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# Clinical Study Synopsis for Public Disclosure

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# 2. ABSTRACT

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| **Name of company:**<br>Boehringer Ingelheim | | | |
| **Name of finished medicinal product:**<br>TRAJENTA | | | |
| **Name of active ingredient:**<br>Linagliptin | | | |
| **Final Report Completed:**<br>27 Sep 2019 | **Study number:**<br>1218.163 | **Version/Revision:**<br>1.0 | **Version/Revision date:**<br>N/A |

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| **Title of study:** | Active surveillance research program for the assessment of the safety and the effectiveness of linagliptin<br>Phase 4 of the BIDM study program<br>Final Report |
| **Keywords:** | Linagliptin, DPP-4 inhibitors, utilization, cohort, oral and non-insulin injected glucose lowering agents. |
| **Rationale and background:** | Dipeptidyl peptidase-4 (DPP-4) inhibitors, including linagliptin, saxagliptin, alogliptin and sitagliptin, are a class of oral glucose lowering agents first approved in the United States in 2006. They are indicated for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Evidence to date suggests that these drugs offer advantages over older therapies in that they are weight-neutral, are associated with a minimal risk of hypoglycemia, and can be administered with once-daily dosing. Linagliptin offers a further advantage in that its dose does not need to be adjusted based on renal or hepatic function. While there do not appear to be contraindications (except for hypersensitivity to the active ingredient or any of the excipients) to the use of linagliptin, the long term safety and effectiveness under routine clinical care are not well characterized.<br>Given the high prevalence of T2DM, it is important to understand the comparative safety and effectiveness of glucose lowering agents. This study comprises a series of comparative effectiveness and safety analyses within periodically updated cohorts of patients initiating linagliptin, other DPP-4 inhibitors, and other available glucose lowering medications, and followed longitudinally for the occurrence of a variety of clinical outcomes. The current report, was based on data from May 2011 through Dec 2016; and is based on sequential updates occurring every 6 months through the last cohort update, December 2016. |
| **Research question and objectives:** | In order to evaluate the effectiveness and safety of linagliptin relative to other diabetes therapies, the relative frequency of occurrence of a variety of clinical outcomes are assessed through a series of analyses within periodically updated cohorts of patients initiating linagliptin, other DPP-4 inhibitors, and other glucose lowering medications. This study has the following objectives: 1) To conduct a multi-year surveillance monitoring |

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| | program that establishes and periodically updates initiator cohorts of linagliptin, within class comparators (saxagliptin, sitagliptin, alogliptin), and out-of-class comparators (glitazones, 2nd generation of sulfonylureas (SUs)), and longitudinally follows these initiator cohorts for the incidence of a variety of health events (e.g.. cardiovascular events, malignancies, acute pancreatitis, severe skin lesions, renal impairment outcomes, mortality). 2) To conduct direct comparisons over time among glucose lowering agents (linagliptin versus other DPP-4 inhibitors, glitazones, 2nd generation of SUs) and quantify the association between treatment choice and the occurrence of pre-defined clinical outcomes.<br>The primary study outcomes are the occurrence of a major cardiovascular event (defined as the composite of coronary revascularization, acute coronary syndrome, ischemic and hemorrhagic stroke) and the individual components of the composite cardiovascular outcome. Heart failure hospitalization, incident end-stage renal disease and acute renal failure are secondary study outcomes. This study includes multiple comparator groups because there are several potential treatment alternatives to linagliptin for patients with T2DM. Although linagliptin is the only DPP-4 inhibitor that does not require dose adjustment for severe renal impairment, within-class comparators are important because they are expected to be prescribed to patients with similar clinical profiles, thus enhancing the comparisons. Additional comparison groups are formed from different classes of medications (specifically second-generation sulfonylureas and pioglitazone) in order to investigate between-class effects. SGLT2 inhibitors were not included as comparators because the first agent in the class, canagliflozin, was not approved until March 2013, and most SGLT2 inhibitors would be available for less than half the study period, reducing the power of comparisons. Patients with prior use of a medication within the same or comparator class in the prior 6 months were excluded from the primary analysis. | | |
| **Study design:** | Observational cohort study | | |
| **Setting:** | US health insurance databases<br>Clinformatics (Optum/UnitedHealth) May 2011 through Dec 2016<br>MarketScan (Truven) May 2011 through Dec 2016 | | |
| **Subjects and study size, including dropouts:** | **Clinformatics:** We identified 574,714 initiators of a non-insulin glucose lowering agent (see Figure-3a, page 52) between May 2011– Dec 2016 with no use of a medication in the same class or a comparator class during the 6 months prior to index date, and who were at least 18 years of age and | | |

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| | enrolled for a minimum of 6 months in Clinformatics before treatment initiation. Amongst these patients, 39,328 had no recorded diagnosis of T2DM prior to index date, 98,457 had a diagnosis of T1DM or secondary diabetes, 1,534 had a diagnosis or treatment for HIV prior to index date, 172,029 had history of cancer, 2,048 had an organ transplant, 3,967 had ESRD 6 months prior to index date, 13,362 experienced deaths, end of eligibility or a nursing home admission prior to or on the index date leaving a total cohort size of 248,380.<br>**MarketScan:**<br>We identified 1,383,069 initiators of a non-insulin glucose lowering agent (see Figure-3b, page 53) between May 2011– Dec 2016 with no use of a medication in the same class or a comparator class during the 6 months prior to index date, who were at least 18 years of age and enrolled for a minimum of 6 months in MarketScan before treatment initiation. Amongst these patients, 89,625 had no recorded diagnosis of T2DM prior to index date, 211,439 had a diagnosis of T1DM or secondary diabetes, 2,968 had a diagnosis or treatment for HIV prior to index date, 443,488 had history of cancer, 4,724 had an organ transplant, 6,020 had ESRD 6 months prior to index date, 24,743 experienced deaths, end of eligibility or a nursing home admission prior to or on the index date, leaving a total cohort size of 610,635. |
| **Variables and data sources:** | Data are from two United States commercial health insurance databases: Clinformatics 2006 through Dec 2016 and MarketScan 2006 through Dec 2016; both with 6-month data updates that are planned to extend through Dec 2016. Data include claims for prescriptions, inpatient and outpatient visits and procedures, and insurance plan enrollment information and demographics. Lab test results are available for a subset of each population. (~30% in Clinformatics and ~5% in MarketScan)<br>Pre-specified outcomes of interest include the following:<br>Primary outcome: Major adverse cardiovascular event as a composite of<br>• Coronary revascularization (elective and non-elective procedure)<br>• Acute coronary syndrome (ACS) hospitalization<br>• Stroke (Ischemic and hemorrhagic stroke)<br>Individual components of the composite major adverse cardiovascular events listed above (ischemic and hemorrhagic stroke, acute MI are assessed separately) |

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| | Secondary outcomes:<br>• Heart failure hospitalization<br>• Incident End-Stage Renal Disease (ESRD)<br>• Acute renal failure (ARF)<br>• ARF that requires dialysis<br>Further outcomes:<br>• Any incident malignant neoplasms<br>• Site-specific incident malignant neoplasms by the Surveillance, Epidemiology, and Ends Results (SEER ) Program category<br>• Glomerular Filtration Rate (GFR) event, among patients with laboratory test results<br>• Acute Pancreatitis<br>• Severe skin reactions<br>o Erythema multiforme, Stevens-Johnson syndrome, or Toxic epidermal necrolysis<br>o Bullous pemphigoid<br>• All-cause mortality<br>Other variables include covariates measured prior to medication initiation for population (baseline) characterization, statistical adjustment, and stratification. |
| **Results:** | In the period between May 2011 and Dec 2016, we identified 248,380 patients in Clinformatics and 610,635 patients in MarketScan newly initiating linagliptin, other DPP-4is, 2nd generation SUs, and pioglitazones that met the cohort inclusion criteria.<br>The mean age of linagliptin initiators was 55.0 to 56.2 yrs (across the 3 comparison groups) in Clinformatics and 54.2 to 55.1 yrs (across the 3 comparison groups) in MarketScan.<br>Linagliptin initiators consistently had the greatest burden of comorbidities compared to the other agents across both data sources, as indicated by Charlson comorbidity scores (~1.7 in Clinformatics and ~1.5 in MarketScan). The burden of comorbidities was well balanced after propensity score (PS) matching.<br>After PS-matching, patient characteristics between linagliptin initiators and new users of other comparator agents were well balanced (all |

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standardized differences <0.1). In Clinformatics, baseline eGFR and HbA1C amongst the ~30% subset with laboratory results were balanced despite not being included in the PS. In MarketScan, moderate imbalances were observed for HbA1C level amongst the ~5% subset of patients with laboratory values for the comparisons of linagliptin vs. pioglitazone and 2nd generation SUs and eGFR level for the comparisons of other DPP-4is and 2nd generation SUs.

Results from the pooled analyses of the individual databases, for the composite outcome of MACE in the pooled analyses, showed that PS-matched linagliptin initiators had a similar risk of MACE compared to initiators of other DPP-4is (HR=0.91 (0.80-1.03)) and pioglitazone (HR=0.96(0.84-1.10)), and a decreased risk compared to 2nd generation SUs initiators (HR=0.75(0.65-0.88)). These results were robust in a 1:1 high-dimensional PS matched analysis that adjusted for additional 500 empirical covariates ((HR=0.92 (0.81-1.05) compared with other DPP-4is; HR=0.92 (0.77-1.10) compared with pioglitazone; and HR=0.73(0.61-0.88) compared with sulfonylureas).

For the outcome of hospitalization for Heart Failure (HHF) in the pooled analyses, PS-matched linagliptin initiators had a similar risk of HHF compared to new users of other DPP-4is (HR=1.17 (0.95-1.44), increased risk compared to pioglitazone (HR=1.34 (1.01-1.77), and similar risk compared to 2nd generation SUs initiators (HR=0.92 (0.70-1.21). As pioglitazone is contraindicated or not recommended among patients with heart failure and edema, channeling of pioglitazone to patients with lower baseline risk for heart failure likely explains the increase in the risk of heart failure hospitalization when compared with linagliptin.

For the outcome of acute renal failure (ARF) in the pooled analyses, PS-matched linagliptin initiators had a similar risk of ARF compared to new users of other DPP-4is (HR=1.11 (1.00-1.24)), increased risk compared to pioglitazone (HR=1.16 (1.02-1.33), and similar risk compared to 2nd generation SUs initiators (HR=0.96 (0.84-1.10). Residual confounding remains a likely explanation for these findings given the channeling of linagliptin to patients with renal impairment previously reported in Phase 2 of this monitoring study program (1218.161). Further analyses confirmed that these findings were due to confounding bias. These included sensitivity analyses, which 1) restricted the analyses to patients with past or current use of metformin,

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to reduce imbalances related to kidney disease for which metformin would be contraindicated, and 2) accounted for baseline renal function, i.e., eGFR (amongst the subset of patients with lab values), by including the eGFR value in the PS model. These least-biased analyses produced results consistent with similar risk of ARF for other DPP-4is (HR=1.07 (0.92-1.23) and HR=1.17 (0.91-1.51), respectively), pioglitazone (HR=0.98 (0.82-1.17) and HR=1.00 (0.74-1.34), respectively), and 2nd generation SUs initiators (HR=0.93 (0.77-1.13) and HR=0.97 (0.71-1.33), respectively).

For the outcome of end-stage renal disease (ESRD) in the pooled analyses, for the PS-matched linagliptin initiators, the results suggest an increased risk of ESRD compared to new users of other DPP-4is (HR=1.36 (1.10-1.69)), an observed increased risk compared to pioglitazone (HR=1.60 (1.18-2.17), and an observed similar risk compared to 2nd generation SUs initiators (HR=1.17 (0.88-1.51)).

Due to the channeling of linagliptin to patients with renal impairment, residual confounding is a likely explanation for these findings. Further analyses confirmed that these findings were due to confounding bias. These included sensitivity analyses, which restricted the analyses to patients with past or current use of metformin, to reduce imbalances related to kidney disease for which metformin would be contraindicated, produced results consistent with similar risk of ESRD for other DPP-4is (HR=1.17 (0.83-1.65)), pioglitazone (HR=1.14 (0.75-1.75), and 2nd generation SUs initiators (HR=0.99 (0.64-1.54)). In a post-hoc analysis, we accounted for baseline eGFR (amongst the subset of patients with lab values) by including the eGFR value in the PS model, and evaluated ESRD in combination with a 25% decrease in eGFR as a composite outcome as previously implemented by Hung et al. [R12-3640], to address the paucity of ESRD events in this eGFR-balanced population. In this analysis, we observed a similar risk compared to other DPP-4s (HR=0.94 (0.81-1.09)), pioglitazone (HR=1.00 (0.82-1.21), and 2nd generation SUs initiators (HR=1.00 (0.81-1.24)).

For the outcome of incident malignant neoplasm in the pooled analyses, PS-matched linagliptin initiators had a similar risk of incident malignant neoplasm compared to new users of other DPP-4is (HR=0.97 (0.89-1.07)), pioglitazone (HR=1.06 (0.95-1.19)), and 2$^{nd}$ generation SUs

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| | initiators (HR=0.99 (0.88 -1.11)).<br>Results were largely consistent in subgroup and sensitivity analyses. | | |
| **Discussion:** | This study includes a series of comparative effectiveness and safety analyses within two cohorts of commercially insured patients (Clinformatics and MarketScan database) initiating linagliptin, other DPP-4s, 2nd generation SUs, and pioglitazone.<br>We found that linagliptin had a reduced risk for MACE compared to 2nd gen SU users. Linagliptin showed no difference regarding MACE and renal endpoints compared with other oral antidiabetic agents.<br>Patients initiating linagliptin had greater burden of comorbidities compared to the comparator groups across both data sources. After PS-matching, differences in claims-based patient characteristics between linagliptin initiators and new users of other comparator agents were well balanced. Final results for the primary outcome of MACE became more precise and remain consistent with those observed in prior reports. Across both databases, we continue to observe a significant decreased risk of MACE amongst linagliptin users compared to 2nd generation SU users and no difference in risk compared to other agents. Residual confounding due to the channeling of linagliptin to patients with renal impairment previously observed in the Phase 2 of this monitoring study program, is likely to explain the increased risk of selected outcomes, i.e., ARF, ESRD, and hospitalization for HF, associated with the use of linagliptin, in particular when compared with pioglitazone, which is contraindicated or not recommended among patients with heart failure and edema. This suggests pioglitazone may not be a proper comparator in the assessment of the association between linagliptin and heart failure hospitalization or renal outcomes. | | |
| **Marketing Authorisation Holder(s):** | Boehringer Ingelheim GmbH | | |
| **Names and affiliations of principal investigators:** | [redacted], MD, ScD, [redacted] | | |