Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

Document Number:	**C20330622**
BI Study Number:	1218.182
BI Investigational Product(s):	Tradjenta
Title:	Real world glycemic effectiveness of linagliptin (Tradjenta®) among type 2 diabetes mellitus adults by age and renal function.
Protocol version identifier:	1.0
Date of last version of protocol:	20 October 2017
PASS:	No
EU PAS register number:	Not applicable
Active substance:	Linagliptin
Medicinal product:	Tradjenta
Product reference:	N/A
Procedure number:	N/A
Joint PASS:	No
Research question and objectives:	The primary study objective is to: • Describe change in HbA1c among adults with T2DM within 60 to 180 days following initiation of linagliptin across pre-defined age and renal function categories. Age categories will be defined as: 40 to 54 years, 55 to 64 years, 65 to 74 years, and ≥ 75 years. Renal function categories will be defined based on eGFR as: <30 ml/min/1.73m^2, 30 to 44 ml/min/1.73m^2, 45 to 59 ml/min/1.73m^2, 60 to 89 ml/min/1.73m^2, and ≥ 90 ml/min/1.73m^2. The secondary study objectives are to: • Compare change in HbA1c among adults with T2DM within 60 to 180 days following initiation of linagliptin across pre-defined age and renal function categories. • Compare the proportion of adults with T2DM who achieve HbA1c < 7.0% within 60 to 180 days following initiation of linagliptin across the pre-defined age and renal function categories.

Country(-ies) of study:	USA
Author:	
Marketing authorisation holder(s):	Boehringer Ingelheim International GmbH Binger Str. 173 *D-55216 Ingelheim am Rhein*
In case of PASS, add: <EU-QPV>	Not Applicable
In case of PASS, add: <Signature of EU-QPV>	Not Applicable
MAH contact person:	Not Applicable
Date:	**20OCT17**

Page 1 of 42

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
DPP-4	Dipeptidyl peptidase-4
eGFR	Estimated glomerular filtration rate
EHR	Electronic health record
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Glycosylated hemoglobin
IRB	Institutional Review Board
Scr	Serum creatinine
SGLT2	Sodium-glucose co-transporter 2
T2DM	Type 2 diabetes mellitus
TZD	Thiazolidinediones

3. RESPONSIBLE PARTIES

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Tradjenta			
Name of active ingredient: Linagliptin			
Protocol date: 20-OCT-2017	**Study number:** 1218.182	**Version/Revision:** 1.0	**Version/Revision date:**
Title of study:	Real world glycemic effectiveness of linagliptin (Tradjenta) among type 2 diabetes mellitus adults by age and renal function		
Rationale and background:	Patients with type 2 diabetes mellitus (T2DM) have progressive decline in renal function and this decline in function is greater than age-related decline in patients without diabetes. Selection of glucose lowering agents is often affected by the level of renal function. Dipeptidyl peptidase-4 (DPP-4) inhibitors are approved to treat hyperglycemia among adults with T2DM with a wide range of renal function. In contrast to most other DPP-4 inhibitors, linagliptin does not require dose adjustment as renal function declines. Without further requirement of dose adjustment, linagliptin affords simplicity for chronic management of HbA1c. Current literature indicate that decline in renal function is also associated with glycemic control, hypertension, albuminuria and dyslipidemia. However, there is limited evidence about the real world effectiveness and safety of linagliptin across different age and renal functions among adults with T2DM. For better management of hyperglycemia it is pertinent to understand the glycemic effectiveness of linagliptin among adults with T2DM with varying age and renal function who are treated in the real world setting. With a potentially larger sample size, it is possible to compare the glycemic effectiveness of linagliptin across the range of ages and renal function. The aim of the current study is to compare real world glycemic effectiveness across a range of ages and renal function among adults with T2DM who are initiated on linagliptin.		
Research question and objectives:	The primary study objective is to: • Describe change in HbA1c among adults with T2DM within 60 to 180 days following initiation of linagliptin across pre-defined age and renal function categories. Age categories will be defined as: 40 to 54 years, 55 to 64 years, 65 to 74 years, and ≥ 75 years. Renal function categories will		

	be defined based on eGFR as: <30 ml/min/1.73m^2, 30 to 44 ml/min/1.73m^2, 45 to 59 ml/min/1.73m^2, 60 to 89 ml/min/1.73m^2, and ≥ 90 ml/min/1.73m^2. The secondary study objectives are to: • Compare change in HbA1c among adults with T2DM within 60 to 180 days following initiation of linagliptin across pre-defined age and renal function categories. • Compare the proportion of adults with T2DM who achieve HbA1c < 7.0% within 60 to 180 days following initiation of linagliptin across the pre-defined age and renal function categories.

Study design:	*Non*-interventional study based on existing data
Population:	Patients with T2DM newly initiated on linagliptin, in the Optum electronic health record (EHR) database, aged 40 and older, and with HbA1c values during the both the 180 days before and the 60 to 180 days after starting linagliptin
Variables:	Outcomes: • Primary: Change in HbA1c within 60 to 180 days after initiation of linagliptin • Secondary: HbA1c goal (< 7.0%) attainment during the 60 to 180 days after initiation of linagliptin Covariates: • Age categories: 40 to 54 years, 55 to 64 years, 65 to 74 years, and ≥ 75 years • Sex • Race • Ethnicity • Geographic region • Pre-index comorbidity score • Pre-index HbA1c value • Pre-index renal function categories (based on the eGFR): <30 ml/min/1.73m^2, 30 to 44 ml/min/1.73m^2, 45 to 59 ml/min/1.73m^2, 60 to 89 ml/min/1.73m^2, and ≥ 90 ml/min/1.73m^2
Data sources:	Optum electronic health record (EHR) data
Study size:	This study is exploratory and not characterized with *a priori* hypotheses. All patients identified in the data that meet the inclusion criteria and do not meet the exclusion criteria will be included in the study population. A sample size calculation was conducted to determine the minimum number of patients that would be required to detect a change in HbA1c of at least 0.5% among the cohort groups. Based on previously published studies, it was assumed that the standard deviation for the 24-week mean change in HbA1c from baseline could range between 1.2 and 1.5. Assuming a SD of 1.2 for the change in HbA1c, at least 92 patients would be needed in each of the two smallest groups of the cohort of interest (e.g., age, renal function, age by renal function) in order to have 80% power to detect a mean difference in HbA1c of at least 0.5% using a two-sided test at an alpha of 0.05. If the standard deviation for the change in HbA1c is 1.5, then 143 patients would be needed in each of the two smallest groups.
Data analysis:	Primary analysis All study variables, including pre-index and outcome measures, will be analyzed descriptively. Pre-index and outcome measures will be reported for the overall study population as well as stratified by predefined subgroups of patients. The following stratifications will be conducted among the overall study population:

	• By age categories defined as 40 to 54 years, 55 to 64 years, 65 to 74 years, and ≥ 75 years • By renal function categories (based on eGFR) defined as: < 30 ml/min/1.73m^2, 30 to 44 ml/min/1.73m^2, 45 to 59 ml/min/1.73m^2, 60 to 89 ml/min/1.73 m^2, ≥ 90 ml/min/1.73m^2, and not available • By race defined as White, African American, Asian, or Other/ Unknown <u>Secondary analysis</u> Comparisons of pre-index characteristics and outcome measures will be provided, and appropriate tests will be used based on the distribution of the measure. Continuous measures will be compared using t-tests and categorical measures will be compared using chi-square tests. P-values and 95% confidence intervals will be reported. Reported p-values will not be adjusted for multiple comparisons. In addition to the descriptive analyses described above, multivariable modelling will be considered to assess change in HbA1c, controlling for an a priori list of covariates. The use of multivariable modelling will be dependent on having robust sample size distribution across age and eGFR categories.
Milestones:	Protocol Completion Data Extraction, Preparation & QA Data Analysis Final Report

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
Optum to deliver first draft of protocol	14 July 2017
BIPI to provide comments on first draft of protocol	28 July 2017
Optum to deliver second draft of protocol	11 August 2017
BI to provide comments on second draft of protocol	25 August 2017
Optum to deliver final protocol	01 September 2017
BIPI approval of final protocol	19 October 2017
Optum to deliver count of qualifying patients in table format following delivery of final protocol	30 November 2017
Optum to deliver descriptive analysis results tables	12 January 2018
Optum to deliver multivariable model results tables	2 February 2018
Optum to deliver draft report	2 March 2018
BIPI to provide comments following delivery of draft report	16 March 2018
Optum to deliver final report	30 March 2018

7. RATIONALE AND BACKGROUND

Patients with type 2 diabetes mellitus (T2DM) have progressive decline in renal function and this decline in function is greater than age-related decline in patients without diabetes (1-4). Selection of glucose lowering agents is often affected by the level of renal function. Dipeptidyl peptidase-4 (DPP-4) inhibitors are approved to treat hyperglycemia among adults with T2DM with a wide range of renal function. In contrast to most other DPP-4 inhibitors (5), linagliptin does not require dose adjustment as renal function declines. Without further requirement of dose adjustment, linagliptin affords simplicity for chronic management of HbA1c.

Current literature indicate that decline in renal function is also associated with glycemic control, hypertension, albuminuria and dyslipidemia (9-11). However, there is limited evidence about the real world effectiveness and safety of linagliptin across different age and renal functions among adults with T2DM.

Data from clinical studies demonstrate that the expected reduction in HbA1c should be similar across the range of ages, but direct comparisons with younger patients are not available. Barnett et al reported on 238 patients aged 70 or older randomized to linagliptin 5 mg daily (n = 160) or placebo (n=78). The placebo adjusted mean difference in HbA1c after 24 weeks was -0.64% (95% CI -0.81 to -0.48) (12). Inzucchi et al reported on 247 patients aged 70 or older randomized to linagliptin (n = 126) or placebo (n = 121) added to basal insulin (13). The placebo adjusted mean difference in HbA1c after 24 weeks was -0.77 (94% CI -0.95 to -0.59). These values are consistent with other studies of linagliptin, but do not provide direct comparison data with younger patients.

Limited data from studies evaluating linagliptin in patients with renal impairment suggest that glycemic control is maintained across different levels of renal function. Groop et al analyzed data from three 24 week linagliptin clinical trials (n = 2,262) in which data from 2,143 subjects were available to calculate renal function using the Modified Diet Renal Disease (MDRD) equation (14). Subjects were divided by renal function into normal renal function (eGFR $\geq$ 90 ml/min/1.73 m^2), mild renal impairment (eGFR 60 to < 90 ml/min/1.73 m^2) and moderate renal impairment (eGFR 30 to < 60 ml/min/1.73m^2). Distribution of subjects assigned to linagliptin vs. placebo by renal function category was as follows: 1) normal renal function: 870 linagliptin subjects and 342 placebo subjects; 2) mild renal function: 620 linagliptin subjects and 218 placebo subjects; and 3) moderate renal function: 68 linagliptin subjects and 25 placebo subjects. The reduction in HbA1c was consistent across ranges of renal function. However, the number of patients in the moderate renal dysfunction category was quite small, so there is greater uncertainty about the magnitude of the HbA1c reduction in this group. These observations support the current proposal to demonstrate comparable effects in glycemic effectiveness across the range of renal function categories and provide more information in patients with low renal function especially in patients with eGFR < 45 ml/min/1.73 m^2.

For better management of hyperglycemia it is pertinent to understand the glycemic effectiveness of linagliptin among adults with T2DM with varying age and renal function who are treated in the real world setting. With a potentially larger sample size, it is possible to compare the glycemic effectiveness of linagliptin across the range of ages and renal function.

The aim of the current study is to compare real world glycemic effectiveness across a range of ages and renal function among adults with T2DM who are initiated on linagliptin.

8. RESEARCH QUESTION AND OBJECTIVES

The purpose of this study is to assess glycemic control among adults with T2DM during the 60 to 180 days following initiation of linagliptin.

The primary study objective is to:

- Describe change in HbA1c among adults with T2DM within the 60 to 180 days following initiation of linagliptin across pre-defined age and renal function categories. Age categories will be defined as: 40 to 54 years, 55 to 64 years, 65 to 74 years, and ≥ 75 years. Renal function categories will be defined based on eGFR as: <30 ml/min/1.73m^2, 30 to 44 ml/min/1.73m^2, 45 to 59 ml/min/1.73m^2, 60 to 89 ml/min/1.73m^2, and ≥ 90 ml/min/1.73m^2.

The secondary study objectives are to:

- Compare change in HbA1c among adults with T2DM within 60 to 180 days following initiation of linagliptin across pre-defined age and renal function categories.
- Compare the proportion of adults with T2DM who achieve HbA1c < 7.0% within 60 to 180 days following initiation of linagliptin across the pre-defined age and renal function categories.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This will be a non-interventional cohort study using existing data from patients in the Optum Clinical Database which contains electronic health record (EHR) data from providers across the United States.
Real-world EHR data will be used to determine whether there is comparable effectiveness of linagliptin 5 mg daily on glycemic effectiveness as determined by the change in HbA1c and the percentage of patients achieving an HbA1c goal of < 7.0% during the 60 to 180 days after initiation of linagliptin across a range of age and renal function categories.

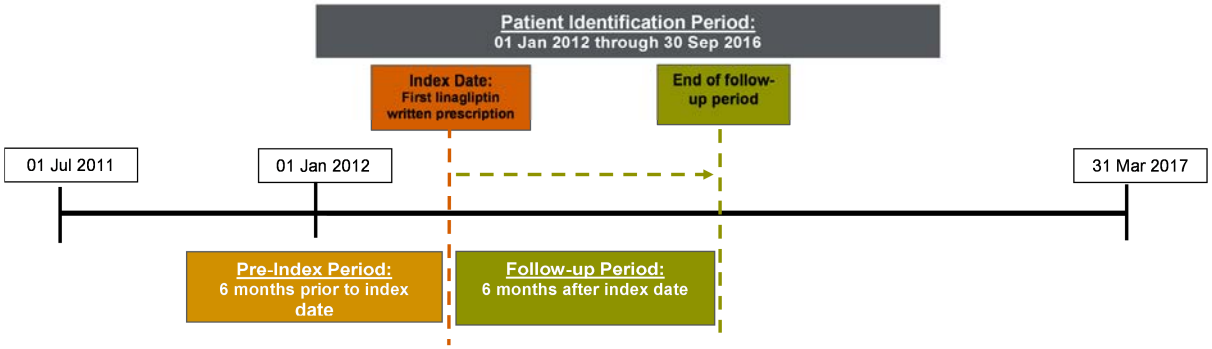
9.2 SETTING

9.2.1 Observation Period

This will be a non-interventional study using existing Optum EHR data for the period of July 1, 2011 through March 31, 2017. Patients with a written prescription for linagliptin will be identified during an identification period starting on January 1, 2012 and ending on September 30, 2016. The date of the first written prescription for linagliptin during the identification period will be designated as the index date without a prior prescription for linagliptin in the pre-index period.

Baseline characteristics will be evaluated during the 180-day period prior to the index date (pre-index period) and on the index date. Outcomes will be assessed during the 180-day period following the index date (follow-up period). A diagram of the study observation period is provided in Figure 1.

Figure 1. Study Observation Period



9.2.2 Inclusion Criteria

To be included in the study sample, patients must meet all of the following criteria:

- ≥ 1 written prescription for linagliptin (Tradjenta®, Jentadueto®, or Jentadueto XR®) in the EHR data during the identification period (medication codes for index medications in Table 1 of Annex 1, Appendix B)
- ≥ 40 years of age based on the year of the index date
- First active date in the EHR is ≥ 180 days prior to the index date
- ≥ 1 diagnosis code representing T2DM in the EHR data during the 180-day pre-index period or on the index date (diagnosis codes in Annex 1, Appendix A)
- ≥ 1 HbA1c value during the 180-day pre-index period or on the index date
- ≥ 1 HbA1c value 60 to 180 days after the index date

9.2.3 Exclusion Criteria

Patients will be excluded from the study sample if they have any of the following:

- ≥ 1 written prescription, medication administration or medication history record for linagliptin or other DPP-4 inhibitor in the EHR data during the 180-day pre-index period (medication codes for DDP-4 inhibitors in Table 2 of Annex 1, Appendix B)
- ≥ 1 written prescription or medication administration for a new antihyperglycemic medication other than linagliptin on the index date
  New antihyperglycemic medication will be defined as a written prescription or medication administration for any antihyperglycemic medication that was not present in the patient's written prescription, medication administration, or medication history records during the 180-day pre-index period. Medication codes for antihyperglycemic medications are shown in Tables 2 through 13 of Annex 1, Appendix B. Individual antihyperglycemic medications will be distinguished by generic name using the column labelled "Medication Name" in Tables 2 through 13. Combination products containing two generic ingredients will be considered as two distinct antihyperglycemic medications.
  Note: This exclusion criterion is designed to exclude patients from the study sample if they start a new antihyperglycemic medication other than linagliptin on the index date. Patients that start a new antihyperglycemic medication in the follow-up period will not be removed from the study sample to avoid creating a biased sample. Addition of a new antihyperglycemic medication during follow-up will be evaluated through the sensitivity analysis described in Section 9.7.4.4. While we will be capturing additions of new therapies, discontinuation of linagliptin is not able to be accurately measured in electronic record data. The electronic record data capture prescriptions written by a prescriber, but it is not possible to know if patients received and adhered to their medication and there are no structured data fields to identify if and when a medication was discontinued by the patient or the provider.
- ≥ 1 diagnosis code or procedure code representing renal transplant, solid organ transplant, or bone marrow transplant in the EHR data during the 180-day pre-index period or on the index date (diagnosis and procedure codes in Annex 1, Appendix A)
- ≥ 1 diagnosis code representing malignancy in the EHR data during the 180-day pre-index period or on the index date (diagnosis codes in Annex 1, Appendix A)

9.2.4 Evaluation of Patient Sample

Before finalizing the study sample, Optum will assess the sample to determine the number of patients excluded and remaining due to the exclusion criterion that requires patients to have no new antihyperglycemic medications other than linagliptin on the index date.

If this evaluation shows that the study sample size would be negatively impacted by excluding these patients, patients with new antihyperglycemic medications on the index date will be kept in the sample and a binary variable will be created to flag the patients for further subanalysis.

9.3 VARIABLES

9.3.1 Exposures

An exposure variable will not need to be created for this study since all the study patients will have linagliptin exposure on the index date.

9.3.2 Outcomes

All outcomes will be measured in the follow-up period.

9.3.2.1 Primary outcomes

The primary outcome variable, change in HbA1c, as defined below, will be evaluated among the overall study sample and stratified across pre-defined age and renal function categories. Age categories will be defined as: 40 to 54 years, 55 to 64 years, 65 to 74 years, and ≥ 75 years. Renal function categories will be defined based on eGFR, , calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (17), and categorized as: < 30 ml/min/1.73m^2, 30 to 44 ml/min/1.73m^2, 45 to 59 ml/min/1.73m^2, 60 to 89 ml/min/1.73m^2, and ≥ 90 ml/min/1.73m^2.

The HbA1c variable definitions assume that the majority of patients will have only one HbA1c measure during the follow-up period because providers are not likely to perform multiple HbA1c tests during a 180-day period. However, if this assumption turns out to be false after examining the data, Section 9.7.3 defines alternative analyses that will be conducted.

- Change in HbA1c—The change in HbA1c will be calculated for each patient by subtracting the patient's last (most recent) HbA1c value during the pre-index period (including the index date) from the patient's last (most recent) HbA1c value 60 to 180 days after the index date.
- Follow-up HbA1c—Follow-up HbA1c will be defined as the last (most recent) HbA1c value 60 to 180 days after the index date. The number of days from the index date to the last (most recent) HbA1c 60 to 180 days after the index date will also be recorded.

9.3.2.2 Secondary outcomes

The secondary outcome variable, HbA1c goal attainment, as defined below, will be evaluated among the overall study sample and stratified across pre-defined age and renal function categories. Age categories will be defined as: 40 to 54, 55 to 64, 65 to 74, and ≥ 75 years. Renal function categories will be defined based on eGFR as: < 30 ml/min/1.73m^2, 30 to 44 ml/min/1.73m^2, 45 to 59 ml/min/1.73m^2, 60-89 ml/min/1.73m^2, and ≥ 90 ml/min/1.73m^2.

- HbA1c goal attainment—A binary variable will be created to designate HbA1c goal attainment 60 to 180 days after the index date. HbA1c goal attainment will be defined as the presence of an HbA1c value < 7.0% any time 60 to 180 days after the index date.

9.3.3 Covariates

Covariates will include demographic and clinical characteristic variables measured during the pre-index period (including the index date) unless otherwise noted.

9.3.3.1 Demographics

- Age—Age will be defined as of the index year.
- Age categories—Patients will be categorized to one of the following age groups:
    - 40 to 54 years
    - 55 to 64 years
    - 65 to 74 years
    - ≥ 75 years
- Sex—Sex will be captured and recorded.
- Race—Race will be categorized as follows:
    - White
    - African American (AA)
    - Asian
    - Other/ Unknown
- Ethnicity
    - Hispanic
    - Non-Hispanic
    - Unknown
    - Not Available

- Geographic region—The U.S. region will be determined and reported. States will be categorized into five geographic regions in accordance with the U.S. Census Bureau's region designations as presented in the table below.

Table 1. United States Geographic Regions

Region	Division	State
Northeast	New England	CT, MA, ME, NH, RI, VT
	Mid Atlantic	NJ, NY, PA
Midwest	East North Central	IL, IN, MI, OH, WI
	West North Central	IA, KS, MN, MO, ND, NE, SD
South	South Atlantic	DC, DE, FL, GA, MD, NC, SC, VA, WV
	East South Central	AL, KY, MS, TN
	West South Central	AR, LA, OK, TX
West	Mountain	AZ, CO, ID, MT, NM, NV, UT, WY
	Pacific	AK, CA, HI, OR, WA
Other	Other	Armed Forces Americas (except Canada), Armed Forces (Europe, Canada, Middle East, Africa), Armed Forces Pacific, American Samoa, Federated State of Micronesia, Guam, Marshall Islands, Commonwealth of the Northern Mariana Islands, Puerto Rico, Palau, Virgin Islands

9.3.3.2 Clinical Characteristics

- Pre-index Quan-Charlson comorbidity score—Quan-Charlson comorbidity score will be calculated based on the presence of diagnosis codes in the pre-index period (including the index date) (16). The Quan-Charlson comorbidity score will also be categorized into the following groups: zero, one to two, three to four, and five or more.
- Pre-index comorbid conditions-General comorbid conditions will be defined using the Clinical Classifications Software managed by the Agency for Healthcare Research and Quality (AHRQ) (17). This measure generates indicator variables for specific disease conditions based on diagnosis codes. The top 20 comorbid conditions will be presented.
- Pre-index antihyperglycemic medications— Pre-index antihyperglycemic medications will be identified based on written prescription, medication administration, and medication history records in the EHR data during the pre-index period. Binary flags, one per medication class and another per distinct medication based on generic name, will be created for the antihyperglycemic medications.
  Medication classes will be determined using the "Medication Class" column in Tables 2 through 13 of Annex 1, Appendix B and will include metformin, sulfonylureas, meglitinides, thiazolidinediones (TZDs), DPP-4 inhibitors other than linagliptin, glucagon-like peptide-1 receptor agonists (GLP-1RA), sodium-glucose co-transporter 2 (SGLT2) inhibitors, basal insulins, bolus insulins, mixed insulins, alpha glucosidase inhibitors, and amylin analogs. Combination products containing two medication classes will be considered as two distinct medication classes.
  Distinct medications will be determined using the "Medication Name" column in Tables 2 through 13 of Annex 1, Appendix B. Combination products containing two generic ingredients will be considered as two distinct antihyperglycemic medications.

- Pre-index antihyperglycemic therapy categories—Patients will be categorized into one of the following groups based on the medication class for their pre-index antihyperglycemic therapies:
    - Metformin only
    - Sulfonylurea only
    - Megilitinde only
    - TZD only
    - GLP-1RA only
    - SGLT2 inhibitor only
    - Basal insulin only
    - Metformin + sulfonylurea
    - Other combination (additional groups will be created for any medication class combinations that are present among least 5% of the study sample)
- New antihyperglycemic medication on the index date – This variable will be created only if the evaluation of the patient sample described in Section 9.2.4 determines that, in order to preserve sample size, it is necessary to retain patients in the study if they have new antihyperglycemic medications other than linagliptin on the index date. A binary flag will be created to indicate whether or not the patient had ≥ 1 new antihyperglycemic medication other than linagliptin on the index date. A new antihyperglycemic medication will be defined as a written prescription or medication administration for any antihyperglycemic medication that was not present in the patient's written prescription, medication administration, or medication history records during the pre-index period (based on the antihyperglycemic medication codes in Tables 2 through 13 of Annex 1, Appendix B). Individual antihyperglycemic medications will be distinguished by generic name using the column labelled "Medication Name" in Tables 2 through 13. Combination products containing two generic ingredients will be considered as two distinct antihyperglycemic medications. In addition, the specific new medications and medication classes on the index date will be captured and reported.
- Number of HbA1c values during the pre-index period (including the index date)—The number of HbA1c values each patient had during the pre-index period (including the index date) will be captured for each patient and categorized as follows: only 1 value, 2 values, or 3 or more values.
- Pre-index HbA1c value—The last (most recent) HbA1c value in the pre-index period (including the index date) will be captured and reported. The number of days from the last (most recent) pre-index HbA1c to the index date will also be recorded.
- Pre-index HbA1c category based on 8% threshold—The last (most recent) HbA1c value in the pre-index period (including the index date) will be used to categorize patients into one of the following categories: HbA1c < 8% or HbA1c ≥ 8%.
- Pre-index HbA1c category based on 9% threshold—The last (most recent) HbA1c value in the pre-index period (including the index date) will be used to categorize patients into one of the following categories: HbA1c < 9% or HbA1c ≥ 9%.
- Pre-index serum creatinine—The last (most recent) serum creatinine value in the pre-index period (including the index date) will be captured and reported.
- Pre-index renal function—Pre-index renal function will be assessed using estimated glomerular filtration rate (eGFR) which will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (18). This equation

requires variables for serum creatinine, age, sex, and race but weight and height are not required because the results are normalized to 1.73 m^2 body surface area (an accepted average adult surface area) (19). The last (most recent) serum creatinine value in the pre-index period (including the index date) will be used for the serum creatinine (Scr) variable. The CKD-EPI equation (18) to estimate GFR in units of ml/min/1.73m^2 after incorporating multiplication factors for race and sex into the intercept is displayed in Table 2. For purposes of this eGFR calculation, race will be categorized as either AA or non-AA (includes White, Asian and Other/Unknown).

Table 2. CKD-EPI equation (Adapted from Reference 18)

Race	Sex	Scr (mg/dL)	Equation for eGFR in units of ml/min/1.73m^2
AA	Female	≤ 0.7	$eGFR = 166\ x\ \left(\frac{Scr}{0.7}\right)^{-0.329}\ x\ (0.993)^{Age}$
AA	Female	> 0.7	$eGFR = 166\ x\ \left(\frac{Scr}{0.7}\right)^{-1.209}\ x\ (0.993)^{Age}$
AA	Male	≤ 0.9	$eGFR = 163\ x\ \left(\frac{Scr}{0.9}\right)^{-0.411}\ x\ (0.993)^{Age}$
AA	Male	> 0.9	$eGFR = 163\ x\ \left(\frac{Scr}{0.9}\right)^{-1.209}\ x\ (0.993)^{Age}$
Non-AA	Female	≤ 0.7	$eGFR = 144\ x\ \left(\frac{Scr}{0.7}\right)^{-0.329}\ x\ (0.993)^{Age}$
Non-AA	Female	> 0.7	$eGFR = 144\ x\ \left(\frac{Scr}{0.7}\right)^{-1.209}\ x\ (0.993)^{Age}$
Non-AA	Male	≤ 0.9	$eGFR = 141\ x\ \left(\frac{Scr}{0.9}\right)^{-0.411}\ x\ (0.993)^{Age}$
Non-AA	Male	>0.9	$GFR = 141\ x\ \left(\frac{Scr}{0.9}\right)^{-1.209}\ x\ (0.993)^{Age}$

- Pre-index renal function categories—Patients will be categorized into one of the following renal function groups based on their eGFR during the pre-index period (including the index date):
  - < 30 ml/min/1.73m^2
  - 30 to 44 ml/min/1.73m^2
  - 45 to 59 ml/min/1.73m^2
  - 60 to 89 ml/min/1.73m^2
  - ≥ 90 ml/min/1.73m^2
  - Not available

9.4 DATA SOURCES

This study will use data from Optum's Clinical Electronic Health Record (EHR) database. This database aggregates clinical treatment data from a provider network of over 140,000 physicians at more than 600 hospitals and more than 6,500 clinics. The EHR database currently has more than 60 million unique patients across the United States and Puerto Rico. The demographics of patients within the Optum EHR data are representative of the United States population (Table 3).

The data are provided by more than 46 contributors, including the nation's leading medical groups, integrated delivery networks (IDNs), and hospital chains. Using deterministic matching technology, Optum collects the provider data from different platforms and IT systems (e.g., Cerner, Epic, GE, McKesson), and then normalizes, validates, and integrates it. The result is a longitudinal record that delivers a comprehensive spectrum of health and medical information. Records in the database are updated quarterly.

Table 3. Optum EHR Data Patient Demographics Compared with the US Population

Attribute	Optum Lives, 2015	US Healthcare Utilizers[1]	US Population[2]
Gender			
Male	43%	47%	49%
Female	57%	53%	51%
Age Group			
0-9	10%	13%	13%
10-17	7%	10%	11%
18-24	7%	8%	10%
25-34	12%	13%	14%
35-44	12%	12%	13%
45-54	14%	13%	14%
55-64	15%	14%	13%

[1] Source of US estimate of healthcare utilizers by age & sex: US Department of Health & Human Services, Agency for Healthcare Research & Quality, Medical Expenditure Panel Survey (MEPS), Projected Expenditure Data File for 2015. Percent of US population with non-zero medical expenditures found from MEPS and applied to US population estimate for 2015 from US Census Bureau, Current Population Survey.

[2] Source of estimate of US population totals alone and by insurance type: US Census Bureau, Current Population Survey, Annual Social and Economic Supplement, 2015.

Attribute	Optum Lives, 2015	US Healthcare Utilizers[1]	US Population[2]
65-74	12%	9%	9%
75+	10%	8%	6%
US Region			
Northeast	13%		18%
Midwest	35%		21%
South	38%		37%
West	14%		24%
Race/Ethnicity			
White	62%	66%	62%
African American	9%	11%	12%
Hispanic	6%	16%	18%
Asian	2%	5%	5%
Other/Unknown	21%	3%	3%
Insurance Coverage			
Commercial	66%	61%	58%
Medicare	14%	17%	16%
Medicaid/ Other gov't	12%	13%	15%
Uninsured	8%	9%	10%

9.5 STUDY SIZE

This study is exploratory and not characterized with *a priori* hypotheses. All patients identified in the data that meet the inclusion criteria and do not meet the exclusion criteria will be included in the study population.

A sample size calculation was conducted to determine the minimum number of patients that would be required to detect a change in HbA1c of at least 0.5% among the cohort groups. Based on previously published studies, it was assumed that the standard deviation for the 24-

week mean change in HbA1c from baseline could range between 1.2 (based on the placebo adjusted value in the MARLINA-T2D trial (20)) and 1.5 (based on retrospective studies of diabetes treatments using electronic medical record data from across the United States (21). Assuming a SD of 1.2 for the change in HbA1c, at least 92 patients would be needed in each of the two smallest groups of the cohort of interest (e.g., age, renal function, age by renal function) in order to have 80% power to detect a mean difference in HbA1c of at least 0.5% using a two-sided test at an alpha of 0.05. If the standard deviation for the change in HbA1c is 1.5, then 143 patients would be needed in each of the two smallest groups.

9.6 DATA MANAGEMENT

Optum stores all extracted data on secure servers. Data files for patients who meet the inclusion criteria will be extracted from the database using Oracle® and SAS® -based tools and housed on Optum UNIX® servers for programming and analysis by Optum staff.

9.7 DATA ANALYSIS

9.7.1 Feasibility Assessment

Feasibility analyses will include determinations of the number of patients in each potential category of age and renal function. Some cells may be too small (e.g. eGFR 30 to 44 ml/min/1.73m^2), but as long as most of the key groups have sufficient numbers (as described in Section 9.5 Study Size) of patients this will not detract from the overall results. The number of AA individuals will not be as large as the full data set and as such some of the age and eGFR groups will be much smaller than for the whole group. Since the AA subgroup analysis is exploratory, having some small groups will not significantly limit the overall clinical interpretation even if statistical comparability cannot be confirmed.

Optum conducted a feasibility analysis using data from the Optum EHR database. There were 63,499 patients identified with a written prescription for linagliptin between January 1, 2012 and June 30, 2016. After excluding patients without data available for a six-month pre-index period, patients with a prescription for linagliptin or other DPP-4 inhibitor, and patients less than 40 years of age, the patient count was reduced to 38,868 patients.

A total of 16,566 patients had at least one HbA1c result during the six-month period prior to the index date and at least one HbA1c result during the six-month period after the index date. Of these, 16,566 adult patients were newly initiated on linagliptin with baseline and follow-up HbA1c results, race/ethnicity was available in 15,289 patients, a serum creatinine value was available for 15,130 patients, and both race/ethnicity and serum creatinine were available for 13,962 patients.

Among the 13,962 patients meeting the criteria and with a baseline serum creatinine, the smallest age group cell (40-54 years) had more than 2,500 patients and the cell with age > 75 years (which is of special interest in this protocol) had more than 3,000 patients. Thus, for the primary end point to assess HbA1c across age ranges, each category is of sufficient size to conduct this study.

9.7.2 Primary Analysis

For the primary analysis, study variables, including pre-index and outcome measures, will be analyzed descriptively. Numbers and percentages will be provided for dichotomous and categorical variables. Means, medians, and standard deviations will be provided for continuous variables.
Results will be stratified by age, renal function, and race/ethnicity. Pre-index and outcome measures will be reported for the overall study population as well as stratified by predefined subgroups of patients.

The following stratifications will be conducted among the overall study population:

- By age categories defined as 40 to 54 years, 55 to 64 years, 65 to 74 years, and ≥ 75 years
- By renal function categories (based on eGFR) defined as: < 30 ml/min/1.73m^2, 30 to 44 ml/min/1.73m^2, 45 to 59 ml/min/1.73m^2, 60 to 89 ml/min/1.73 m^2, ≥ 90 ml/min/1.73m^2, and not available
- By race defined as White, African American, Asian, or Other/Unknown

9.7.3 Secondary Analysis

For the secondary analysis, results will be stratified by age, renal function, and race/ethnicity. Comparisons of pre-index characteristics and outcome measures across age, renal function, and race/ethnicity strata will be provided, and appropriate tests will be used based on the distribution of the measure. Continuous measures will be compared using t-tests and categorical measures will be compared using chi-square tests. P-values and 95% confidence intervals will be reported. Reported p-values will not be adjusted for multiple comparisons.

In addition, as part of the secondary analysis, multivariable modelling will be considered to assess change in HbA1c, controlling for an a priori list of covariates. The use of multivariable modelling will be dependent on having robust sample size distribution (as defined in Section 9.5 Study Size) across age and eGFR categories.

Since the primary outcome of change in HbA1c is calculated using just two timepoints, pre-index and follow-up, multivariable analysis will be conducted using ordinary least squares (OLS). In the event that the assumption that the majority of patients have only one HbA1c measure during the follow-up period turns out to be false and there are multiple HbA1c values per patient during this timeframe, mixed models repeated measures (MMRM) will be used to control for the correlation of multiple HbA1c observations from the same patient.

Following standard procedure, regression diagnostics will be performed for each model to assess goodness of fit and violations of model assumptions (e.g., multicollinearity,

heteroskedasticity). When there are violations of the model, Optum will note them and make appropriate corrections to the data (i.e., typically through transformation of either the independent or dependent variables) or in the method of estimation.

The following list of covariates will be included in the model provided sufficient sample size distribution:

- Age categories (40 to 54 years, 55 to 64 hears, 65 to 74 years, and ≥ 75 years)
- Sex
- Race
- Ethnicity
- Geographic region
- Pre-index HbA1c
- Pre-index renal function categories based on eGFR (< 30 ml/min/1.73m^2, 30 to 44 ml/min/1.73m^2, 45 to 59 ml/min/1.73m^2, 60 to 89 ml/min/1.73m^2, and ≥ 90 ml/min/1.73m^2)
- Pre-index Quan-Charlson comorbidity score
- Pre-index individual comorbidities (each of the AHRQ top 20 comorbidities identified for this population will be included unless the comorbidity is already included in the Charlson Comorbidity Index)

Age and renal function categories will be assessed for adequate sample size across categories based on the sample size calculation reported in Section 9.5. If the sample size distribution is not sufficient to evaluate age as a categorical variable, age will be included as a continuous variable in the model. The eGFR categories of 45 to 59 ml/min/1.73m^2 (Stage 3A kidney disease) and 30 to 44 ml/min/1.73m^2 (Stage 3B kidney disease) will be collapsed into one category (Stage 3 kidney disease) if there is not sufficient sample to evaluate as separate categories.. If the sample size distribution is still not sufficient across the eGFR categories, then eGFR will be included as a continuous variable in the model.

9.8 QUALITY CONTROL

To generate an accurate dataset, Optum incorporates quality assurance checks during dataset construction. Multiple checks are used by project team members throughout the dataset construction process. An additional final overall verification is performed before the dataset is released for analysis. Quality checks used include:

- Verification of sample selection
- Version control, when necessary
- Checks for dataset merge or join problems
- Review of raw data used for creation of constructed variables
    - Checks on record identifiers (e.g., uniqueness)
    - Checks for missing or out-of-range variables
    - Other edit or logic checks (e.g., verifying skip patterns, null values, flag versus continuous measures)
    - Visual checks of text fields
- Careful review of analytic variable specifications
    - Review of all constructed variable definitions by a second analyst
    - Confirmation of complex variable definitions with study experts (i.e., medical director, pharmaceutical specialist)
- Multiple checks on each constructed variable
    - Checks for missing or out-of-range variables
    - Record-level verification of all data elements for a sample of records
    - Double programming of select variables
    - Cross-tabs
    - Logic checks and code review
- Internal team review of the implementation of the dataset construction process

All amendments to the study protocol will be discussed with and agreed upon by the sponsor. Actual amendments to the study protocol will be made by the vendor and sent to BIPI for review and approval. The date of the amendments will be documented on the cover page of the study protocol.

9.9 LIMITATIONS OF THE RESEARCH METHODS

This study has several limitations inherent to its non-interventional study design. There may be baseline differences in the different age and renal function categories. In randomized clinical trials, these differences are mitigated by randomization. Among the important considerations is if there are substantial differences in baseline HbA1c. It is well known that the change from HbA1c is a function of baseline HbA1c, ie, the higher the baseline HbA1c, the greater the change from baseline even with comparable doses of the glucose lowering medication. This observation has been confirmed by Esposito et al (22) in their analyses of several DPP4 inhibitors.

Second, we have selected a follow up window of 6 months rather than a longer window e.g. up to 1 year. Maximal effectiveness is usually achieved by 6 months, although in randomized controlled trials HbA1c values may be lower at later time points. This limitation is balanced against the observation that medication persistence at 6 months will likely be

better than at 12 months and the fact that we wish to maximize the numbers of patients in each of the age and renal function cells.

Third, duration of T2DM is likely to be longer in patients with lower renal function. Increased duration of diabetes is also associated with greater reductions in beta cell function. Since one of the mechanisms of DPP4 inhibitor medications is to increase GLP-1 mediated insulin secretion, reduced renal function could theoretically be associated with diminished glycemic effectiveness. If the current study supports this observation, this will confound the claim of comparable glycemic effectiveness across the range of renal function, but it will be an important observation for the management of T2DM patients. Lajra et al reported on a retrospective analysis of 202 patients from two separate trials in which patients with > 10 years of diabetes were randomized to linagliptin 5 mg (n = 122) or placebo (n = 80)(15). The placebo adjusted mean difference in HbA1c was -0.66% (95% CI -0.85 to -0.38). No direct comparisons were made with shorter duration of diabetes. However, these data suggest that differences in duration of diabetes are unlikely to have a major effect on the data obtained in the current proposal.

Fourth, in contrast to many real world evidence studies, this study does not have an active comparator. Since all other DPP4 inhibitors require dose adjustment for declining renal function, a comparator study to show similar/different effectiveness would be difficult to design to be able to account for all the patient factors that contribute to medication distribution, elimination and dosing and likely would require an inordinately large data base.

Fifth, due to the descriptive nature of this study, multiple different comparisons are being conducted to evaluate change in HbA1c by age, renal function, and race categories. We have not adjusted our p values for multiplicity but we may perform post hoc adjustments if requested by reviewers during the publication process.

Finally, the findings from this study are expected to have limitations that are common to analyses conducted with retrospective EHR data. The possibility of misclassification exists in all studies that rely on retrospective data. Evidence of conditions and events that are based on reported diagnosis codes or procedure codes may not reflect confirmed diagnoses. While EHR data capture prescriptions written by a prescriber, it is not possible to know if patients received and adhered to their medication and there are no structured data fields to identify if and when a medication was discontinued by the patient or the provider. The EHR database does not include the entire medical chart for the patient, which raises the possibility of missing data. Unlike claims data, EHR data do not contain eligibility information and continuous eligibility is not able to be assessed. Services provided to the patient by facilities and providers outside of the healthcare systems providing EHR data to Optum will not be captured although this is not expected to be a major limitation in this study because the primary outcome, HbA1c, is likely to be measured by the same provider who wrote the patient's prescription for linagliptin. However, there may be circumstances where a patient may receive care that falls outside of their provider's electronic record system such as being treated at an out of network hospital.

Despite these limitations, EHR data are a powerful source of data for the examination of health outcomes in the "real world" setting away from the highly controlled environment of

clinical trials. This study offers the advantage of a large sample of patients with diverse demographics and medical histories.

9.10 OTHER ASPECTS

Ethical Approval: This study will be conducted using a limited electronic health record database which complies with HIPAA. Institutional Review Board and Independent Ethics Committee approvals will not be obtained for this study.

9.11 SUBJECTS

Subjects that meet the study inclusion and exclusion criteria defined in Sections 9.2.2 and 9.2.3 will be selected from the Optum Clinical Electronic Health Record Database. The inclusion and exclusion criteria are designed to result in a sample of patients geographically dispersed across the United States with T2DM and newly started on linagliptin.

9.12 BIAS

As noted in Section 9.9, the possibility of bias exists in all studies that rely on retrospective observational data. Information bias is inherent in the use of EHR databases since electronic health records are only available from those healthcare providers and facilities that contribute their data to the database. The study design requires that patients have an HbA1c value during the pre-index period and during the follow-up period which could lead to selection bias since not all of the patients newly started on linagliptin are included. Further, patient selection will be based on diagnosis and procedure codes which may have misclassification errors as noted in Section 9.9. Pre-index variables will be based on the 180-day period prior to the index date which may result in misclassification of clinical characteristic variables if complete medical history is not documented during the EHR data during this timeframe. These limitations will be acknowledged in the final study report.

10. PROTECTION OF HUMAN SUBJECTS

This study will be conducted using a limited electronic health record dataset which complies with HIPAA. No patient's identity or medical records will be disclosed for the purposes of this study except in compliance with applicable law.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a retrospective observational study using secondary data, in which all patient data will be collected and analyzed in aggregate. Individual patient safety related information will not be captured during this study. Thus, individual safety reporting is not applicable for this study.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Example table shells showing the data layout for the results for the overall population and for the AA subanalysis are provided in the analysis plan.
Results will be shared with the internal medical/marketing team as soon as they have been completed and validated. Manuscript of all of the results will be considered. If the AA data are robust, this may be a separate publication.

If abstract submission would not hold up publication this may be a consideration. However, getting the data into the public domain so that it can be used to answer external questions is important.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. The Uniform Requirements state that all persons designated as authors should qualify for authorship, and all those who qualify should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. One or more authors should take responsibility for the integrity of the work as a whole, from inception to published article.

Authorship credit should be based on:

- Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content; and
- Final approval of the version to be published

Authors should meet all three conditions.

13. REFERENCES

13.1 PUBLISHED REFERENCES

1. http://www.ajkd.org/issues?issue_key=S0272-6386(16)X0002-9**.** USRDS (United States Renal Data System) 2015 report. accessed 18Oct2016.
2. https://www.usrds.org/adr.aspx**.** 2015 CDC report on CKD. Accessed 18Oct2015.
3. www2.kidney.org/...ckd/p4_class_g1.htm**.** KDOQI Clinical Practice Guidelines for Chronic Kidney Disease. accessed 20 Oct 2016.
4. Stanton RC**.** Frontiers in diabetic kidney disease: introduction. Am J Kidney Dis. 2014;63(2 Suppl 2):S1-2.
5. https://www.merck.com/product/usa/pi_circulars/j/.../januvia_pi.pdf**.** accessed 18Oct2016.
6. Bryson CL, Ross HJ, Boyko EJ, Young BA**.** Racial and ethnic variations in albuminuria in the US Third National Health and Nutrition Examination Survey (NHANES III) population: associations with diabetes and level of CKD. Am J Kidney Dis. 2006;48(5):720-6.

7. Derose SF, Rutkowski MP, Crooks PW, Shi JM, Wang JQ, Kalantar-Zadeh K, et al. Racial differences in estimated GFR decline, ESRD, and mortality in an integrated health system. Am J Kidney Dis. 2013;62(2):236-44.
8. Tarver-Carr ME, Powe NR, Eberhardt MS, LaVeist TA, Kington RS, Coresh J, et al. Excess risk of chronic kidney disease among African-American versus white subjects in the United States: a population-based study of potential explanatory factors. J Am Soc Nephrol. 2002;13(9):2363-70.
9. American Diabetes A**.** 5. Glycemic Targets. Diabetes Care. 2016;39 Suppl 1:S39-46.
10. American Diabetes A**.** 7. Approaches to Glycemic Treatment. Diabetes Care. 2016;39 Suppl 1:S52-9.
11. American Diabetes A**.** 9. Microvascular Complications and Foot Care. Diabetes Care. 2016;39 Suppl 1:S72-80.
12. Barnett AH, Huisman H, Jones R, von Eynatten M, Patel S, Woerle HJ**.** 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. Lancet. 2013;382(9902):1413-23.
13. Inzucchi SE, Nauck MA, Hehnke U, Woerle HJ, von Eynatten M, Henry RR**.** Improved glucose control with reduced hypoglycaemic risk when linagliptin is added to basal insulin in elderly patients with type 2 diabetes. Diabetes Obes Metab. 2015;17(9):868-77.
14. Groop PH, Del Prato S, Taskinen MR, Owens DR, Gong Y, Crowe S, et al. Linagliptin treatment in subjects with type 2 diabetes with and without mild-to-moderate renal impairment. Diabetes Obes Metab. 2014;16(6):560-8.
15. Lajara R, Aguilar R, Hehnke U, Woerle HJ, von Eynatten M**.** Efficacy and safety of linagliptin in subjects with long-standing type 2 diabetes mellitus (>10 years): evidence from pooled data of randomized, double-blind, placebo-controlled, phase III trials. Clin Ther. 2014;36(11):1595-605.
16. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am. J. Epidemiol. 2011;173(6):676-82.
17. Clinical Classification Software (CCS) for ICD-9-CM. Agency for Healthcare Research and Quality, Rockville, MD. http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp
18. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.
19. National Institue of Diabetes and Digestive and Kidney Diseases. Estimating Glomerular Filtration Rate (GFR). Accessed on July 3, 2017 at: https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx#goto-2
20. Groop PH, Cooper ME, Perkovic V et al. Linagliptin and its effects on hyperglycemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial. Diabetes Obes Metab 2017; Jun 21 [Epub ahead of print]
21. Singhal M, Unni S, Schaerhamer M et al. Real-world glycemic control from GLP-1RA therapy with and without concurrent insulin in patients with type 2 diabetes. JMCP 2017;23:267-77.

22. Esposito K, Cozzolino D, Bellastella G et al. Dipeptidyl peptidase-4 inhibitors and HbA1c target of < 7% in type 2 diabetes: meta-analysis of randomized controlled trials. Diabtes Obes Metab 2011;13(7):594-603.

13.2 UNPUBLISHED REFERENCES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Appendix A. Diagnosis and procedure codes for identifying study conditions

Code	Code Type	Description	Type	Comment
00868	CPT	Anesthesia for extraperitoneal procedures in lower abdomen, including urinary tract; renal transplant (recipient)	Allogenic	Anesthesia
50323	CPT	Backbench standard preparation of cadaver donor renal allograft prior to transplantation, including dissection and removal of perinephric fat, diaphragmatic and retroperitoneal attachments, excision of adrenal gland, and preparation of ureter(s), renal vein(s), and renal artery(s), ligating branches, as necessary	Allogenic	Associated Service
50325	CPT	Backbench standard preparation of living donor renal allograft (open or laparoscopic) prior to transplantation, including dissection and removal of perinephric fat and preparation of ureter(s), renal vein(s), and renal artery(s), ligating branches, as necessary	Allogenic	Associated Service
50327	CPT	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; venous anastomosis, each	Allogenic	Associated Service
50328	CPT	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; arterial anastomosis, each	Allogenic	Associated Service
50329	CPT	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; ureteral anastomosis, each	Allogenic	Associated Service
50360	CPT	Renal allotransplantation, implantation of graft; without recipient nephrectomy	Allogenic	Transplant ation
50365	CPT	Renal allotransplantation, implantation of graft; with recipient nephrectomy	Allogenic	Transplant ation
76776	CPT	Ultrasound, transplanted kidney, real time and duplex Doppler with image documentation	Unknown	Imaging
S2065	HCPCS	Simultaneous pancreas kidney transplantation	Allogenic	Transplant ation
T8610	ICD-10 Dx	Unspecified complication of kidney transplant	Unknown	Complicatio n
T8611	ICD-10 Dx	Kidney transplant rejection	Unknown	Complicatio n
T8612	ICD-10 Dx	Kidney transplant failure	Unknown	Complicatio n
T8613	ICD-10	Kidney transplant infection	Unknown	Complicatio

	Dx			n
T8619	ICD-10 Dx	Other complication of kidney transplant	Unknown	Complicatio n
Z4822	ICD-10 Dx	Encounter for aftercare following kidney transplant	Unknown	Aftercare
Z940	ICD-10 Dx	Kidney transplant status	Unknown	Transplant Status
0TY00Z0	ICD-10 PCS	Transplantation of Right Kidney, Allogeneic, Open Approach	Allogenic	Transplant ation
0TY00Z1	ICD-10 PCS	Transplantation of Right Kidney, Syngeneic, Open Approach	Syngenic	Transplant ation
0TY00Z2	ICD-10 PCS	Transplantation of Right Kidney, Zooplastic, Open Approach	Xenograft	Transplant ation
0TY10Z0	ICD-10 PCS	Transplantation of Left Kidney, Allogeneic, Open Approach	Allogenic	Transplant ation
0TY10Z1	ICD-10 PCS	Transplantation of Left Kidney, Syngeneic, Open Approach	Syngenic	Transplant ation
0TY10Z2	ICD-10 PCS	Transplantation of Left Kidney, Zooplastic, Open Approach	Xenograft	Transplant ation
996.81	ICD-9 Dx	Complications of transplanted kidney	Unknown	Complicatio n
V42.0	ICD-9 Dx	Kidney replaced by transplant	Unknown	Transplant Status
55.69	ICD-9 Proc	Other kidney transplantation	Unknown	Transplant ation

Appendix B. Codes for identifying study medications

NDC	**Product Name**	**Medication Name**	**Medication Class**
50458014030	INVOKANA	CANAGLIFLOZIN	SGLT2 INHIBITOR
50458014090	INVOKANA	CANAGLIFLOZIN	SGLT2 INHIBITOR
50458014130	INVOKANA	CANAGLIFLOZIN	SGLT2 INHIBITOR
50458014190	INVOKANA	CANAGLIFLOZIN	SGLT2 INHIBITOR
50458054160	INVOKAMET	CANAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
50458054360	INVOKAMET	CANAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
50458054260	INVOKAMET	CANAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN

50458054060	INVOKAMET	CANAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
50458094001	INVOKAMET XR	CANAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
50458094101	INVOKAMET XR	CANAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
50458094201	INVOKAMET XR	CANAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
50458094301	INVOKAMET XR	CANAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00003142811	FARXIGA	DAPAGLIFLOZIN	SGLT2 INHIBITOR
00310621030	FARXIGA	DAPAGLIFLOZIN	SGLT2 INHIBITOR
00003142711	FARXIGA	DAPAGLIFLOZIN	SGLT2 INHIBITOR
00310620530	FARXIGA	DAPAGLIFLOZIN	SGLT2 INHIBITOR
00310625030	XIGDUO XR	DAPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00310627030	XIGDUO XR	DAPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00310626030	XIGDUO XR	DAPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00310626060	XIGDUO XR	DAPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00310628030	XIGDUO XR	DAPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597015230	JARDIANCE	EMPAGLIFLOZIN	SGLT2 INHIBITOR
00597015237	JARDIANCE	EMPAGLIFLOZIN	SGLT2 INHIBITOR
00597015290	JARDIANCE	EMPAGLIFLOZIN	SGLT2 INHIBITOR
00597015330	JARDIANCE	EMPAGLIFLOZIN	SGLT2 INHIBITOR
00597015337	JARDIANCE	EMPAGLIFLOZIN	SGLT2 INHIBITOR
00597015390	JARDIANCE	EMPAGLIFLOZIN	SGLT2 INHIBITOR
00597018230	GLYXAMBI	EMPAGLIFLOZIN/LINAGLIPTIN	SGLT2 INHIBITOR/DPP4 INHIBITOR
00597018239	GLYXAMBI	EMPAGLIFLOZIN/LINAGLIPTIN	SGLT2 INHIBITOR/DPP4 INHIBITOR
00597018290	GLYXAMBI	EMPAGLIFLOZIN/LINAGLIPTIN	SGLT2 INHIBITOR/DPP4 INHIBITOR
00597016430	GLYXAMBI	EMPAGLIFLOZIN/LINAGLIPTIN	SGLT2 INHIBITOR/DPP4

			INHIBITOR
00597016439	GLYXAMBI	EMPAGLIFLOZIN/LINAGLIPTIN	SGLT2 INHIBITOR/DPP4 INHIBITOR
00597016490	GLYXAMBI	EMPAGLIFLOZIN/LINAGLIPTIN	SGLT2 INHIBITOR/DPP4 INHIBITOR
00597017518	SYNJARDY	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597017560	SYNJARDY	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597016818	SYNJARDY	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597016860	SYNJARDY	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597015918	SYNJARDY	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597015960	SYNJARDY	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597018018	SYNJARDY	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597018060	SYNJARDY	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597029020	SYNJARDY XR	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597029059	SYNJARDY XR	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597029074	SYNJARDY XR	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597030020	SYNJARDY XR	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597030045	SYNJARDY XR	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597030093	SYNJARDY XR	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597028036	SYNJARDY XR	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597028073	SYNJARDY XR	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597028090	SYNJARDY XR	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN

00597029561	SYNJARDY XR	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597029578	SYNJARDY XR	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN
00597029588	SYNJARDY XR	EMPAGLIFLOZIN/METFORMIN	SGLT2 INHIBITOR/METFORMIN

Appendix C. Example table shells for analysis of overall study population see the analysis plan

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

Not applicable