Alogliptin Use in Elderly People: A Pooled Analysis from Phase 2 and 3 Studies

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OBJECTIVES: To compare the efficacy and safety of alogliptin, a dipeptidyl peptidase-4 (DPP-4) enzyme inhibitor, in elderly (≥65) and younger (<65) patients with type 2 diabetes mellitus.

DESIGN: Pooled analysis of six randomized, double-blind, placebo-controlled studies of alogliptin.

PARTICIPANTS: Patients aged 18 to 80 with type 2 diabetes mellitus and inadequate glycemic control.

INTERVENTIONS: Elderly (mean age 70.0; n = 455) and younger (mean age 51.8; n = 1,911) patients received alogliptin 12.5 mg (n = 922), alogliptin 25 mg (n = 910), or placebo (n = 534) for 26 weeks (12 weeks in a Phase 2 study). The studies evaluated alogliptin as monotherapy and coadministered with pioglitazone, glyburide, metformin, or insulin.

MEASUREMENTS: Efficacy endpoints included change from baseline in glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), weight, and lipid values. Safety variables included hypoglycemic events, adverse events, and blood pressure.

RESULTS: Least-squares mean HbA1c decreased from baseline by 0.7% and 0.8% in elderly patients receiving alogliptin 12.5 and 25 mg, respectively, and 0.5% and 0.6%, respectively, in younger patients ($P < .001$ for both alogliptin doses vs placebo for both age groups $P = .70$ for 12.5 mg and .68 for 25 mg for differences between age groups). Results were similar for FPG. Incidence of hypoglycemia was 8.3% or less in all alogliptin groups (≤10.5% for placebo), with no apparent difference between elderly and younger patients. Changes in weight were negligible in all treatment groups in both age categories. The safety profiles of alogliptin were similar in the age and dose groups.

CONCLUSION: Alogliptin was effective and well tolerated in the elderly patients enrolled in these studies. Improvements in HbA1c were similar to those seen in younger patients, and no increase in the risk of hypoglycemia, weight gain, or other adverse events was apparent in elderly patients. **J Am Geriatr Soc 57:2011–2019, 2009.**

Key words: alogliptin; type 2 diabetes mellitus; elderly

The prevalence of diabetes mellitus in elderly people, diagnosed and undiagnosed, approaches and may exceed 20%.[1,2] Diabetes mellitus is a strong predictor of functional decline in this population,[3,4] leading to rates of hospitalization and utilization of outpatient services that are twice as high as those of elderly persons without diabetes mellitus.[5] The risks of micro- and macrovascular complications of diabetes mellitus are markedly higher in elderly people,[6,7] as is the prevalence of cardiovascular disease.[8] Overall, elderly individuals with diabetes mellitus have a mortality rate twice that of those without.[9]

Effectively treating diabetes mellitus and its complications poses particular challenges in the elderly population. The risk of developing hypoglycemia in response to treatment with oral antidiabetic agents or insulin increases dramatically with age, owing in part to less secretion of counterregulatory hormones such as glucagon.[10] Furthermore, awareness of the autonomic signs of hypoglycemia is often impaired in elderly people.[3,11] Other challenges to effective treatment include the presence of numerous and significant comorbidities, greater susceptibility to adverse events due to such conditions as age-related renal impairment, and the risk of treatment-limiting drug interactions associated with polypharmacy (including the potential of some concomitant medications to alter glucose metabolism).[3,12]

These concerns often lead to undertreatment of diabetes mellitus in elderly patients. One study of data from the

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National Health and Nutrition Examination Survey found that more than half of elderly patients with diabetes mellitus have glycosylated hemoglobin (HbA1c) values above the treatment goal of 7.0%.[1] Although current trends toward individualization of therapy may lead clinicians to relax the goal in elderly people, inadequate glycemic control is closely associated with poor outcome in elderly patients with diabetes mellitus. One study in patients with a mean age of 69 showed that fatal and nonfatal cardiovascular complications were significantly more frequent when HbA1c values remained above 7.0%.[13]

The dipeptidyl peptidase-4 (DPP-4) enzyme inhibitors are a new class of antidiabetic agents that may hold particular promise in elderly patients with type 2 diabetes mellitus.[12,14] The DPP-4 enzyme rapidly inactivates glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), incretin hormones released postprandially from gut endocrine cells that stimulate insulin secretion and inhibit postprandial glucagon secretion in a glucose-dependent manner.[15,16] An impaired incretin effect may contribute to hyperglycemia in type 2 diabetes mellitus.[17] By prolonging the half-life of active GLP-1 and GIP, DPP-4 inhibition enhances β- and α-cell function, increasing insulin secretion and suppression of glucagon to improve glycemia.[15,18,19] Although the efficacy and safety profiles of these agents remain to be fully characterized, they are promising for use in elderly people because they carry a lower risk of hypoglycemia, are associated with reductions in fasting and postprandial glucose, and so far have shown favorable safety and tolerability results.[12,14]

Alogliptin (chemical name 2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2 H)-yl}methyl)benzonitrile monobenzoate) is a potent and highly selective oral DPP-4 inhibitor[20] that has been investigated in one Phase 2 and five Phase 3 studies in patients with type 2 diabetes mellitus, both as monotherapy[21] and coadministered with standard antidiabetic agents.[22,23] The objective of the present analysis was to compare the efficacy, safety, and tolerability of alogliptin in elderly and younger patients in pooled data from these six studies.

METHODS

Study Designs

The six studies included in this analysis were randomized, double-blind, placebo-controlled assessments of the efficacy and safety of alogliptin in patients with type 2 diabetes mellitus. The pooled efficacy analysis included data from five Phase 3 studies; the safety analysis included safety data from these five studies and a Phase 2 study.

In the Phase 3 studies, patients underwent a 4-week run-in and stabilization period. Patients were then randomized to receive 26 weeks of treatment with placebo, alogliptin 12.5 mg every day, or alogliptin 25 mg every day. Four of the Phase 3 studies incorporated coadministration of other antidiabetic agents into the design so that patients also received pioglitazone, glyburide, metformin, or insulin throughout the treatment period according to predefined dosage criteria; one Phase 3 study assessed alogliptin monotherapy. Each study had a planned enrollment between 325 and 500 patients; four employed an unbalanced randomization scheme in which each alogliptin group enrolled twice as many patients as the placebo group.

In the Phase 2 study, 234 patients were planned to be randomized to receive alogliptin at a dose of 6.25, 12.5, 25, 50, or 100 mg per day or placebo for 12 weeks, with each treatment group planned to include the same number of patients. Patients were treatment naive or discontinued antidiabetic treatment at least 2 weeks before enrollment. During the study, no coadministration with other antidiabetic agents was allowed.

Patients

Inclusion criteria were similar across the five Phase 3 studies. Patients were required to be aged 18 to 80 with a diagnosis of type 2 diabetes mellitus and inadequate glycemic control. Their HbA1c concentration at screening was required to be between 7.0% and 10.0% (four of the studies) or 8.0% or higher (the insulin coadministration study) and the C-peptide level to be 0.8 ng/mL or higher. In the coadministration studies, patients were required to already be receiving the companion drug intended for the study (insulin and metformin studies) or a drug in the same therapeutic class (pioglitazone and glyburide studies). Additional entry criteria included a body mass index (BMI) between 23.0 and 45.0 kg/m^2 and values within certain prespecified ranges for blood pressure, hemoglobin, alanine aminotransferase, creatinine, and thyroid-stimulating hormone. Individuals with anemia or liver function abnormalities were excluded from participation.

The primary entry criteria in the Phase 2 dose-finding study included age 18 to 75, type 2 diabetes mellitus with inadequate glycemic control, HbA1c concentration between 6.8% and 11.0%, C-peptide level of 0.8 ng/mL or higher, and BMI between 23.0 and 40.0 kg/m^2.

All of the studies were conducted using Good Clinical Practice according to the Declaration of Helsinki. Ethics committees at the investigational sites approved the protocols, and patients provided written informed consent before participating in any study-related procedures.

Outcome Measures and Analysis

Standard efficacy and safety monitoring measures were employed throughout the treatment period in all of the studies. In the Phase 3 studies, patients returned to the study site for efficacy and safety assessments at Weeks 4, 8, 12, 16, 20, and 26; in the Phase 2 study, visits took place at Weeks 1, 2, 3, 4, 6, 8, 10, and 12.

In the assessment of patient disposition, hyperglycemic rescue was defined as follows: through the Week 4 visit, a confirmed fasting plasma glucose (FPG) level of 300 mg/dL or greater; after Week 4 but before Week 8, a confirmed FPG of 275 mg/dL or greater; after Week 8 but before Week 12, a confirmed FPG of 250 mg/dL or greater; from Week 12 through the final visit, a confirmed HbA1c of 8.7% or greater with 0.5% or less reduction from baseline. Withdrawal and hyperglycemic rescue were mutually exclusive; patients withdrawing for meeting the predefined rescue criteria were not counted among discontinued patients.

For this pooled analysis, efficacy was assessed using the efficacy population, which included all randomized

patients who took at least one dose of double-blind placebo, alogliptin 12.5 mg, or alogliptin 25 mg during one of the five Phase 3 studies. Efficacy endpoints included changes from baseline to Week 26 in HbA1c, FPG, weight, and lipid values (total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides). Missing data were imputed using the last observation carried forward method. A responder analysis was also performed in which clinical response was defined as a Week 26 (or time of early withdrawal) HbA1c value of 7.0% or lower. All endpoints used in this analysis were identified in the original Phase 3 protocols as primary or secondary efficacy measures.

For each efficacy measure, comparisons between both alogliptin groups and placebo were conducted for younger and elderly patients, defined as patients younger than 65 and aged 65 and older, respectively. For assessment of continuous efficacy variables, changes from baseline were compared using analysis of covariance (ANCOVA). Each model included treatment, age group, geographic region, companion therapy (if applicable), and age group–by-treatment interaction as class effects and baseline value as a continuous covariate. For both alogliptin groups, the least-squares mean differences from placebo in change from baseline at Week 26, with corresponding *P*-values, were calculated according to age using contrasts derived from the ANCOVA model. A test of age group–by-treatment interaction was also conducted using the ANCOVA model to investigate the consistency of the treatment effect between age groups. Subgroup analyses of HbA1c and FPG according to baseline HbA1c value were performed using the same model. The responder analysis employed a logistic regression model to generate odds ratios and *P*-values. Because placebo responses were inconsistent, some variables were compared between age groups by examining placebo-corrected differences, which simply represent differences after subtracting the placebo response.

P-values were two-sided and assessed at the .05 significance level. No adjustments were made for multiple comparisons. Investigator sites were pooled according to geographic region for efficacy analyses.

Safety was assessed using the safety population, which included all patients who took at least one dose of double-blind study medication in the five Phase 3 studies and the Phase 2 study. Safety variables assessed in this pooled analysis included hypoglycemic events, adverse events, and blood pressure.

All of the studies included monitoring for hypoglycemic events, which were prospectively defined. In the Phase 3 protocols, mild to moderate hypoglycemia was defined as a blood glucose level less than 60 mg/dL in the presence of symptoms or a blood glucose level less than 50 mg/dL with or without symptoms; severe hypoglycemia was an episode requiring the assistance of another person, associated with a blood glucose level less than 60 mg/dL (if obtainable). In the Phase 2 protocol, mild to moderate hypoglycemia was prospectively defined as any glucose level less than 70 mg/dL, with or without symptoms, or an individual patient's typical hypoglycemic symptoms without glucose measurement. Severe hypoglycemia was any episode that required assistance from another person to resolve or involved coma or seizure.

RESULTS

Disposition of Patients and Baseline Characteristics

A total of 2,366 patients in North, Central, and South America, Europe, South Africa, Australia, and New Zealand received double-blind study medication in the six studies: 1,911 younger and 455 elderly patients. Disposition of all treated patients, and the reasons for withdrawing from a study, are summarized for the safety population in Figure 1. (A total of 133 patients received alogliptin 6.25 mg, 50 mg, or 100 mg in the Phase 2 study; these patients are not included in the results described in this report.) In both age groups, larger proportions of patients in the two alogliptin groups than in the placebo group completed the study. A corresponding increase in hyperglycemic rescue was seen with placebo. In both alogliptin groups, larger percentages of elderly patients completed the study than younger, and smaller percentages of elderly patients withdrew for hyperglycemic rescue; these differences between age groups were smaller for placebo. Distributions of reasons for withdrawal from study participation were similar between elderly and younger patients.

Baseline demographic and other clinical characteristics are displayed in Table 1. The mean age of the elderly group was almost 20 years older than of the younger group, and there was a slightly higher proportion of men in the elderly group. In general, the two age groups were similar in baseline measures, although mean weight, BMI, HbA1c, FPG, total cholesterol, and LDL-C were all somewhat lower in the elderly group. In contrast, use of the most common types of concomitant medications (representing use at baseline and during the study) was markedly more frequent in elderly people. Use of antidiabetic treatment other than alogliptin was similar between the age groups and high in frequency, because four of the five Phase 3 studies included companion diabetes mellitus therapy per protocol and carefully restricted use of nonprotocol antidiabetic agents.

Efficacy

Figure 2 displays changes in least-squares mean HbA1c according to age group from baseline to Week 26 in the five Phase 3 studies. In both age groups, the decreases for both doses of alogliptin were statistically significantly larger than those for placebo ($P<.001$). Despite the lower baseline values in the elderly group, the decreases were slightly larger for elderly patients (-0.7% and -0.8% for alogliptin 12.5 and 25 mg, respectively) than younger patients (-0.5% and -0.6%, respectively), although the differences between age groups were not statistically significant ($P=.91$ for age group–by-treatment interaction).

As Figure 2 shows, baseline HbA1c values were between 8.0% and 8.4% across the three treatments in both age categories. A further analysis according to baseline HbA1c value, using a cutoff value of 8.0%, was also conducted. As in the overall analysis, alogliptin 12.5 and 25 mg were associated with statistically significantly greater decreases than with placebo in both age groups, in patients with baseline HbA1c values of 8.0% or below and greater than 8.0% ($P\leq.02$). Patients with baseline HbA1c values greater than 8.0% had larger absolute decreases than those with baseline values of 8.0% or below in both age groups, although in patients receiving alogliptin, placebo-corrected

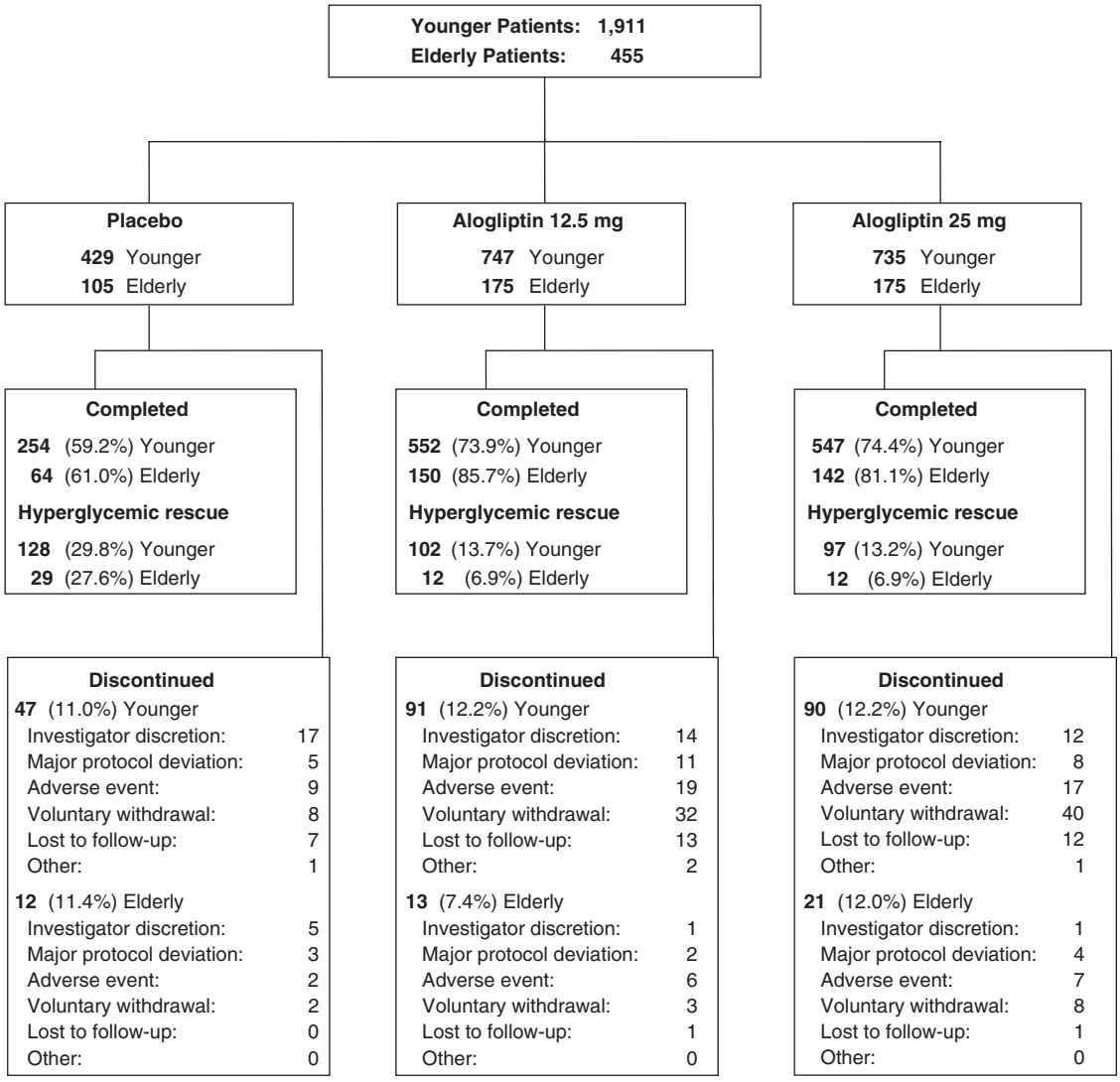

Figure 1. Disposition of patients (safety population). Numbers represent all patients receiving study medication.

decreases from baseline were somewhat larger for elderly (−0.62% and −0.61% for 12.5 and 25 mg, respectively) than for younger patients (−0.43% and −0.44% for 12.5 and 25 mg, respectively) with baseline values of 8.0% or below and essentially the same between age groups in those with baseline values greater than 8.0% (−0.48% and −0.63% for 12.5 and 25 mg, respectively, in younger patients; −0.41% and −0.63%, respectively, in elderly patients). No age group–by-treatment interaction was detected in either group defined according to baseline HbA1c value ($P = .29$ and $P = .89$ for baseline HbA1c values of $\leq 8.0\%$ and $> 8.0\%$, respectively).

Changes in FPG from baseline to Week 26 are displayed in Figure 3 and show results consistent with those seen for HbA1c. From baseline values that ranged from 169 to 182 mg/dL, statistically significantly greater reductions were seen with both doses of alogliptin in elderly (−20.6 and −23.1 mg/dL for alogliptin 12.5 and 25 mg, respectively) and younger patients (−8.8 and −12.6 mg/dL for alogliptin 12.5 and 25 mg, respectively) than with placebo (changes of 3.3 mg/dL in the younger group and −6.8 mg/dL in the elderly groups). The absolute reductions in the two elderly alogliptin dose groups were larger than those in the corresponding younger groups, but the placebo-corrected differences between the age groups were not statistically significant. In the analysis of changes in FPG based on baseline HbA1c values (data not shown), placebo-corrected decreases in FPG associated with alogliptin treatment were similar between age groups within baseline HbA1c groups and alogliptin dose groups.

In the responder analysis, the proportions of patients with Week 26 HbA1c values of 7.0% or lower were 17.1%, 36.6%, and 36.9% for placebo, alogliptin 12.5 mg, and alogliptin 25 mg, respectively, in the younger group. Corresponding percentages in the elderly group were 20.4%, 44.8%, and 45.4%, respectively. All of the differences between alogliptin and placebo were statistically significant at $P < .001$. Although the percentages of responders were higher for elderly than younger patients in both alogliptin groups, the differences between age groups were not statistically significant ($P = .95$ for age group–by-treatment interaction).

As shown in Table 1, mean weight in the elderly group at baseline was approximately 5 kg lower than in younger

Table 1. Demographic and Clinical Characteristics at Baseline According to Age: Safety Population

Variable	<65 n = 1,911	≥65 n = 455
Age, mean ± SD (range)	51.8 ± 8.5 (21–64)	70.0 ± 3.9 (65–80)
Sex, n (%)		
Female	952 (49.8)	200 (44.0)
Male	959 (50.2)	255 (56.0)
Race, n (%)		
White	1,337 (70.0)	382 (84.0)
Black	156 (8.2)	18 (4.0)
Asian	220 (11.5)	21 (4.6)
Other	198 (10.4)	34 (7.5)
Hispanic or Latino, n (%)	615 (32.2)	126 (27.7)
Weight, kg, mean ± SD	89.6 ± 20.7	84.2 ± 17.8
Body mass index, kg/m^2, mean ± SD	32.1 ± 5.6	30.6 ± 4.8
Duration of diabetes mellitus, years, mean ± SD	6.7 ± 5.7	10.2 ± 7.4
Therapy for diabetes mellitus, n (%)		
None	374 (19.6)	85 (18.7)
Insulin (with or without metformin)	326 (17.1)	63 (13.8)
Metformin	432 (22.6)	92 (20.2)
Sulfonylurea	370 (19.4)	130 (28.6)
Thiazolidinedione (with or without metformin or a sulfonylurea)	409 (21.4)	85 (18.7)
Glycosylated hemoglobin, %, mean ± SD	8.3 ± 1.0	8.0 ± 0.9
Fasting plasma glucose, mg/dL, mean ± SD	178 ± 54	171 ± 47
Total cholesterol, mg/dL, mean ± SD	188.1 ± 42.0	182.6 ± 44.1
Low-density lipoprotein, mg/dL, mean ± SD	107.0 ± 34.7	101.5 ± 36.8
High-density lipoprotein, mg/dL, mean ± SD	43.0 ± 11.1	45.3 ± 10.7
Creatinine clearance, mL/min, mean ± SD	111.3 ± 33.5	74.9 ± 21.6
Blood pressure, mmHg, mean ± SD		
Systolic	126.8 ± 14.1	132.1 ± 15.4
Diastolic	78.2 ± 8.7	75.9 ± 8.5
Concomitant medication, n (%)*		
Antihypertensives	37 (1.9)	30 (6.6)
Anti-inflammatory or antirheumatic	215 (11.3)	74 (16.3)
Anti-thrombotic agents	63 (3.3)	46 (10.1)
Acetylsalicylic acid	574 (30.0)	222 (48.8)
Beta-blocking agents	288 (15.1)	128 (28.1)
Calcium channel blockers	181 (9.5)	107 (23.5)
Cardiac therapy	322 (16.8)	98 (21.5)
Diuretics	293 (15.3)	139 (30.5)
Lipid-modifying agents	846 (44.3)	256 (56.3)

*Includes medications taken during the study.
SD = standard deviation.

patients (84.2 vs 89.6 kg). Changes in weight from baseline to Week 26 were negligible in all treatment groups in both age categories. All of the least-squares mean changes were less than 0.6 kg, and none of the differences between either alogliptin dose and placebo or between age groups was statistically significant ($P \geq .25$).

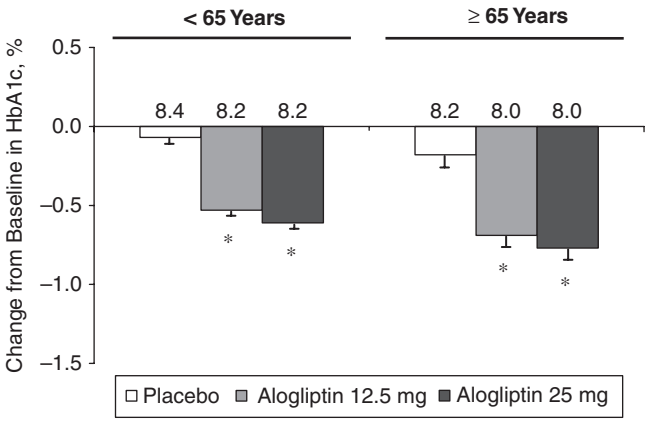

Figure 2. Changes from baseline to Week 26 in glycosylated hemoglobin (HbA1c) values (least-squares mean ± standard error) (efficacy population). Numbers above bars represent mean baseline values. *$P < .001$ versus placebo. Placebo-corrected differences between age groups were not statistically significant.

No noteworthy differences between the two age groups were seen in lipid results. Changes in total cholesterol from baseline to Week 26 in the younger group were 4.6, −1.0, and −0.2 mg/dL for placebo, alogliptin 12.5 mg, and alogliptin 25 mg, respectively. The corresponding changes in elderly people were −0.4, −3.4, and −6.5 mg/dL, respectively. The differences between both doses of alogliptin and placebo were statistically significant only in the younger group. Small changes in LDL-C were seen across age and treatment groups, and all changes from baseline in HDL-C were negligible. In triglycerides, the changes from baseline in the elderly group (−22.4 and −10.4 mg/dL for alogliptin 12.5 mg and 25 mg, respectively) were larger than in the younger group (−1.2 and −1.3 mg/dL, respectively) for both doses of alogliptin, although the differences from the placebo changes (11.0 mg/dL in the younger group and −6.1 mg/dL in the elderly group) were not statistically significant. Throughout the lipid measures, no differences between younger and elderly patients within any treatment group were statistically significant.

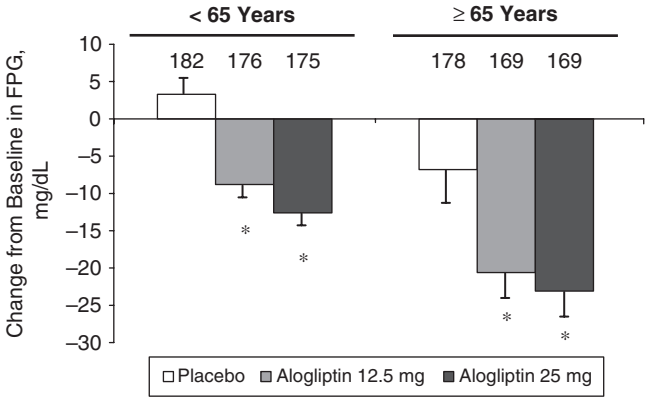

Figure 3. Changes from baseline to Week 26 in fasting plasma glucose (FPG) values (least-squares mean ± standard error) (efficacy population). Numbers above bars represent mean baseline values. *$P < .05$ versus placebo. Placebo-corrected differences between age groups were not statistically significant.

Safety and Tolerability

The proportions of patients with hypoglycemic events are summarized in Figure 4. Incidences of any hypoglycemic event were 8.3% or less in the alogliptin groups in both age categories. Across all categories of hypoglycemic severity, the highest incidences in elderly patients were seen in the placebo group. Hypoglycemia classified as severe occurred in three younger and four elderly patients; three of these seven patients (one younger and two elderly) received placebo. Finally, no differences in the incidence of hypoglycemia were apparent between the two alogliptin doses in either age category. Approximately 80% of patients experiencing hypoglycemia, and all but one of those experiencing severe hypoglycemia, were enrolled in the glyburide or insulin coadministration studies.

Adverse events are summarized according to treatment group and age group in Table 2. The proportions of patients experiencing treatment-emergent adverse events at any time during study participation were similar between treatment and age groups, ranging from 63.4% to 66.9%. Overall, the most common adverse events reported in the analysis were urinary tract infection, nasopharyngitis, headache, diarrhea, and upper respiratory tract infection. Incidences of adverse events were generally similar between the age groups and between treatments within age groups. Of patients receiving alogliptin, higher percentages of elderly patients than younger patients experienced pruritus, and the incidence of falls was higher for alogliptin 12.5 mg in the elderly group than for either alogliptin dose in the younger group. None of the events classified as falls were associated with dizziness or hypoglycemia or were considered by the investigator to be related to the study drug.

The percentages of patients with at least one adverse event considered by the investigator to be related to the study medication were also similar between the age groups; no greater incidence of such events was evident in elderly patients. Adverse events leading to withdrawal occurred in slightly higher percentages of elderly patients than younger patients receiving alogliptin, although no noteworthy difference was seen within an individual body system or type of event. No single adverse event led to discontinuation in more than one patient except for abnormal liver function test results, for which two younger patients withdrew from the alogliptin 12.5 mg group.

The incidence of serious adverse events was also somewhat higher in elderly patients than younger, with the largest differences in the placebo group (2.4%) and the alogliptin 25 mg group (3.5%). Because this increase was seen for placebo as well as for alogliptin, it may represent the effects of comorbidities associated with aging. Furthermore, no trend toward differential effects in elderly and younger relating to any particular body system was apparent in the serious adverse event results. Only two such events in elderly patients were considered possibly related to study medication: congestive cardiac failure and road traffic accident, both occurring in the alogliptin 25 mg group.

Three deaths were reported in the patients included in this analysis, one in each of three Phase 3 studies. All three occurred in patients receiving alogliptin 12.5 mg, two younger and one elderly. The three patients all had relevant risk factors in their medical history, and the investigators at the study sites considered two of the deaths (hypertensive heart disease and sudden death) to be unrelated to study drug. The third was a sudden death of unknown cause that occurred after 42 days of alogliptin treatment in a 62-year-old man with a history of smoking and hyperlipidemia. The investigator considered this event to be possibly related to the study drug.

As was shown in Table 1, baseline systolic blood pressure was 126.8 mmHg in younger patients and 132.1 mmHg in elderly patients. Corresponding baseline diastolic blood pressures were 78.2 and 75.9 mmHg, respectively. After 26 weeks of treatment, no substantial changes in systolic or diastolic values were seen in either age group. Table 1 also shows baseline creatinine clearance values of 111 and 75 mL/min in younger and elderly patients, respectively. After 26 weeks of treatment, group mean

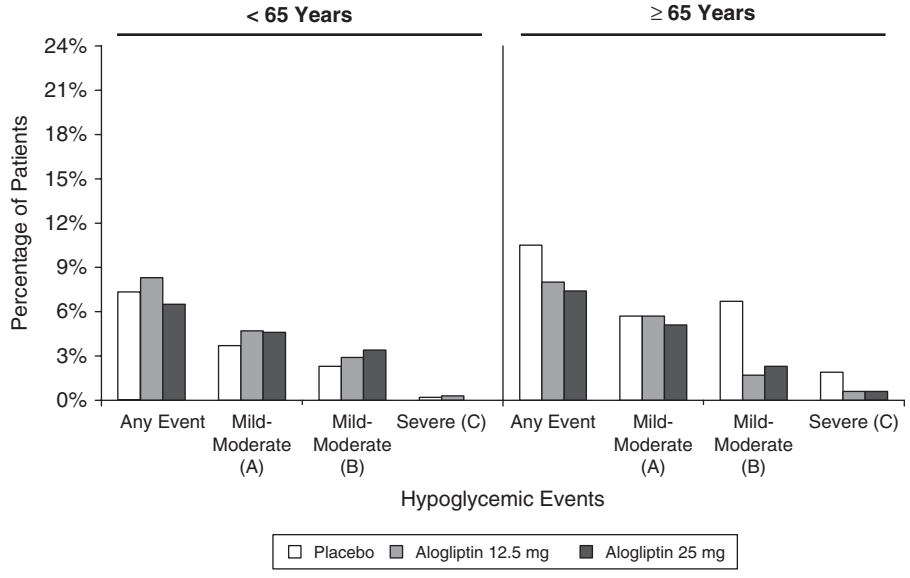

Figure 4. Incidence of hypoglycemic events (safety population). (A) Symptomatic with glucose <60 mg/dL; (B) symptomatic or asymptomatic with glucose <50 mg/dL; (C) required assistance, with glucose <60 mg/dL.

Table 2. Summary of Adverse Events According to Age: Safety Population

	n (%)					
	<65			≥65		
Variable	Placebo n = 429	Alogliptin 12.5 mg n = 747	Alogliptin 25 mg n = 735	Placebo n = 105	Alogliptin 12.5 mg n = 175	Alogliptin 25 mg n = 175
Any adverse event	279 (65.0)	492 (65.9)	475 (64.6)	68 (64.8)	117 (66.9)	111 (63.4)
Any event leading to withdrawal*	9 (2.1)	15 (2.0)	15 (2.0)	2 (1.9)	6 (3.4)	7 (4.0)
Any related event†	57 (13.3)	119 (15.9)	124 (16.9)	11 (10.5)	26 (14.9)	27 (15.4)
Any serious event	14 (3.3)	28 (3.7)	29 (3.9)	6 (5.7)	8 (4.6)	13 (7.4)
Most common events‡						
Diarrhea	15 (3.5)	24 (3.2)	26 (3.5)	3 (2.9)	1 (0.6)	4 (2.3)
Dyspepsia	4 (0.9)	8 (1.1)	11 (1.5)	5 (4.8)	1 (0.6)	3 (1.7)
Peripheral edema	11 (2.6)	18 (2.4)	24 (3.3)	3 (2.9)	5 (2.9)	8 (4.6)
Bronchitis	13 (3.0)	18 (2.4)	13 (1.8)	2 (1.9)	4 (2.3)	1 (0.6)
Nasopharyngitis	20 (4.7)	36 (4.8)	41 (5.6)	7 (6.7)	11 (6.3)	8 (4.6)
Sinusitis	13 (3.0)	13 (1.7)	10 (1.4)	2 (1.9)	0 (0.0)	4 (2.3)
Upper respiratory tract infection	22 (5.1)	31 (4.1)	30 (4.1)	6 (5.7)	5 (2.9)	2 (1.1)
Urinary tract infection	20 (4.7)	37 (5.0)	30 (4.1)	5 (4.8)	10 (5.7)	7 (4.0)
Fall	1 (0.2)	4 (0.5)	2 (0.3)	1 (1.0)	8 (4.6)	2 (1.1)
Back pain	9 (2.1)	21 (2.8)	21 (2.9)	4 (3.8)	3 (1.7)	6 (3.4)
Dizziness	8 (1.9)	15 (2.0)	13 (1.8)	2 (1.9)	6 (3.4)	5 (2.9)
Headache	20 (4.7)	30 (4.0)	34 (4.6)	1 (1.0)	8 (4.6)	6 (3.4)
Pruritus	1 (0.2)	7 (0.9)	12 (1.6)	1 (1.0)	4 (2.3)	9 (5.1)
Hypertension	13 (3.0)	22 (2.9)	26 (3.5)	3 (2.9)	6 (3.4)	6 (3.4)

*Not including withdrawal owing to hyperglycemic rescue.
†Includes all events considered by the investigator to be possibly, probably, or definitely related to study medication.
‡Includes all events with incidence ≥3% in any treatment group.

changes in estimated creatinine clearance were negligible (increases of <1 mL/min) in both age groups at both doses of alogliptin.

DISCUSSION

The prevalence of type 2 diabetes mellitus is on the rise in elderly people,[1] and elderly people represent a growing segment of the population. Given that elderly persons with diabetes mellitus are at greater risk of morbidity and mortality,[5–9] identifying effective treatment regimens with acceptable safety profiles remains an unmet medical need in this population.

The results of the present analysis demonstrate no differences in the efficacy of alogliptin between elderly and younger patients. The effect of alogliptin on HbA1c and FPG was slightly, although not significantly, greater for elderly people than younger people, despite lower baseline values and a longer duration of diabetes mellitus in elderly people. In the HbA1c analysis according to baseline HbA1c values, no age group–by-treatment interaction was found, although slightly greater efficacy of alogliptin 25 mg in reducing HbA1c was seen. The FPG results supported those seen with HbA1c. Despite a modest FPG reduction in elderly patients receiving placebo, both doses of alogliptin were associated with statistically significant reductions in FPG. Although the absolute reductions in elderly patients receiving alogliptin were larger than those in younger people, markedly different placebo changes between the age groups hamper interpretation of these differences.

The incidence of hyperglycemic rescue was lower in elderly people than in younger people in both alogliptin groups (6.9% vs 13.7% for alogliptin 12.5 mg, and 6.9% vs 13.2% for alogliptin 25 mg). No corresponding difference was seen with placebo (incidences of 27.6% and 29.8%, respectively). These data were collected as part of patient disposition and were not subjected to statistical analysis. Nonetheless, they represent a supportive measure of clinical response.

The results relating to weight gain, which represents an efficacy and a safety measure, are also of interest. Many antidiabetic agents, particularly insulin, sulfonylureas, and thiazolidinediones, cause weight gain.[24] The majority of patients included in this analysis were taking one of these three types of medications according to protocol design, yet weight gain was negligible across the treatment groups despite consistent improvements in hyperglycemia. No difference in weight gain was apparent between placebo and alogliptin in either age group, suggesting that alogliptin is weight-neutral in elderly and younger patients. This finding has also been reported for other DPP-4 inhibitors.[14,25]

As noted above, hypoglycemia is a safety concern associated with treating diabetes mellitus in elderly people and can indirectly lead to inadequate treatment.[3,10,11] Three recent trials have investigated the effects of intensive glycemic control (the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, Action in Diabetes and

Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, and Veterans Affairs Diabetes Trial of Glycemic Control and Complications in Diabetes Mellitus Type 2 (VADT)).[26–28] These trials enrolled significant numbers of older subjects, and mean ages of the patients were 60 to 66. Results from the ACCORD and VADT trials suggest an association between severe hypoglycemia and mortality, along with substantial weight gain, in patients receiving intensive glycemic control. In the ADVANCE trial, neither severe hypoglycemia nor weight gain was seen in the intensive treatment arm, and overall mortality was not higher. Taken together, these studies suggest that hypoglycemia represents an important marker of overall risk in type 2 diabetes mellitus. In the present analysis, incidences of hypoglycemia in both alogliptin groups were similar between age groups and represented fewer than 10% of patients. As expected, the highest incidences of hypoglycemia occurred in the glyburide and insulin coadministration studies, but adding alogliptin to either of these treatments did not appear to increase the risk of hypoglycemia.[11,29] In elderly patients, the highest incidences of hypoglycemia, overall and in all three categories of severity, were seen with placebo. Although these studies were based on standard, not intensive, glycemic goals, the results of the current study, along with those reported for vildagliptin,[25] suggest that treatment with a DPP-4 inhibitor in combination with other antidiabetic agents enhances glycemic control without increasing this treatment-limiting and potentially serious side effect. In contrast, in a recent study of sitagliptin in patients already taking a sulfonylurea, a hypoglycemic event was reported for 12.2% of patients in the sitagliptin–glimepiride coadministration group, compared with 1.8% of patients receiving glimepiride and placebo.[30]

Despite the expected higher incidences of comorbid medical conditions and use of concomitant medications in elderly people than in younger people, adverse events were similar between the treatment groups and between the age groups. Adverse events causing withdrawal were modestly greater in elderly people, as were certain individual adverse events such as falls (which did not appear to be dose related) and pruritus. These differences should be interpreted with caution, partly because of the imbalance in numbers of patients and also because the data suggest higher incidences in elderly placebo patients as well. The same is true for the overall incidence of serious adverse events. Because all elderly patients in this analysis were 80 and younger, it is not known to what degree the present results are generalizable to patients older than 80.

Each study included in this analysis was designed to be conducted and interpreted as a stand-alone clinical trial. The pooled analyses reported herein represent an ad hoc endeavor; as a result, although all of the studies included elderly patients, the pooled age groups were not balanced with respect to numbers of patients. Nonetheless, several factors support the validity of the present results: the study populations were fairly homogeneous, that is, the selection criteria for these studies were identical in many respects, with the exception of companion medications; the studies were of similar size and duration, so that no one study was able to disproportionately affect the results; and the efficacy and safety variables used in the current analysis were all prospectively defined as primary and secondary variables in each of the individual studies.

The present results, combined with clinical results published so far on vildagliptin[25] and sitagliptin,[31] suggest that, as a class, DPP-4 inhibitors are safe and effective in elderly individuals with type 2 diabetes mellitus. Thus far, no differences in safety or efficacy between the individual members of this novel class of agents have been identified, although studies directly comparing members of the class have not been performed.

In this pooled analysis, alogliptin 12.5 and 25 mg were similarly efficacious in elderly and younger patients. Furthermore, there was no greater risk of hypoglycemia, weight gain, or other adverse events in elderly patients. These results suggest that alogliptin may be a useful option for treating type 2 diabetes mellitus in elderly patients.

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Conflict of Interest: P. Fleck, C. Wilson, and Q. Mekki are all employees of Takeda Global Research & Development Center, Inc. T. McCall is an employee of Takeda Pharmaceuticals North America. Q. Mekki owns > $10,000 in stock of Takeda Pharmaceuticals. R. Pratley is a consultant or member of a scientific advisory panel/board of directors or speakers bureau for Takeda, GSK, Novo Nordisk, Merck, Novartis and Roche. He owns stock in Novartis. He has received grants or research support from Takeda, GSK, Merck, Novartis, Lilly, and Sanofi Aventis and has received honoraria from Takeda, GSK, Novo Nordisk, Merck, Novartis, and Roche.

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