percentage of patients reaching predefined glycemic control goals (A1C <8 and <7%) at week 24 was analyzed using the method of logistic regression (21). The hypoglycemic event rate ratio was estimated using the survival analysis counting process approach for recurrent events, where the analysis model included only a term for treatment (22).

RESULTS

Demography and baseline characteristics

Of 768 patients screened, 476 were randomized to treatment, and 456 qualified for the intent-to-treat analysis: 234 patients to INH and 222 patients to glibenclamide (Fig. 1). Demographic and clinical characteristics were similar between the INH and glibenclamide groups at study entry for all A1C arms; results for the combined A1C arms are shown in Table 1.

Efficacy

In the combined A1C arms, mean adjusted A1C changes from baseline were −2.03 and −1.88% in the INH and glibenclamide groups, respectively. The mean difference in adjusted changes of −0.17% (95% CI −0.34 to 0.01, P = 0.058) did not meet the significance level of 0.025 but was consistent with the noninferiority comparison (Table 1; Fig. 2*A*). INH demonstrated improved glycemic control to glibenclamide for patients in the very high A1C arm (A1C >9.5%) (Fig. 2*B*) and noninferior glycemic control for patients in the moderately high A1C arm (A1C ≤9.5%) (Fig. 2*C*). For the A1C >9.5% arm, the mean adjusted change from baseline was −2.23% (INH) and −1.86% (glibenclamide); between-treatment difference −0.37% (95% CI −0.62 to −0.12; P = 0.004) (Table 1). For the A1C ≤9.5% arm, mean adjusted A1C changes were −1.84 and −1.89%, respectively (0.04% [−0.19 to 0.27; P = 0.733]).

At baseline, only three and four pa-

Table 1—*Demographic and baseline characteristics and week 24 outcome data for patients with type 2 diabetes poorly controlled on metformin monotherapy randomized to adjunctive INH versus adjunctive glibenclamide*

	INH + metformin			Glibenclamide + metformin		
Parameter	Combined	A1C >9.5%	A1C ≤9.5%	Combined	A1C >9.5%	A1C ≤9.5%
n (male/female)	239 (136/103)	109 (62/47)	130 (74/56)	231 (132/99)	105 (53/52)	126 (79/47)
n (completing 24 weeks)	213	96	117	201	95	106
Age (years)	55.5 (35–77)	54.6 (35–74)	56.2 (35–77)	55.5 (36–77)	54.4 (36–77)	56.3 (37–74)
Weight (kg)	90.5 (55–168)	89.6 (60–162)	91.2 (55–168)	88.2 (47–131)	87.8 (50–125)	88.6 (47–131)
BMI (kg/m^2)	31.8 (19–51)	31.7 (22–47)	31.8 (19–51)	31.1 (22–47)	31.1 (22–47)	31.2 (22–45)
Diabetes duration (years)	8.4 (0.6–35.6)	9.2 (0.6–35.6)	7.7 (0.6–30.3)	7.8 (0.3–29.5)	8.4 (0.5–29.5)	7.4 (0.3–27.5)
Fasting C-peptide (pmol/ml)	1.20 (0.30–4.60)	1.30 (0.36–4.60)	1.12 (0.36–4.20)	1.29 (0.26–6.50)	1.41 (0.30–6.50)	1.19 (0.26–4.40)

	INH + metformin		Glibenclamide + metformin		Difference between adjusted mean change (95% CI)*
	Baseline	Week 24 (LOCF)	Baseline	Week 24 (LOCF)	
Average total daily dose of study drug (mg)†					
Combined	10.1 ± 5.0	13.2 ± 7.3	4.5 ± 1.5	7.6 ± 3.0	
A1C >9.5%	11.4 ± 5.1	14.9 ± 7.7	4.8 ± 1.3	8.5 ± 2.4	
A1C ≤9.5%	9.0 ± 4.7	11.8 ± 6.7	4.3 ± 1.7	6.8 ± 3.3	
A1C (%)					
Combined	9.46 ± 1.05	7.34 ± 0.98	9.57 ± 1.11	7.52 ± 1.13	−0.17 (−0.34 to 0.01); $P = 0.058$
A1C >9.5%	10.40 ± 0.70	7.50 ± 1.13	10.56 ± 0.73	7.97 ± 1.22	−0.37 (−0.62 to −0.12); $P = 0.004$
A1C ≤ 9.5%	8.64 ± 0.45	7.20 ± 0.81	8.71 ± 0.50	7.13 ± 0.88	0.04 (−0.19 to 0.27); $P = 0.733$
Patients achieving A1C <8%, *n* (%)					Odds ratio (95% CI)
Combined		180 (76.9)		161 (72.5)	1.12 (0.70–1.80)
A1C >9.5%		79 (72.5)		58 (56.3)	1.91 (1.02–3.55)
A1C ≤ 9.5%		101 (80.8)		103 (86.6)	0.49 (0.23–1.06)
Patients achieving A1C <7%					Odds ratio (95% CI)
Combined		87 (37.2)		69 (31.1)	1.32 (0.87–2.00)
A1C >9.5%		37 (33.9)		18 (17.5)	2.54 (1.27–5.08)
A1C ≤9.5%		50 (40.0)		51 (42.9)	0.85 (0.49–1.46)
Mean insulin antibodies (μU/ml)	1.25 ± 3.26	11.65 ± 28.74	1.03 ± 0.30	1.01 ± 0.15	
Median percentage binding	1.00	4.30	1.00	1.00	
FPG (mmol/l)‡	203.0 ± 56.0	161.0 ± 43.0	216 ± 54.0	164 ± 48.0	0.98 (−7.13 to 9.10)
2-h PPG (mmol/l)§	216.3 ± 49.6	155.7 ± 32.6	227.8 ± 48.1	169.2 ± 42.8	−11.08 (−18.37 to −3.78)
Total cholesterol (mmol/l)	5.09 ± 1.08	5.13 ± 0.92	5.26 ± 1.02	5.23 ± 1.02	0.02 (−0.11 to 0.14)
LDL cholesterol (mmol/l)	2.97 ± 0.91	3.07 ± 0.83	3.07 ± 0.84	3.10 ± 0.82	0.04 (−0.07 to 0.14)
Triglycerides (mmol/l)	2.20 ± 1.52	1.87 ± 1.07	2.54 ± 2.01	2.27 ± 1.89	−0.16 (−0.34 to 0.01)
HDL cholesterol (mmol/l)	1.18 ± 0.31	1.25 ± 0.36	1.14 ± 0.31	1.18 ± 0.35	0.05 (−0.001 to 0.10)
FEV_1 (l)	2.99 ± 0.72	2.90 ± 0.74	2.93 ± 0.72	2.89 ± 0.72	−0.04 (−0.084 to 0.004)
DL_{CO} (ml · min^{-1} · mmHg^{-1})	26.75 ± 6.75	26.32 ± 6.67	26.41 ± 6.31	25.63 ± 6.27	0.23 (−0.45 to 0.90)
FVC (l)	3.64 ± 0.87	3.58 ± 0.88	3.60 ± 0.90	3.55 ± 0.91	−0.008 (−0.061 to 0.045)
TLC (l)	5.73 ± 1.19	5.78 ± 1.29	5.74 ± 1.22	5.66 ± 1.24	0.116 (0.002–0.231)

Data are *n* (%), means ± SD, or means (range). *Values are difference between adjusted mean change unless specified otherwise. †Average total daily INH and glibenclamide dose at week 4. ‡Fasting plasma glucose (FPG), after at least an 8-h fast, was measured at weeks 0, 6, 18, and 24. The change from baseline in FPG was calculated from the average of all available week 0 and 24 values. §2-h postprandial plasma glucose (PPG) was calculated from home glucose measurements; a 24-h home glucose profile (seven samples per day, taken before and 2 h after each meal and at bedtime) was obtained 6, 4, and 2 days prior to the week 0 and 24 clinic visits. The change from baseline in 2-h PPG was calculated as the average of all available postprandial data across all meals. FVC, forced vital capacity; LOCF, last observation carried forward; TLC, total lung capacity.

tients in the INH and glibenclamide groups, respectively, had an A1C <8% (although the study entry criteria specified an A1C of 8–12%, these subjects had an A1C >8% at screening that had dropped by the time of randomization); as defined, these were all in the A1C ≤9.5% arms. No patients in either treatment group had an A1C <7%. In the combined A1C arms there was no difference between treatment groups in the number of patients achieving A1C <8 and <7% goals. In the INH A1C >9.5% arm a significantly greater number of patients achieved the A1C <8 and <7% goals compared with glibenclamide (Table 1).

There were no differences between the A1C arms by treatment group for either fasting plasma glucose or 2-h postprandial glucose; thus, results are pre-

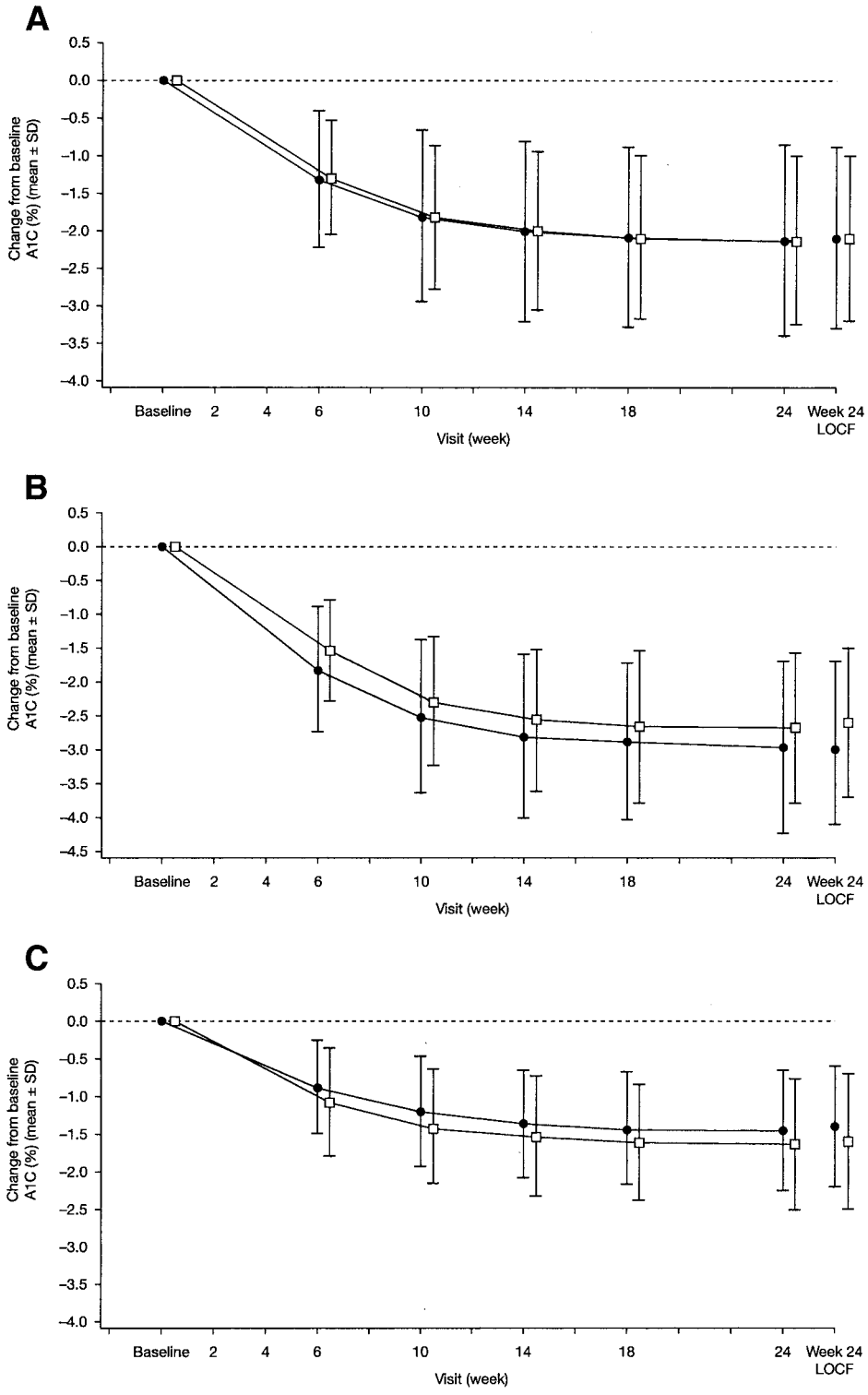

Figure 2—*Change from baseline in A1C (%) for patients with type 2 diabetes failing metformin therapy randomized to adjunctive INH or glibenclamide.* A*: Combined A1C arms.* ●*, metformin + INH* (n* = *234; 213*); □*, metformin + glibenclamide* (n* = *222; 201*). B*: Very high baseline A1C arm (>9.5 to ≤12%).* ●*, metformin + INH* (n* = *109; 96*); □*, metformin + glibenclamide* (n* = *103; 95*). C*: Moderately high A1C arm (≥8 to ≤9.5%).* ●*, metformin+ INH* (n* = *125; 177*); □*, metformin + glibenclamide* (n* = *119; 106*). n*, *number of subjects at baseline; number of subjects at week 24.*

sented for the combined A1C arms. The decrease in fasting plasma glucose from baseline to week 24 was similar in both groups, and the difference between treatment groups was small (Table 1). At week 24, there were similar, substantial decreases from baseline in 2-h postprandial glucose (Table 1).

The increase in mean body weight during the study was comparable between the INH and glibenclamide groups: 2.4 and 2.0 kg, respectively. The differ-

ence between the adjusted mean changes was 0.32 (95% CI −0.34 to 0.97). In both groups, weight gain was more rapid in the first 10 weeks followed by a more gradual increase.

Fasting lipid values did not differ between A1C arms by treatment; thus, results are presented for the combined A1C arms. No differences in treatment effect were observed between the groups for total, HDL, and LDL cholesterol (Table 1). Although baseline fasting triglyceride levels were higher in the glibenclamide group, the treatment effect and 95% CIs suggest that there were greater reductions in triglycerides with INH than glibenclamide (Table 1).

Safety profile

All safety profile data are presented for combined A1C arms, unless there were notable differences in which case they are discussed separately. In the INH group, 192 (80.3%) patients experienced a total of 557 all-causality adverse events, and in the glibenclamide group, 168 (72.7%) patients experienced 551 all-causality adverse events. A total of 245 and 217 adverse events that were possibly or probably related to the treatment regimens were experienced by 137 (57.3%) and 114 (49.4%) patients in the INH and glibenclamide groups, respectively.

Most adverse events were of mild or moderate severity. Six patients discontinued due to treatment-related adverse events: five (2.1%) in the INH group (abdominal pain and nausea; headache, nausea, and dizziness; chest pain, headache, and respiratory disorders; and two cases of increased cough) and one (0.4%) in the glibenclamide group (tachycardia, dyspnea, sweating, and abnormal vision). There were 5 serious adverse events in the INH group and 19 in the glibenclamide group; none were considered treatment related. Three deaths (two myocardial infarctions and one road traffic accident) were reported during the study in the glibenclamide group; none were considered treatment related.

The most common adverse event was hypoglycemia, and all incidences were treatment related. A total of 76 (31.8%) INH patients had a hypoglycemic event (63 mild and 13 moderate). In the glibenclamide group, 71 (30.7%) patients had a hypoglycemic event (52 mild and 19 moderate). There were no severe events and no discontinuations due to hypoglycemia. In the combined A1C arms, the number of hypoglycemic events was comparable between the two treatment groups, whereas in the A1C >9.5% arms there were significantly more hypoglycemic events in the INH than glibenclamide groups: 40 (36.7%) INH and 22 (21.4%) glibenclamide patients experienced 107 and 46 events, respectively. The rates of overall hypoglycemia (events/subject-month) for INH compared with glibenclamide were 0.18 vs. 0.08, respectively. This translated into a risk ratio of 2.24 (95% CI 1.58–3.16) for INH versus glibenclamide.

Increased cough was experienced by 20 (8.4%) INH and 6 (2.6%) glibenclamide patients. The majority of coughs in the INH group were mild or moderate; one patient reported a severe cough event. The median duration of the period of increased cough was 2.1 weeks in the INH group and 3.1 weeks in the glibenclamide group. In the INH group, 18 cases of increased cough were considered treatment related compared with none in the glibenclamide group. Two (0.8%) patients in the INH group discontinued due to cough.

Small declines in FEV_1 and DL_{co} occurred in both INH and glibenclamide groups over the 24 weeks. Declines in FEV_1 were slightly greater in the INH group and declines in DL_{co} greater in the glibenclamide group (Table 1).

Antibody responses were higher in the INH compared with the glibenclamide group (Table 1). Routine monitoring of patients did not reveal any clinical manifestations of increased insulin antibody percent binding.

CONCLUSIONS — In this study, the antihyperglycemic effect of adjunctive INH or the addition of a second oral agent, glibenclamide, was compared in patients poorly controlled with metformin. While desirable, a double-blind study was not possible for two principal reasons: *1*) it was not possible to manufacture a suitable placebo INH, and 2) it is generally inappropriate to blind treatment when individualized flexible dose titration is needed for effective management with exogenous insulin.

Adjunctive INH and adjunctive glibenclamide were similarly effective in improving glycemic control in the combined A1C arms. Glycemic control was also compared in two predefined A1C arms: A1C >9.5% (very high) and A1C ≤9.5% (moderately high). As expected, in the A1C ≤9.5% arm (noninferiority comparison), reductions in A1C from baseline were similar. The β-cell defect is probably less severe in these patients so that adding a secretagogue such as glibenclamide to metformin is sufficient to control glycemia.

In contrast, in the predefined subgroup with very high A1C (>9.5%), INH provided significantly better glycemic control compared with the addition of glibenclamide, with a mean A1C difference of 0.37% favoring INH at 24 weeks, corroborating findings from a similar study in which adjunctive INH provided improved glycemic control compared with the addition of metformin in patients very poorly controlled with a sulfonylurea (23). An A1C of >9.5% is strongly associated with an increased risk of macrovascular disease yet, according to data from the Third National Health and Nutrition Examination Survey, 18% of patients with diabetes have A1C levels that exceed this value (24). This figure may be significantly higher in areas where obesity is highly prevalent (25,26). While it is not possible to say whether an A1C difference of 0.37% constitutes a clinically significant effect based on the results of this study, it is certainly clear that there is no threshold for A1C lowering for any type of diabetes complication (27).

Over the 6 months of the study, a greater proportion of patients reached A1C levels <7% in the INH compared with the glibenclamide groups (37 vs. 31%). While the majority of patients were still not achieving current recommended A1C targets, thus requiring the addition of further agents, it should be noted that the ADA A1C action level at the time of the study was 8% (3). Blood glucose titration targets were therefore not planned to achieve an A1C of <7%.

Two additional factors to consider when deciding whether an antihyperglycemic drug has a clinically significant effect include the incidence of hypoglycemic episodes and the duration of effect. INH was well tolerated by patients in this trial. The incidence of hypoglycemic episodes was higher in the INH group compared with glibenclamide, but the risk incurred was no greater than that expected with combined oral antidiabetic agent and subcutaneous insulin therapy (28,29).

Diabetes is a progressive disease, and while oral agents may initially achieve a level of glycemic control, most patients will eventually require insulin therapy (30). In the A1C >9.5% arm, mean A1C values of 7.5 and 8.0% were achieved with adjunctive INH and glibenclamide,

respectively. Thus, many patients remained uncontrolled based on current accepted recommendations (2,3). Further improvement in glycemic control may thus require higher insulin doses and/or the addition of a third oral agent (31).

Weight gain is a concern in patients with type 2 diabetes while treated with insulin. However, for patients receiving metformin the addition of INH did not cause significantly more weight gain than the addition of a sulfonylurea. Furthermore, INH was associated with a significantly better decrease in fasting triglycerides compared with glibenclamide, an important consideration given that hypertriglyceridemia may be an independent risk factor for coronary artery disease (32).

There were small but statistically and clinically insignificant treatment group differences in pulmonary function between groups. Antibody levels were higher in INH patients but had no relation to efficacy measures, or to pulmonary or other adverse events, in agreement with longer-term data for INH (33).

New, noninvasive methods of insulin delivery may assist in achieving and maintaining long-term optimal glycemic control. The results of this study demonstrate that adding INH or glibenclamide to patients poorly controlled on metformin was similarly effective in improving glycemic control. Patients with very high A1C (>9.5%) were more effectively treated with the addition of INH to failing oral agent monotherapy from the standpoint of glycemic control. This benefit, however, must be weighed against hypoglycemia and weight changes. We suggest that INH in combination with metformin therapy should be considered a viable alternative to the addition of a second oral agent in patients with high A1C levels failing to achieve satisfactory glycemic control with metformin alone.

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