Sodium-Glucose Cotransporter-2 Inhibitor Use and Risk of Fournier's Gangrene: Validating the US Food and Drug Administration Drug Warning

MarketScan Commercial Claims and Encounters Database, 2012-2017

Study Protocol, 06.05.2019

Notes:

- We declare that we have no knowledge, through advance exploratory analyses, of the likely ultimate findings of the study at the time that this protocol is submitted.

BACKGROUND

In August 2018, the US Food and Drug Administration (FDA) released a safety warning associating sodium-glucose cotransporter-2 inhibitors (SGLT2i), the newest class of antihyperglycemic drugs, with increased incidence of Fournier's gangrene (FG), a rare, necrotizing fasciitis of the perineum.[1] This warning, which quickly attracted media attention,[2] was based on 12 FG cases (7 men, 5 women) reported through the FDA Adverse Event Reporting System (FAERS) from 2013-2018, as well as individual case reports in the medical literature.[3–5] Although the overall incidence of FG in the US is low (1.6 cases per 100,000 male patients),[6] it is accompanied by poor management options and prognosis,[7] and leads to debilitating complications and disfigurement in most infected patients. Approximately 7.5% of FG patients die.[6,8–10]

The observed increase in FG risk associated with SGLT2i use has not yet been validated in large, real-world populations.[11] A recent review of the FAERS and case reports identified 55 FG cases among patients receiving SGLT2i from 2013-2019, compared to 19 FG cases among patients receiving other antihyperglycemic agents from 1984-2019.[12] However, the structure and quality of FAERS reporting precluded any ability to estimate comparative incidence or establish causality. To address these limitations, we propose to evaluate the association between SGLT2i initiation and FG risk using a large healthcare administrative claims database from the commercially-insured U.S. population. We will apply the active comparator, new user (ACNU) study design[13] to estimate and compare the incidence of FG between patients who initiated SGLT2i and those who initiated comparable second-line glucose-lowering drugs (GLDs), dipeptidyl peptidase-4 inhibitors (DPP4i) and sulfonylureas (SU). This study will contribute to

the evidence behind the FDA warning and inform clinicians' efforts to balance the risks and benefits of this newest class of GLDs.

SPECIFIC AIMS

Aim 1: To evaluate and compare the association between SGLT2i initiation, relative to other second-line glucose lowering drugs (GLDs), on the incidence and risk of Fournier's gangrene, based on an active comparator, new-user (ACNU) study design.

STUDY DESIGN

Data Sources

- MarketScan Commercial Claims and Encounters (CCAE) Database, 2012-2017

Study Population

The base population for the analysis will consist of all MarketScan CCAE beneficiaries with at least one prescription dispensing claim for a SGLT2i or an active comparator drug (see table below) between April 1, 2013 and June 30, 2017, identified using National Drug Codes (NDCs). The first eligible date of April 1, 2013 was chosen to reflect the FDA approval and US market entry date of canagliflozin, the first SGLT2i agent, which occurred during March 2013.[14] The last eligible date of June 30, 2017 was chosen to allow all eligible patients the opportunity to have at least 6 months of follow-up after cohort entry, before the administrative study end date of December 1, 2017.

Comparisons	Index Drug	Comparator Drug
I	SGLT2i (canagliflozin, dapagliflozin, empagliflozin)	DPP-4i (sitagliptin, saxagliptin, linagliptin, alogliptin)
II	SGLT2i (canagliflozin, dapagliflozin, empagliflozin)	Sulfonylureas (glyburide, glipizide, glimepiride)

Inclusion criteria:

1. MarketScan enrollees aged 18-64

Exclusion criteria:

1. To ensure new use of either SGLT2i or an active comparator drug, we will exclude all individuals who do not have at least 12 months of continuous enrollment in the MarketScan CCAE database prior to the first prescription dispensing claim, during which no other prescription for any of the study drug classes is observed (washout period). **Note**: patients will be allowed, but not required, to be taking metformin and other antidiabetics at the time of initiation of either SGLT2i or an active comparator drug.
2. We will exclude all patients with prior Fournier's gangrene diagnosis in the 12 months prior to drug initiation.

Exposure

Exposure to a study drug will be defined by at least two same-drug class prescription dispensing claims of either a SGLT2i or an active comparator drug. We believe this approach restricts the analysis to a cohort for whom we are reasonably confident were taking the cohort drugs. The dispensing of the second prescription, whose date will be the index date for the analysis, must occur within a specified time window of the first prescription (day's supply + "grace period"), to ensure that patients are undergoing continued therapy. For primary analyses, we will use a 30-day grace period and will consider longer grace periods if this initial interval is overly restrictive. We will also test the impact of differing grace periods on results via sensitivity analyses.

Outcomes

Fournier's gangrene will be defined by ICD-9 diagnosis code 608.83 ("vascular disorders, including Fournier's disease") and ICD-10 diagnosis code N49.3 ("Fournier's gangrene"). We will identify and evaluate additional related ICD-9 and ICD-10 codes that result from a forward-backward mapping approach using the General Equivalence Mappings (GEMS) crosswalk provided by the Center for Medicare and Medicaid Services (CMS).[15] Because there are no specific codes for Fournier's gangrene in women, we will use a combination of codes listed below. This approach has been used in previous epidemiologic study of Fournier's gangrene.[6,8,9] All FG diagnosis codes must either occur in an inpatient setting, or be accompanied by hospital admission within 7 days.

To maximize outcome specificity, we will additionally require any FG diagnosis code to be followed by a claim for a systemic antibiotic, debridement, AND related surgical procedure[8] within 7 days. However, acknowledging the extremely low incidence of FG in the US population (1.6 cases per 100,000 males)[6] and lack of standard, validated claims-based definitions, we will consider the following, less stringent, outcome definitions if the above outcome definition is overly restrictive and yields too few cases for study. If the primary outcome definition proves feasible for study, we will consider the definitions below in sensitivity analyses.

1) Any FG diagnosis (occurring in an inpatient setting, or be accompanied by hospital admission within 7 days), followed by a claim for a systemic antibiotic, debridement, OR related surgical procedure within 7 days.
2) Any FG diagnosis (occurring in an inpatient setting, or be accompanied by hospital admission within 7 days), followed by a claim for a debridement OR related surgical

procedure within 7 days. We consider this definition because we do not expect NDCs for systemic antibiotics to be billed during inpatient stays.

Definition[6,8,9,16]	**ICD-9 Codes**	**ICD-10 Codes**	**HCPCS/CPT Codes**
Fournier's gangrene (men)	608.83	N49.3	
Fournier's gangrene (women)	785.4, 616.3, 616.4	N75.1, N76.4, I96	
IV antibiotics[16]			90788, 99556, S9539 S0030, J2543, J1580, J0456, J3370, J0690, J0694, S0077, J0290, J0696, J2010, J3260, J0744, J3243
Debridement	48.8–48.82, 48.9, 49.0, 49.01, 49.02, 49.04, 49.39, 49.93, 54.0, 54.3, 61.0–61.99, 62.0–62.19, 62.2–62.42, 63.3, 63.4, 64.0, 64.2, 64.3, 64.92, 64.98, 71.0, 71.09, 71.22, 71.24, 71.29, 71.3, 71.5, 71.6–71.62, 71.8, 71.9, 83.0–83.09, 83.19, 83.21, 83.3–83.39, 83.4, 83.42, 83.44–83.49, 86.0, 86.04, 86.09, 86.22, 86.28, 86.3, 86.4, 86.9 and 86.99	Equivalent ICD-10 procedure code lists will be created using a combination of the validated ICD-9 to ICD-10 forwards-backwards mapping approach using the Center for Medicare and Medicaid Services General Equivalence Mapping (GEMs)[15] and clinical input.	11000, 11040, 11041, 11042, 11043, 11044, 11750, 11752, 11765, 97597, 97598, 97601, 97602
Related surgical procedures	Suprapubic tube placement (codes 57.1–57.19), penectomy (code 64.3), orchiectomy (codes 62.3–62.42), colostomy (codes 46.0, 46.01, 46.03, 46.1–46.13, 46.2–46.23, 46.3, 46.39) and	Equivalent ICD-10 procedure code lists will be created using a combination of the validated ICD-9 to ICD-10 forwards-backwards mapping approach using the Center for Medicare and Medicaid Services	

	surgical wound closure with or without skin grafting (codes 61.49, 64.43, 64.44 and 86.60).	General Equivalence Mapping (GEMs)[15] and clinical input.	

Systemic Antibiotics:

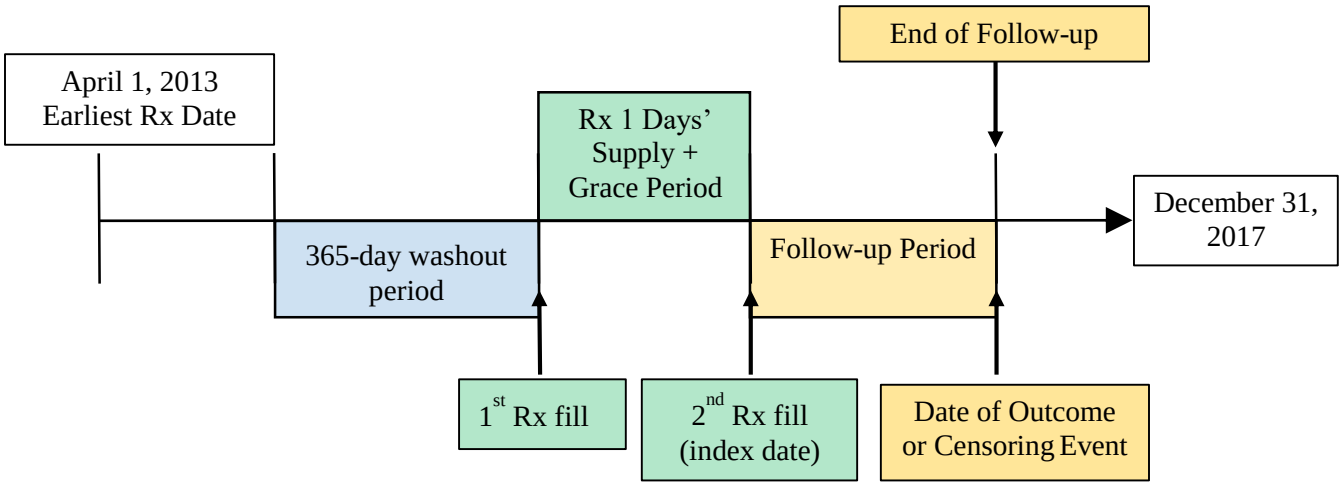
- Vancomycin
- Piperacillin-tazobactam
- Clindamycin
- Daptomycin
- Meropenem
- Imipenem
- Ertapenem
- Ampicillin-sulbactam
- Ticarcillin-clavulanate
- Metronidazole
- Erythromycin
- Gentamicin
- Tobramycin
- Amikacin
- Ciprofloxacin
- Cefotetan
- Cefoxitin
- Cefuroxime
- Ceftriaxone
- Ceftazidime plus avibactam
- Ceftazidime

Follow-up

The primary analysis will be carried out in an "as-treated" fashion. Follow-up will begin at index date (date of 2nd prescription) and end at the time an individual experiences either an outcome of interest or censoring event. Patients will be censored for treatment discontinuation/switch/ augmentation, disenrollment from the insurance plan, or administrative study end (December 31, 2017), whichever comes first.

Treatment discontinuation, switch, and augmentation will be defined using a combination of days' supply, found on each prescription dispensing claim, and a pre-defined "grace period" defined in the above sections. Patients will be considered to have discontinued treatment if they have no new prescription of the cohort drug class within a (days' supply + grace period) time window after the last prescription of the cohort drug class. Censoring will occur at the end of the same (days' supply + grace period) time window. We will vary the length of this grace period in sensitivity analyses to examine the robustness of the primary analysis results to changes in grace period.

Patients will be considered to have switched or augmented treatment if they fill a prescription for a comparator drug within the (days' supply + grace period) time window after the last prescription of the cohort drug. Censoring will occur at the fill date of the comparator drug class. Patients who switch between or augment with drugs within the same class will not be censored under this definition.



Statistical Analysis

The active comparator, new user study design tends to synchronize patients with respect to diabetes severity and duration. We will assess this balance by looking at the crude distribution of

claims data based covariates across treatment cohorts. We will consider strong predictors of treatment choice as additional exclusion criteria. Once balanced cohorts have been identified, we will use propensity scores to remove remaining imbalances in measured potential confounders between study cohorts. Our primary aim is to identify active comparator drug initiators that will allow us to estimate what would have happened to the SGLT2i initiators if they had not initiated SGLT2i. To achieve this goal, we will estimate the treatment effect in the treated (ATT) by reweighting the comparator drug initiators by the propensity score odds (PS/(1-PS)).[17]

We will estimate the crude incidence rates of FG during follow-up for both the SGLT2i and comparator drug cohort, by dividing total number of observed cases during follow-up by the total person-time at risk. We will additionally estimate and compare the cumulative incidence of study outcomes for each study cohort using weighted Kaplan-Meier methods. Finally, crude and adjusted hazard ratios (HRs) for study outcomes will be estimated using weighted Cox proportional hazards models, controlling for age, sex, as well as any potential confounders that remain unbalanced after propensity score implementation.

- Baseline covariates, measured in the 12 months prior to index date (primary analysis):
    - (1) <u>Demographics:</u>
        - Age, sex
    - (2) <u>Comorbidity:</u>
        - **Risk factors or confounders specific to Fournier's gangrene**:[4,5,9–11] Diabetes complications (neuropathy, nephropathy, retinopathy), peripheral artery disease (PVD), obesity, alcohol abuse, chronic obstructive pulmonary disease (COPD), liver disease, renal insufficiency/failure,

cancer, human immunodeficiency virus (HIV)

- **General health comorbidities**: Hypertension, congestive heart failure (CHF), acute myocardial infarction (AMI), cerebrovascular disease (CBD), peptic ulcer disease, coagulopathy, smoking, dyslipidemia, ischemic heart disease, depression
- *All above co-morbidity variables are categorized into binary variables (yes or no), defined as at least one diagnosis code.*

- (3) Medications:
  - Statins, ACE inhibitors, ARBs, beta blockers, calcium channel blockers, loop diuretics, non-loop diuretics, aspirin, glucocorticoids, digoxin
  - Prior use of other GLDs (metformin, thiazolidinediones, glucagon-like peptide-1 receptor agonists, long-acting insulin, DPP4i, SU)
  - *All medication variables are categorized into binary variables (yes or no), defined as at least one prescription or refill records.*
- (4) Health Care System Use:
  - Number and total days of hospitalizations, number of physician encounters (identified using CPT codes for evaluation and management during physician office visits), number of emergency department visits, number of lipid tests, number of HbA1c tests, general utilization (flu vaccination, other health screenings)
  - *All health care system use variables will be treated as both continuous variables and categorical variables.*

- Subgroup analyses for effect measure modification:
    - Age on index date
    - Sex on index date
    - Urogenital infection during baseline period
        - Urinary tract infection
        - Genital infection

Sensitivity Analyses

To examine the robustness of our primary results to changes in study population and condition definitions, we plan to perform the following sensitivity analyses;

1. To quantify possible impact of outcome misclassification, we will repeat the analysis using a relaxed outcome definition (higher sensitivity, lower specificity) that requires diagnosis codes only (without requiring subsequent antibiotic, hospitalization, or surgery). Diagnosis codes will still be required to occur in an inpatient setting, or be accompanied by hospital admission within 7 days.
2. Repeat primary analysis using intent-to-treat (ITT) design (no censoring for drug switching, augmentation, or discontinuation).
3. Repeat analysis to include individuals with only 1 prescription for a study drug.
4. Repeat analysis using a comparator group of all non-SGLT2i GLD classes (metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, long-acting insulins), since this was the comparison that was cited in the FDA warning.[1] For this analysis, we will exclude patients who have use of any GLD during the 12 months prior to initiation of either SGLT2i or a comparator drug.

5. Repeat primary analysis subsetting to drug initiation before or after October 1, 2015, to verify that results are consistent across the ICD-9 to ICD-10 transition.
6. Repeat primary analysis excluding patients with index dates between October 1, 2015 and December 31, 2015 to account for the ICD-9 to ICD-10 transition period, during which changing billing practices may result unstable covariate prevalence estimates.
7. Repeat analysis including both incident and prevalent FG cases, by including patients both with and without observed claims for FG during the 12-month baseline period.
8. Repeat analysis restricting to patients with baseline metformin use. This approach has been shown to improve confounding control and covariate balance by restricting to populations that are using study drugs as second-line therapies following initial metformin use.
9. Repeat analysis using 15-, 60- and 90-day grace periods.
10. Repeat analysis using 60-, 90-, and 180-day lag periods, if possible, both between drug initiation and start of follow-up (induction period) and between drug discontinuation, switch, and augmentation, and end of follow-up for outcome assessment (latent period).
11. Repeat analysis with 1%, 2.5%, and 5% asymmetric trimming of the propensity score distribution.[18]

REFERENCES

1. FDA. FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes. https://www.fda.gov/Drugs/DrugSafety/ucm617360.htm. Published 2018.
2. Lee BY. How One Class Of Diabetes Medications May Lead To Flesh-Eating Genital Infections. Forbes.com. https://www.forbes.com/sites/brucelee/2018/09/01/how-one-class-of-diabetes-medications-may-lead-to-flesh-eating-genital-infections/#75c509976193. Published 2018.
3. Chi WC, Lim-Tio S. Fournier's syndrome: a life threatening complication of SGLT2 inhibition in poorly controlled diabetes mellitus (Poster #265). http://ads-adea-2016.m.asnevents.com.au/schedule/session/9239/abstract/36604.
4. Kumar S, Costello AJ, Colman PG. Fournier's gangrene in a man on empagliflozin for treatment of Type 2 diabetes. *Diabet Med*. 2017;34(11):1646-1648. doi:10.1111/dme.13508
5. Onder CE, Gursoy K, Kuskonmaz SM, Kocer U, Culha C. Fournier's gangrene in a patient on dapagliflozin treatment for Type 2 Diabetes. *J Diabetes*. 2019. doi:10.1111/1753-0407.12896
6. Sorensen MD, Krieger JN. Fournier's Gangrene: Epidemiology and Outcomes in the General US Population. *Urol Int*. 2016;97(3):249-259. doi:10.1159/000445695
7. Kranz J, Schlager D, Anheuser P, et al. Desperate need for better management of Fournier's Gangrene. *Cent Eur J Urol*. 2018:360-365. doi:10.5173/ceju.2018.1740
8. Sorensen MD, Krieger JN, Rivara FP, Klein MB, Wessells H. Fournier's Gangrene: Management and Mortality Predictors in a Population Based Study. *J Urol*.

2009;182(6):2742-2747. doi:10.1016/j.neuroimage.2013.08.045.The

9. Sorensen MD, Krieger JN, Rivara FP, et al. Fournier's Gangrene: Population Based Epidemiology and Outcomes. *J Urol*. 2009;181(5):2120-2126. doi:10.1016/j.juro.2009.01.034.Fournier

10. Singh A, Ahmed K, Aydin A, Khan MS, Dasgupta P. Fournier's gangrene: A clinical review. *Arch Ital di Urol e Androl*. 2016;88(3):157-164.

11. Bloomgarden Z, Einhorn D, Handelsman Y, Grunberger G. Fournier's gangrene and sodium-glucose cotransporter-2 inhibitors: Is there a causal association? *J Diabetes*. 2019:10-12. doi:10.1111/1753-0407.12897

12. Bersoff-Matcha SJ, Chamberlain C, Cao C, Kortepeter C, Chong WH. Fournier Gangrene Associated With Sodium – Glucose Cotransporter-2 Inhibitors: A Review of Spontaneous Postmarketing Cases. *Ann Intern Med*. 2019;ePub ahead. doi:10.7326/M19-0085

13. Lund JL, Richardson DB, Sturmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep*. 2015;2(4):221-228. doi:10.1007/s40471-015-0053-5.The

14. Mosley JF, Smith L, Everton E, Fellner C. Sodium-Glucose Linked Transporter 2 (SGLT2) Inhibitors in the Management Of Type-2 Diabetes: A Drug Class Overview. *Pharm Ther*. 2015;40(7):451-462.

15. CMS. 2018 ICD-10 CM and GEMs. https://www.cms.gov/Medicare/Coding/ICD10/2018-ICD-10-CM-and-GEMs.html. Accessed May 5, 2019.

16. Roberts S, Upadhyay U, Liu G. Roberts SCM, Upadhyay UD, Liu G, et al. Association of facility type with procedural-related morbidities and adverse events among patients undergoing induced abortions. JAMA. doi:10.1001/jama.2018.7675. Supplementary

Online Content. *JAMA*. 2018;319(24):2497–2506. doi:10.1001/jama.2018.7675

17. Sato T, Matsuyama Y. Marginal structural models as a tool for standardization. *Epidemiology*. 2003;14(6):680-686. doi:10.1097/01.EDE.0000081989.82616.7d

18. Stürmer T, Rothman KJ, Avorn J, Glynn RJ. Treatment effects in the presence of unmeasured confounding: Dealing with observations in the tails of the propensity score distribution-A simulation study. *Am J Epidemiol*. 2010;172(7):843-854. doi:10.1093/aje/kwq198

Appendix A - New User Algorithm

Definitions/Conventions

Washout Period (WP) = minimum length of time that a patient must be drug-free prior to becoming eligible for the new user cohort

Grace Period (GP) = maximum length of time that a user can go after the last prescription date plus the days supply without a drug before being considered discontinued from drug use

Days Supply (DS) = assumed (or imputed) number of days supply to use as Days Supply when true value is unknown (usually 30 days)

Wi = Days since start of washout period prior to 1st RX fill of ith period of use for patient

Gj = Days from last day covered by the jth RX fill to the (j+1)th RX fill date

Cohort Eligibility

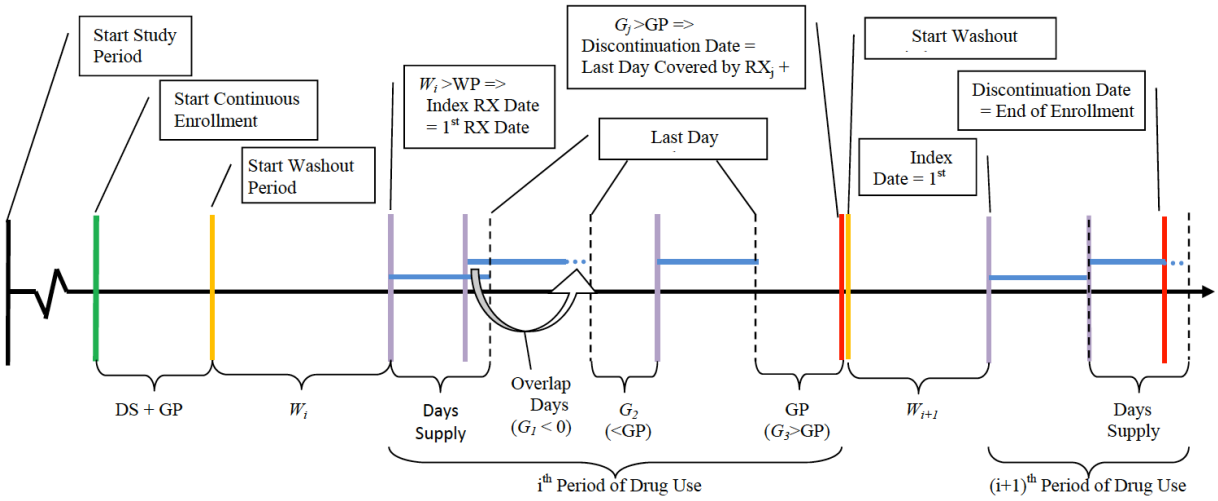
If W1 > WP then patient's period of drug use is eligible for the new user cohort.

If Wi > WP and i>1 then patient's ith period of drug use is eligible for new user cohort IFF the analysis allows for previous users to become new users.

Drug Discontinuation/Censor Date

If Gj > GP then the patient is considered discontinued from drug use on the last day covered by the jth RX fill + GP

If (End of Enrollment) – GP < (Last Day Covered by an RX Fill) then the patient is censored at End of Enrollment



Algorithm

1. Set (Last Day Covered) = (Start of Continuous Enrollment) + (Days Supply) + (Grace Period).

2. Set (Index Date) = (1st RX Fill Date following Start of Continuous Enrollment).

3. Let W = (Index Date) – (Last Day Covered). If W > (Washout Period) then flag the period of drug use as eligible for the new user cohort.

4. Let G = (RX Fill Date) – (Previous Last Day Covered). Sequentially cycle through the subsequent prescription claims for the patient, applying the appropriate step below, until (Discontinuation Date) is set:

a. If G > (Grace Period) then set (Discontinuation Date) = max(Previous Last Day Covered, RX Fill Date) + (Days Supply) + (Grace Period).

b. If G <= (Grace Period) then set (Last Day Covered) = max(Previous Last Day Covered, RX Fill Date) + (Days Supply). If (Last Day Covered) + (Grace Period) > (End of Continuous Enrollment) and the patient has no additional RX claims with (RX Fill Date) <= (End of Continuous Enrollment), then set (Discontinuation Date) = (End of Continuous Enrollment). Otherwise, repeat Step 3 for the next prescription.

5. If the record was flagged for inclusion in the new user cohort in Step 3, output the record

containing Index Date and Discontinuation Date3.

6. Set (Index Date) = (1st RX Fill Date following Discontinuation Date).

a. If the patient is continuously enrolled from (Discontinuation Date) to (Index Date), set (Last Day Covered) = (Discontinuation Date).

b. If the patient has a gap in enrollment between (Discontinuation Date) and (Index Date), then set (Last Day Covered) = (Start of Next Period of Continuous Enrollment) + (Days Supply) + (Grace Period) and set (Index Date) = (1st RX Fill Date following Start of Next Period Continuous Enrollment).

7. Repeat Steps 3-7 for the patient's remaining RX fills.