Linagliptin for Patients aged 70 years or older with type 2 diabetes inadequately controlled with common antidiabetes treatments

By Michael Wong, PharmD; Kevin Wu, PharmD; Justin Yu 2014, PharmD; and Craig Stern, PharmD, MBA, FCPhA

Introduction

This study was conducted to evaluate the efficacy of linagliptin in outpatients aged 70 years or older with type 2 diabetes inadequately controlled with common antidiabetes treatments. The study compared linagliptin versus placebo on select background antidiabetes medications such as metformin, sulfonylureas, basal insulin, or combinations of these drugs. The primary endpoint is the HbA1c change from baseline at 24 weeks.

Based on the results of a 24-week randomized, double-blind, placebo-controlled trial, the authors concluded that linagliptin was efficacious in lowering glucose with a safety profile similar to placebo in elderly patients with type 2 diabetes. The purpose of this evidence-based evaluation is to determine the validity of the evidence presented for linagliptin in the aforementioned patient population and to determine the drug's clinical relevance.

Grade: B-U

Element	Criteriax	Comments
Study Design Assessment	• Is the design appropriate to the research question? Is the research question useful? • For **efficacy**, use of **experimental study design** (meaning there was no choice made to determine intervention) • **Clinically significant area** for study (morbidity, mortality, symptom relief, functioning and health-related quality of life) and reasonable **definitions for clinical outcome such as response, treatment success or failure** • If **composite endpoints** used, reasonable combination used — and used for safety if used for efficacy	**Threat:** Concomitant medications used with varying dosages and baseline medications were not balanced across both groups (e.g. metformin plus sulfonylurea plus insulin = 9/162 (5.6%) for the linagliptin arm, 0/79 (0%) for the placebo arm), making it difficult to assess the efficacy and safety of linagliptin alone versus placebo in this population.
Internal Validity Assessment	• Can bias, confounding or chance explain the study results? • Ensure **prespecified** and **appropriate** 1) research questions, 2) populations to analyze, and 3) outcomes	**Threat:** In the study, 241 patients were randomized; randomization of about 243 patients was needed, assuming a 5% dropout. Ultimately 220 (linagliptin = 146, placebo = 74) completed the study. Hence, the study was less than 90% powered (because 231 patients were needed) and deviated from protocol. **Threat:** Doses of background treatments were maintained for the first 12 weeks of randomized treatment, after which dose adjustments were permitted. This allows for selective adjustment of treatment arms as they are not controlled or monitored. This introduces bias and removes randomization between the two arms by allowing the investigator to selectively adjust a patient's treatment. **Threat:** Criteria for rescue medication for hyperglycemia differed during weeks 1-12 (>240 mg/dL) and weeks 13-24 (>200 mg/dL), which creates inconsistencies in patient management over different time periods.

Selection Bias	• Groups are **appropriate** for study, of appropriate size, **concurrent** and **similar** in **prognostic variables** • Methods for generating the group assignment sequence are truly **random,** sequencing avoids potential for anyone **affecting assignment** to a study arm and **randomization remains intact** • **Concealment of allocation** strategies are employed to prevent anyone affecting assignment to a study arm	**Threat:** The two groups were not equal to begin with. There were more men in the linagliptin group versus the placebo group (71.6% vs. 62%). The linagliptin group also tended to have more people with more severe HbA_{1c} values (in the $\geq$8% to <9% group and $\geq$9% group). It should also be noted that the types of concomitant antidiabetics used were not equal between the two groups.
Performance Bias	• **Double-blinding** methods employed (i.e., subject and all working with the subject or subject's data) and achieved • Reasonable **intervention** and reasonable **comparator** used (e.g., placebo) • **No bias or difference, except for what is under study, between groups during course of study** (e.g., intervention design and execution, care experiences, co-interventions, concomitant medication use, adherence, inappropriate exposure or migration, cross-over threats, protocol deviations, measurement methods, study duration, changes due to time etc.)	**Threat:** Patients in the study concomitantly received metformin, sulfonylureas, basal insulin, or combinations of these drugs at various dosages, which could have confounded the results. Investigators remain blinded to treatment assignments and adjusted only concomitant drug dosagesafter 12 weeks to target patient-specific HbA_{1c} goals. A clinical endpoint committee (CEC), consisting of three academic cardiologists and three academic neurologists and masked to assignment, reviewed events suspected to be stroke or cardiac ischemia. Other assessments were performed by individual, respective investigators who were masked to treatment assignment throughout study. No formal committee was mentioned to provide confirmation of initial assessments.
Attrition Bias	• Might **attrition**, including missing data, discontinuations or loss to follow-up, have resulted in distorted outcomes?	**Threat:** Last observation carried forward (LOCF) was used to impute missing variables for patients that discontinued treatment (placebo = 5, linagliptin = 16) and no HbA_{1c} levels were reported at time of discontinuation. This dropout discrepancy introduces potential bias favoring the control arm as more patients discontinued due to adverse events (n=8) compared to placebo (n=1). Using LOCF for a greater number of dropouts in the control arm can lead to an apparent decrease in efficacy of linagliptin compared to placebo. Patients that drop out before linagliptin is able to exert its full therapeutic effect will have a higher A1c carried forward, thus decreasing the treatment difference between linagliptin and placebo and biasing results toward non-significance.
Assessment Bias	• Assessors are **blinded** • Low likelihood of findings due to **chance, false positive and false negative outcomes** • **Non-significant findings** are reported, but the **confidence intervals include clinically meaningful differences** • **Intention-to-Treat Analysis (ITT)** performed for efficacy (**not safety**) (all people are analyzed as randomized + reasonable method for imputing missing values which puts the intervention through a challenging trial or reasonable sensitivity analysis) or missing values are very small. • If **time-to-event analysis** performed, appropriate, transparent and unbiased. • Evaluate **censoring** rules. • **Analysis methods** are appropriate and use of **modeling** only with use of reasonable assumptions • No problems of **selective reporting or selective exclusion of outcomes**	**Threat:** The full analysis set consisted of 238 patients. As 241 patients were randomized, that would indicate that three patients were excluded and no ITT analysis was performed. The treated set, defined as all those who received a dose (n=241), was used to assess safety. Since the study was powered for efficacy, it is unlikely that it was adequately powered to assess all the safety endpoints. **Threat:** While there was no issue with selective reporting, the conclusions related to the incidence of hypoglycemia would have been stronger had they mentioned what concomitant antidiabetic drugs the patients were on when these adverse events occurred.
Usefulness	• **Clinically significant area + sufficient benefit size** = meaningful clinical benefit (consider efficacy vs. effectiveness)	**Threat:** A change in HbA_{1c} of -0.64% versus placebo represents a change in a surrogate marker of disease. This change is of unknown clinical significance and may not justify the use of this drug over other efficacious pharmacologic and non-pharmacologic options (e.g. diet and exercise) given the high costs.

External Validity	• **How likely are research results to be realized in the real world considering population and circumstances for care?** • Review n, inclusions, exclusions, baseline characteristics and intervention methods—this is a **judgment call**.	**Threat:** Majority of the patients studied were White, which limits the external validity of the study considering the majority of patients suffering from diabetes are non-White (per American Diabetes Association statistics). Baseline included ~96% White, 56.9-66.7% with HbA_{1c} ≥7 and <8%, ~ 70% men, 83-88% taking metformin at screening, mean weight 86 kg and BMI 30 kg/m^2, and did not include cardiovascular characteristics which are pertinent in diabetic patients.
Patient Perspective	• Consider benefits, harms, risks, costs, uncertainties, alternatives and satisfaction	**Threat:** Linagliptin is currently a branded drug that costs approximately $913.61 for 90 days (Medi-Span). Depending on a patient's co-pay, the high cost of the drug may limit access to patients. **Threat:** The clinical benefit of a change in HbA_{1c} of -0.64% may also be questionable. This change may in fact be achievable through diet and exercise alone or using the other drugs that were excluded (i.e. a thiazolidinedione, alpha-glucosidase inhibitor, meglitinide, GLP1 analogue, DPP4 inhibitor, or anti-obesity drug). The risk of hypoglycemia with linagliptin is a concern, especially in combination with other unknown hypoglycemic agents such as sulfonylureas.
Provider Perspective	• Satisfaction, acceptability (includes adherence issues, potential for abuse, dependency issues), likely appropriate application and actionability (e.g., FDA approval, affordability, external relevance, circumstances of care, able to apply, tools available)	**Threat:** Linagliptin is a costly new DPP4 inhibitor that shows minimal reduction in HbA_{1c} (i.e. -0.64). **Threat:** Other PO alternatives, such as alpha-glucosidase inhibitors, are less expensive albeit with a different side effect and tolerability profile. A one-month supply of acarbose (Precose), a drug class with equal HbA_{1c} lowering efficacy ~0.5% that also does not have to be renally adjusted, is about $90-$200 a month depending on the dosage strength. **Threat:** Sitagliptin and saxagliptin can still be used with very low CrCl and in hemodialysis. There are no contraindications for renal function for sitagliptin and saxagliptin, although greater monitoring may be warranted to optimize dosing.

Author's Results and Conclusions

The placebo-adjusted mean change in HbA1c with linagliptin was -0.64% (95% CI, -0.81 to -0.48, p<0.001). Patients in both the linagliptin and placebo groups reported a 75.9% adverse event rate, although the rate of serious adverse events was higher in the linagliptin group versus the placebo group (8.6% vs. 6.3%). Adverse events such as non-fatal ischemic stroke, unstable angina, and neoplasms were deemed unrelated to linagliptin by the investigators. The treatment arm had a nonsignificant higher rate of hypoglycemia compared to the placebo arm (24.1% vs. 16.5%, 95% CI, 0.78-3.78, p=0.2083), which was attributed to the greater number of sulfonylurea users in the linagliptin group.

Reviewer's Conclusions

In the study population, linagliptin had a modest effect on the reduction in HbA1c compared to placebo, which calls into question its clinical efficacy and value in a real-world patient population. Furthermore, approximately 96% of the patients in the study were White, potentially limiting the external validity of the study. This is particularly important because the American Diabetes Association (ADA) states that African Americans are 1.8 times more likely to develop diabetes than their Caucasian counterparts. According to 2007-2009 statistics from the ADA, diabetes prevalence in people ages 20 or older was 7.1% in non-Hispanic whites, 8.4% in Asian Americans, 12.6% in non-Hispanic blacks, and 11.8% in Hispanics. Additional studies in non-White elderly populations may also reveal additional information on the efficacy, safety, and tolerability of linagliptin. Referencing the primary outcome, a 0.64% decrease in HbA1c can likely be achieved by diet and exercise alone, although the population studied was one with longstanding diabetes inadequately controlled with metformin, sulfonylureas, basal insulin, or combinations of these drugs.

One of the greatest weaknesses of the studies was that the two treatment arms were not equal

in relation to their baseline characteristics; although unstated, there appeared to be clinically meaningful differences between them. The treatment arm, for example, had more males and more severe HbA1c values compared to the placebo arm. Additionally, the two arms were not equal in terms of concomitant glucose-lowering drugs, which may have confounded the study results. In addition, dosage adjustment after 12 weeks was allowed and rescue medication criteria for hyperglycemia changed after 12 weeks to be less strict (240 mg/dl vs. 200 mg/dL) and together may have led to inconsistent patient management.

Based on the above findings, recommendations for linagliptin's place in therapy is more clear. Although linagliptin possesses several advantages, including a lack of need for renal adjustment and evidence for efficacy and safety in a rarely studied population, the impact of this drug may be limited due to the aforementioned statements and due to its high cost ($913.61 for a 90-day supply, per Medi-Span). Although there is no need for renal dosing with linagliptin, it would not provide linagliptin with a significant advantage over other DPP4 inhibitors in the setting of moderately decreased but stable renal function. Lastly, alternative medications such as alpha-glucosidase inhibitors provide a comparable HbA1c lowering efficacy while also possessing no need for renal dosing. These agents are less expensive, with costs ranging from $89.94 to $203.92 (per Medi-Span) for slightly more than one month's supply.

About the Authors

Michael Wong is a 2014 PharmD Candidate at the USC School of Pharmacy.

Kevin Wu is a 2014 PharmD Candidate at the USC School of Pharmacy.

Justin Yu is a 2014 PharmD Candidate at the USC School of Pharmacy.

Craig Stern, PharmD, MBA is president of ProPharma Pharmaceutical Consultants, Inc. and Chair of the CPhA Editorial Review Committee. Dr. Stern has no bias to disclose.

Guest Editor: Cynthia Jackevicius, PharmD is an expert in critical appraisals. The chart is adapted from "Delphini Group, LLC, Short Clinical Appraisal Checklist: U."

References

1. Barnett AH et al. Linagliptin for patients aged 70 years or older with type 2 diabetes inadequately controlled with common antidiabetes treatments: a randomised, double-blind, placebo-controlled trial. *The Lancet* 382(9902):1413-1423, October 2013.

Delfini Evidence Grading Scale
Grade A Evidence: Useful The evidence is strong and appears sufficient to use in making health care decisions – it is both valid and useful (e.g., meets standards for clinical significance, sufficient magnitude of effect size, physician and patient acceptability, etc.).
Grade B Evidence: Probably Useful The evidence appears potentially strong is probably sufficient to use in making health care decisions. Some threats to validity were identified.
Grade B-U Evidence: Possible to Uncertain Usefulness The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.
Grade U Evidence: Uncertain Usefulness There is sufficient uncertainty that caution is urged regarding its use in making health care decisions.