Protocol 2019-8636; B5K-MC-B014
Treatment Patterns, Treatment Outcomes, and Out-of-Pocket Pharmacy Costs Before and After Humulin R U-500 Initiation Among Type 2 Diabetes Patients in the United States Utilizing a Total Daily Dose of >180 units per Day

HUMULIN R U-500 (LY041001)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Observational Study Protocol Electronically Signed and Approved by Lilly

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3. Background and Rationale

Diabetes is a serious and growing public health concern. Nearly 9.4% (30.3 million) of the US population had diabetes in 2015 and the prevalence of those who had diagnosed diabetes was estimated to be 7.2% (23.1 million).[1] It is reported that approximately 90% to 95% of all diabetes cases were type 2 diabetes mellitus (T2DM).[1] The consistent rise in diabetes prevalence may be attributed to a corresponding rise in the prevalence of overweight and obesity diagnoses; epidemiological studies have shown strong positive associations between adiposity measures including body mass index (BMI), waist circumference, and diabetes.[2,3,4,5] According to previous studies using the National Health and Nutrition Examination Surveys (NHANES) data, the prevalence of obesity continues to increase, alarmingly, over the period of 2007-2008 and 2015-2016. [6] The 2013-2014 NHANES survey results further confirmed the increased prevalence of obesity, along with a persistent rise in the T2DM since 1999-2000.[7] Despite major breakthrough in understanding the relationship between insulin resistance and both obesity and T2DM, the underlying mechanisms remain puzzled (Kahn 2006).[8] Together with an obesity epidemic, the process of reducing the national health care burden from diabetes is impeded.

It is often challenging to achieve desired blood glucose levels among T2DM patients with severe insulin resistance, using 100 units/mL (U-100) insulin.[9] Patients often require 4-8 daily injections to meet their high insulin requirements; these repeated injections may lead to a painful injection site reaction, which can adversely affect adherence to the insulin replacement therapy.[10]Concentrated insulin products were designed to help meet the insulin requirements among patients with increased insulin resistance. However, the use of these products may be associated with an increased risk of severe hypoglycemia, which may be attributed to insulin stacking resulted from an unanticipated prolonged duration of effect from these products. [11]

U-500 regular insulin (U-500R) is a five-fold concentrated form of insulin (contains 500 units of insulin per mL) indicated to improve glycemic control in adults and children with diabetes mellitus requiring more than 200 units of insulin per day. It was first approved in 1994 by the United States Food and Drug Administration (FDA).[12,13] To avoid dosing errors, it is currently available for administration through pens and vials with the dedicated U-500R syringe.[14] U-500R has unique prandial/basal actions[15] and thus can be used as insulin monotherapy. However, the safety and efficacy of U-500R used in combination with other insulins has not yet been determined. Also, the safety and efficacy of U-500R delivered by continuous subcutaneous infusion is been determined in a recent clinical study.[16] An open-label trail evaluated transitioning from high-dose U-100 to U-500R and demonstrated that similar reduction in A1c could be achieved with twice or thrice-daily regimens of U-500R, which mitigate physical discomfort and potential barriers to adherence associated with U-100.[11] Measures of disease burden were reduced with both regimens while the compliance domain improved in patients receiving U-500R.[17] In the real-world setting, U-500R (vial) has been shown to improve glycated hemoglobin (HbA1c) levels among patients with T2DM,**Error! Bookmark not defined.** and is associated with lower health care costs and better adherence than U-100 users prescribed a similar dose.[17,18]A recent real-world study found that, U-500R Kwikpen initiation was associated with a clinically significant drop (~0.7% drop) in HbA1c accompanied by an average increase of 0.21 hypoglycemic event per year after adjusting for age, gender, race, BMI, CCI score, and TDD. [19] The insulin dose increased more than 80 units/day on

average after U-500R Kwikpen initiation and the medication adherence as measured by PDC improved.[19]

The use of U-500R has evolved over time and this is especially the case with the introduction of U-500R Kwikpen in 2016. Physicians and patients have found different ways to utilize U-500R in real-life setting , resulting in the real-world utilization of U-500R to be divergent from the FDA label indication. This is likely attributed to the need of prescribing individualized dose based on patient's specific metabolic needs, glucose level, and goal of glycemic control.[20] Physicians are becoming more familiar with the concentrated insulins and recognized benefit of U-500R brought by reduced volume, fewer injections, and insulin monotherapy for patients who may or may not be on more than 200 units/day of insulin. Moreover, U-500R Kwikpen offers a more convenient option than syringe for patients. Currently, at least 50% of U-500R patients use Kwikpen and the proportion is still increasing (internal data-on-file). We have noticed that in a large ongoing, real-world study, 62% patients had an average TDD of ≤200 units before initiating U-500R via Kwikpen, and 27% of the T2DM patients remained on TDD≤200 units after Kwikpen initiation.[19]

In addition, off-label continuous subcutaneous insulin infusion (CSII) administration has been employed by roughly 20% of the U-500R users.[21] A RCT has recently demonstrated the safety and efficacy of U-500R together with improved patient reported outcomes.[16,19]

Currently, the treatment patterns, compliance, and outcomes with U-500R among those who did not utilize U-500R consistent with the FDA label in the real-world setting is unknown. Neither is the treatment patterns, adherence behavior, and outcomes among those who did utilize U-500R in the manner that was consistent with FDA label. All previous real-world evidence (RWE) studies have studied all available U-500R patients (full RWE cohort) without distinguishing the manner that U-500R was utilized although more recent studies revealed a significant amount of off-label use. Therefore, as part of a series of studies for U-500R, the aim of this study is to examine the treatment patterns, compliance, effectiveness and safety outcomes among those utilizing U-500R consistently with the FDA label (high-dose cohort). Another study will be conducted in parallel to understand those who did not utilize U-500R consistently with the FDA label (Lower-dose cohort). Prior to any analysis, it is necessary to capture the real-world definition for the high-dose population based on the prescribing pattern and insulin titration consideration. In a clinical trial conducted by Hood et al, a reduction of dose up to 20% in the first U-500R insulin dose was recommended, and to keep patients at target the dose of insulin was titrated to a target with a -10% to +15% dose change with all insulins. At the end of the study, 2.3% of patients were taking ≤150 units of insulin and 11.2% were on ≤200 units of insulin.[15] Similar treat to target algorithms were also used in another clinical trial conducted by Grunberger et al.[16] Given these attributes, a 10% reduction of recommended dose of U-500 insulin (>180 units) is justifiable to define the high-dose cohort. Additionally, in a large ongoing real-world study evaluating the treatment patterns among U-500R initiators, U-500R syringe initiators and U-500R Kwikpen initiators had a mean TDD of 198 ± 78 units (median: 189 units) and 188 ± 72 units (median: 176 units), respectively. This data suggest that exclusion of patients receiving a TDD of <180 units in both U-500R syringe and Kwikpen cohorts (which consists of >25% of all observed patient data) would most likely yield an aggregate median and mean TDD>200 units of insulin which is consistent with Humulin R-U500

FDA approved label. In this study, we will evaluate patient characteristics, treatment patterns, treatment compliance, treatment outcomes (including HbA1c and hypoglycemia), and insulin-related out-of-pocket pharmacy costs among T2DM patients who initiated U-500R high-dose, defined by having an average TDD >180 units/day both before and after U-500R initiation, insulin monotherapy with U-500R after initiation with no evidence of pump use (instead of 200 units/day).

As pointed out by Hood et al 2015, compliance may be an issue among patients who were on high dose U-100 insulin. However, there are multiple aspects to the medication compliance.[15] According to Cramer et al 2008, compliance "refers to the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency.[22] It may be defined as "the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen." Since insulin treatment is required for patients on a daily basis, for practical purpose, adherence is measured by proportion of days covered (PDC). Dosage, calculated as both total daily dose (TDD) and average daily dose (ADD), is another compliant aspect that is critical to the outcomes of insulin treatment. However, with claims data, the observed dosage reflects only the amount of insulin purchased by a patient, not the actual dose taken or prescribed. Nevertheless, comprehensively comparing PDC and TDD/ADD together with treatment outcomes (HbA1c, hypoglycemia) before and after U-500R initiation will provide a picture on how U-500R might affect the medication compliance and its impact on outcomes. Since this study focuses on only high-dose cohort, we will refrain from studying medication persistence defined as "the duration of time from initiation to discontinuation of therapy." This is because, to ensure only patients with U-500R insulin monotherapy were included in the high-dose cohort, the exclusion criteria used will remove any patient that had more than one insulin use in the post-index period and inadvertently remove some patients who had early U-500R discontinuation and switched to other therapies. Medication persistence has been studied in the full RWE cohort.

Before U-500R use, the patients should be on basal-bolus regimen with more than one type of insulins. In contrast, U-500R is an insulin monotherapy. Because each type of insulin requires a copay at each refill, for the same amount of insulin purchased, it is likely more than one copay is required for basal-bolus regimen while only one copay is needed for U-500R. It is hypothesized that U-500R may have the potential to help reduce the out-of-pocket costs for patients while helping patients achieving their necessary insulin dose requirement. However, there is evidence that patients needed high dose insulin may be under-insulinized before switching to U-500R.[15,19] These patients may have skipped a large amount of insulin as a result of avoiding injection pain or inconvenience due to large injection volume and multiple injections with multiple insulins. Under use is likely to lead to under purchase. Since the out-of-pocket costs would be dependent of the amount of insulin purchased, an artificially low out-of-pocket cost may be observed before U-500R initiation. In this study, we will examine the out-of-pocket costs together with other outcomes variables to understand whether this hypothesized scenarios played out in the real-world setting. We will further employ appropriate methodology to understand the factors that affect the out-of-pocket costs level and test whether the out-of-pocket costs differed before and after U-500R initiation after taking into consideration the factors that may affect the insulin purchasing behavior. In this study we will focus on out-of-pocket costs of those in the high-dose cohort. It is also interesting to see if the higer-dose cohort in this study may exhibit a different pattern of out-of-

pocket costs from the lower-dose cohort in a parallel study. Please note that no statistical comparison will be made between the high-dose and the lower-dose cohorts as this is not the interest of the current study.

The treatment patterns and outcomes of two sub-groups are of great interests. The first subgroup is the elderly. Given the highly concentrated nature of U-500R, physicians have hesitation in using U-500R with their elderly patients. Even though elderly accounted for about 50% of the U-500R initiators in an ongoing study (full RWE cohort), no studies have explicitly examined the safety and efficacy of U-500R in elderly. Information on the effectiveness and safety of U-500R among elderly will be valuable to HCPs and patients. The other subgroup of interests are those whose U-500R daily dose is in the range of 201-300 units/day. While most physicians are confident with the use of U-500R when patients insulin needs exceed 300 units/day, this is not the case in the range of 201-300 units for some physicians. Currently only less than 20% of patients on 201-300 units/day insulins use U-500R (internal data-on-file). Therefore, it is important to understand the compliance, effectiveness, and safety among those who were on 201-300 units/day of U-500R insulin. Additionally, the U-500R Kiwkpen was launched in 2016. Therefore, a 9-months pre- and post-index period will be applied in the VHA to ensure adequate sample size due to the recent launch of the Kwikpen. Since VHA does not have reliable cost data, Truven database is used to understand out-of-pocket costs and will be assessed using a 12-months pre- and post-index period to ensure deductibles are properly caputured for all patients.

The aim of this study is to provide a comprehensive understanding of U-500R in high-dose cohort (defined by having an average TDD of >180 units per day, with no additional insulin used concomitantly with U-500R or pump use), including compliance, effectiveness, safety, and out-of-pocket costs, rather than just one particular aspect of U-500R. Ideally, an integrated database with both claims and EMR data will be needed for such a study. Unfortunately, while VHA database is an integrated claims and EMR database, it lacks reliable costs data. As a result, out-of-pocket costs aspect will be examined separately using IBM MarketScan data.

4. Objectives

4.1 Research Objectives

Research Objective 1: Treatment Patterns

- **Primary Objective 1:** Evaluate the patient characteristics and treatment patterns of insulin including observed TDD in claims, adherence, prescription fill rate, claim gaps, and concomitant medication use among T2DM patients before and after high-dose U-500R syringe initiation and high-dose U-500R Kwikpen initiation separately, as well as before and after any High-dose U-500R initiation
  - Characterize high-dose U-500R Kwikpen patients, syringe patients, and any high-dose U-500R initiators
  - Determine differences between treatment patterns before and after high-dose U-500R Kwikpen initiation
  - Determine differences between treatment patterns before and after high-dose U-500R syringe initiation
  - Determine differences between treatment patterns before and after any high-dose U-500R initiation
  - Determine differences between treatment patterns among elderly T2DM patients (≥65 years) before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and any high-dose U-500R initiation
  - Determine differences between treatment patterns before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and any high-dose U-500R initiation among T2DM patients whose TDD is 201-300 units/day in the post-index
  - Determine differences between treatment patterns before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and any high-dose U-500R initiation among T2DM patients whose TDD is >300 units/day in the post-index (optional)
  - Evaluate factors associated with insulin adherence among high-dose U-500R Kwikpen initiators, high-dose U-500R syringe initiators, and any high-dose U-500R initiators
  - Evaluate factors associated with insulin adherence among elderly T2DM patients (≥65 years) as well as among patients by dose range 201-300 units/day, >300 units/day (optional), before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and any high-dose U-500R initiation

Research Objective 2: Treatment Outcomes

- **Primary Objective 2:** Evaluate the HbA1c level among T2DM patients before and after high-dose U-500R syringe initiation and high-dose U-500R Kwikpen initiation separately, as well as before and after any high-dose U-500R initiation

- Determine differences between HbA1c level before and after high-dose U-500R Kwikpen initiation
- Determine differences between HbA1c level before and after high-dose U-500R syringe initiation
- Determine differences between HbA1c level before and after any high-dose U-500R initiation
- Determine differences between HbA1c level among elderly T2DM patients (≥65 years) before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and any high-dose U-500R initiation
- Determine differences between HbA1c level before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and any high-dose U-500R initiation among T2DM patients whose TDD is 201-300 units/day in the post-index
- Determine differences between HbA1c level before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and any high-dose U-500R initiation among T2DM patients whose TDD is >300 units/day in the post-index (optional)
- Evaluate factors associated with HbA1c level in the pre-and post-index periods among high-dose U-500R Kwikpen initiators, high-dose U-500R syringe initiators, and any high-dose U-500R initiators
- Evaluate factors associated with HbA1c level in the pre-and post-index periods among elderly T2DM patients (≥65 years), as well as among patients by dose range 201-300 units/day, >300 units/day (optional), before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and any high-dose U-500R initiation

❖ **Secondary Objective 2a:** Evaluate the hypoglycemic events among T2DM patients before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation separately, as well as before and after any high-dose U-500R initiation

- Determine differences between hypoglycemia events before and after high-dose U-500R Kwikpen initiation
- Determine differences between hypoglycemia events before and after high-dose U-500R syringe initiation
- Determine differences between hypoglycemia events before and after any high-dose U-500R initiation
- Determine differences between hypoglycemia events among elderly T2DM patients (≥65 years) before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and any high-dose U-500R initiation
- Determine differences between hypoglycemia events before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and any high-dose U-500R initiation among T2DM patients whose TDD is 201-300 units/day in the post-index

- Determine differences between hypoglycemia events before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and any high-dose U-500R initiation among T2DM patients whose TDD is >300 units/day in the post-index (optional)
- Evaluate factors associated with the number of hypoglycemia events in the pre-and post-index periods among high-dose U-500R Kwikpen initiators, high-dose U-500R syringe initiators, and any high-dose U-500R initiators
- Evaluate factors associated with the number of hypoglycemia events in the pre-and post-index periods among elderly T2DM patients (≥65 years) as well as among patients by dose range 201-300 units/day, >300 units/day (optional), before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and any high-dose U-500R initiation

Research Objective 3: Health Care Costs

❖ **Expoloratory Objective 3:** Evaluate out-of-pocket pharmacy costs (all-cause, diabetes-related, and insulin-related) before and after high-dose U-500R syringe initiation and high-dose U-500R Kwikpen initiation separately, as well as before and after any high-dose U-500R initiation Determine differences between out- of- pocket pharmacy costs before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and any high-dose U-500R initiation

- Determine what the costs will be if the patient did not change the dose from their pre-index among high-dose U-500R Kwikpen initiators
- Determine what the costs will be if the patient did not change the dose from their pre-index among high-dose U-500R syringe initiators
- Determine what the costs will be if the patient did not change the dose from their pre-index among any high-dose U-500R initiators
- Evaluate the mediator effect of adherence and observed TDD on insulin-related pharmacy costs among high-dose U-500R Kwikpen initiators
- Evaluate the mediator effect of adherence and observed TDD on insulin-related pharmacy costs among high-dose U-500R syringe initiators
- Evaluate the mediator effect of adherence and observed TDD on insulin-related pharmacy costs among any high-dose U-500R initiators

5. Research Design

5.1 Summary of Research Design

This will be a retrospective cohort study using the Veterans Health Administration (VHA) database and the Truven® MarketScan® claims databases.

Study outcomes will be assessed using multiple datasets to ensure availability of target outcomes (e.g., out-of-pocket costs are available in the Truven dataset but not the VHA dataset; HbA1c data are available in the VHA dataset but not the Truven dataset). Furthermore, the patient population in the VHA primarily consists of veterans across the country (non-commercial database), whereas Truven is an employment-based health insurance (commercial database). Therefore, conducting the analysis separately in each of these databases will give a more comprehensive and complete picture of the real-world treatment patterns and outcomes in this patient population.

- To meet the analytical requirement of multiple research objectives, the following criteria will be used:
  - The first prescription claim date for U-500R syringe or U-500R Kwikpen administration will be considered U-500R initiation and designated as Index Event (syringe: Index Event **a**; Kwikpen: Index Event **b**; Any U-500R use: Index Event **c**).
  - The study period will range from 01APR2013–31MAR2018 for VHA; and 01JUL2013–30JUN2018 for Truven MarketScan claims.
  - The identification period will be 01JAN2014–30JUN2017 for VHA; and 01JUL2014–30JUN2017 for Truven MarketScan claims; the pre- and post-index periods will be 9 months for the VHA and 12 months for the Truven databases, respectively (Figures 1-3).

Figure 1 Study Design for U-500R Syringe Initiation (Index Event a)

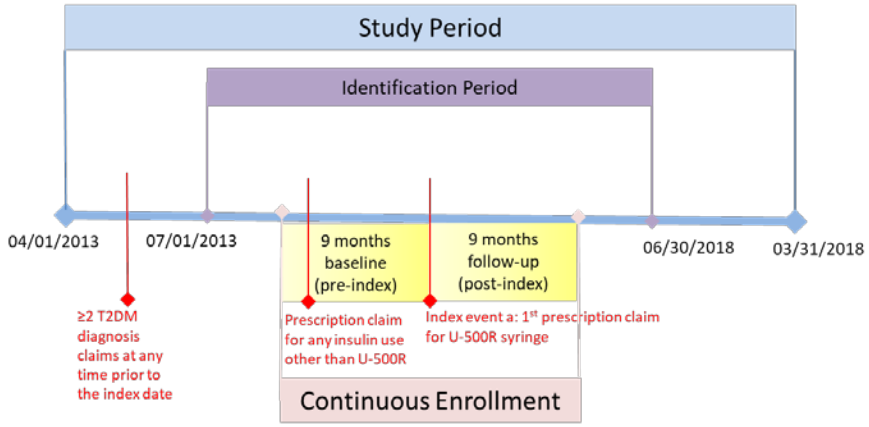


Figure 2 Study Design for U-500R Kwikpen Initiation (Index Event b)

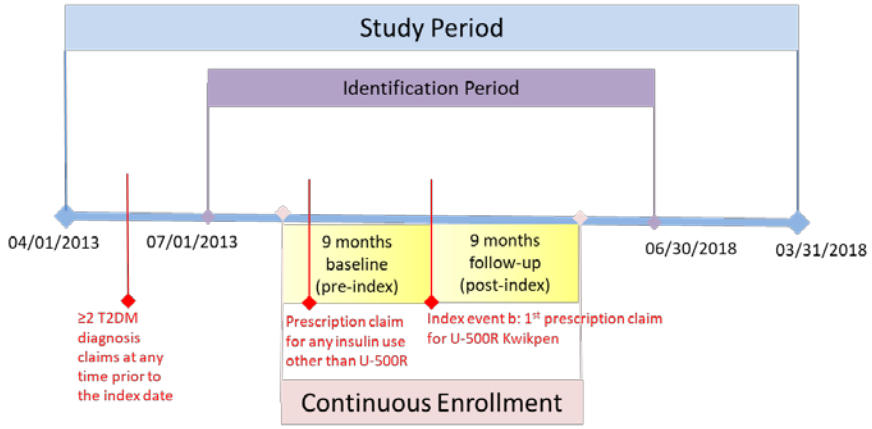
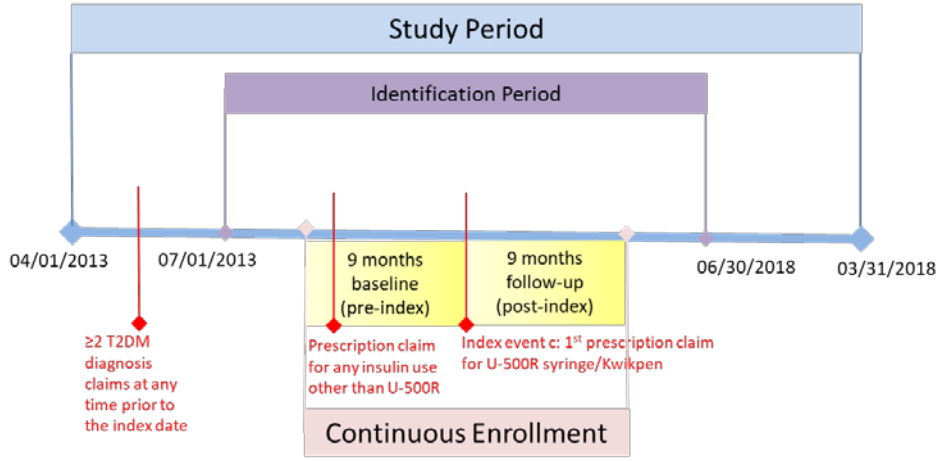


Figure 3 Study Design for Any U-500R Initiation (Index Event c)



Note: The figures above depict a schematic representation of the study design using the study periods for the VHA database. For analysis conducted in the Truven database, a 12-month pre-index period and a 12-month post-index period will be used instead of 9 months to ensure deductibles are properly captured for all patients.

5.2 Data Source

Truven MarketScan Claims Database (01JUL2013-30JUN2018)

MarketScan offers the largest proprietary claims-based convenience sample available, with 69 million unique patients since 1996. In the most recent data year, the databases contain data on 29 million covered lives. The stability of MarketScan data sources allows superior continuity of patients over multiple years, which is generally longer than other claims databases. This is due to the fact that the majority of the data is sourced from large employers. Employer-provided data also allow tracking of patients across health plans. This tracking ability is useful because people change health plans more often than they change jobs, and these data are able to capture patients who are "lost" in plan-based data sources—upward of 17% of patients in those databases. In the most recent 5 years of MarketScan data, nearly 29 million patients (73%) have at least 12 months of continuous enrollment.

The MarketScan claims databases contain complete information on outpatient prescriptions. These databases afford distinct advantages over others that track only prescription fills, as the data allow for disease type identification (from medical claims) and can be used to determine whether clinical, demographic, and provider characteristics influence prescribing patterns. Because individual patients' prescription fills are recorded, therapies prescribed concurrently (and presumably used in combination) can also be identified. This provides vital information about actual drug use patterns, as opposed to individual drug prescription trends.

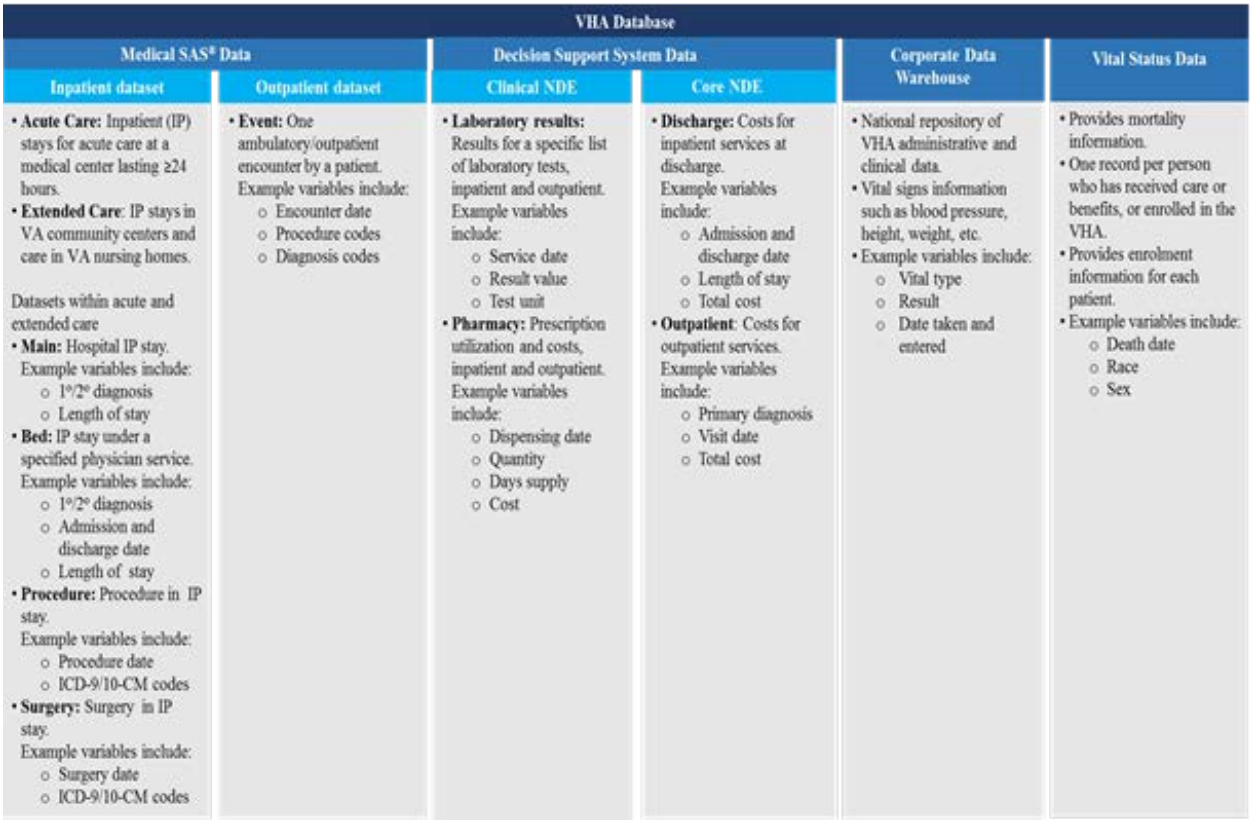
VHA Database (01APR2013-31MAR2018)

The VHA is the largest integrated health care system in the US, providing quality care at efficient prices for >9 million veterans across the country. According to VA estimates, there were about 22 million living US veterans in 2014.[23]

The size and structure of the VHA system differs from most private care organizations. The system includes:

- 153 medical centers;
- 136 nursing homes;
- 207 Vet Centers;
- 882 ambulatory care and community-based outpatient clinics;
- 45 residential rehabilitation treatment programs;
- 92 comprehensive home-based care programs;
- 13,000 physicians;
- nearly 55,000 nurses; and
- >9 million enrollees[24,25]

Figure 4 **VHA Data Elements**



IP: inpatient stays; NDE: National Data Extracts; VA: Veterans Administration; 1º/2º: primary/secondary.

The VHA Medical SAS® datasets are national administrative data for VHA-provided health care used by veterans. The datasets are provided in SAS format by fiscal year (01OCT–30SEP). These data are extracted from the National Patient Care Database and maintained by the VHA Office of Information at the Austin Information Technology Center (the central repository for VA data).

VHA Medical SAS Inpatient Datasets

The Medical SAS Inpatient datasets cover the care received in acute, extended care settings. Within these categories, there are 4 datasets:

- main—a patient's inpatient stay (episode of care);
- bed section—a patient's inpatient stay under a specified physician treating for a specialty service;
- procedure—1 day's procedure during an inpatient stay; and
- surgery—1 day's surgery during an inpatient stay.

Inpatient variables describing each hospital admission include date, time, facility, and the primary diagnosis at admission. Discharge data include date, time, destination (e.g., home, hospice,

community nursing home), type of discharge (e.g., regular, transfer to another hospital, death), and length of stay (LOS).

VHA Medical SAS Outpatient Datasets

Each outpatient data record represents 1 date of service for 1 outpatient and includes the facility identifier, date, and time of visit. Visits on a single day to multiple clinics, laboratories, and treatment programs are reported.

Outpatient care is reported by diagnoses (ICD-9-CM and ICD-10-CM codes) and procedures (CPT codes), including dates and times.

Currently, there is 1 Medical SAS dataset for outpatient care:

- Event: 1 ambulatory encounter (coded as Decision Support System [DSS] Identifier).

VHA Decision Support System

The VHA DSS is a managerial cost accounting system based on the commercial software Eclipsys©. The VHA must populate data elements required to allocate VHA costs to VHA products (goods and services provided during patient care). Towards that end, the VHA has modified Eclipsys to interact with VistA and other VA national databases. The VHA DSS was introduced in 1994 and fully implemented in all facilities by 1999.

The VHA DSS data files comprise a longitudinal, secondary relational database combining selected clinical and cost data. The DSS provides a mechanism for integrating expenses, workload, and patient utilization. DSS information supports process and performance improvements by measuring quality of care, clinical outcomes, and financial impact. Within a fiscal year, periodic rollups of production data are performed to produce year-to-date, non-destructive examinations.

DSS Clinical National Data Extract

- Laboratory Results: laboratory test results for a specific list of tests (inpatient and outpatient)
- Pharmacy: pharmacy prescription utilization and costs (inpatient and outpatient)

VA Vital Status Files

The VHA Vital Status File (VSF) contains the date of death for veterans and eligible non-veterans who have received care from the VHA since 1992, have enrolled in the VHA, or have received compensation or pension benefits from the VHA since 2002. The VHA VSF file is updated quarterly.

Sources for vital status available to the VA include the VA Beneficiary Identification and Record Locator System, the Death Master File from the Social Security Administration (SSA), patient treatment file, and Medicare vital status. The primary source for dates of death in the Vital Status file is the SSA Death Master File. The impetus for the development of the VHA VSF was the VA Information Resource Center's (VIReC) Veterans Administration National Death Index (NDI) Data Merge Project. This work was supported by funding from the Health Services Research and

Development Service (SDR 03-157) and VIReC (SDR 98-004). The project compared the dates of death from sources available within the VA to those obtained from the NDI, a repository of data from death certificates that is considered the gold standard for mortality data in the United States. The study found that using a combination of the available death data sources in the VA resulted in death ascertainment nearly as complete as using the NDI.

The stability of VHA data sources allows for superior analysis of the continuity of care of patients over multiple years.

Data Limitations

While claims data are extremely valuable for the efficient and effective examination of health care outcomes, they are collected for administration and not research. Therefore, the use of claims data has certain limitations. For example, the presence of a claim for a filled prescription does not indicate that the medication was consumed or taken as prescribed. Medications filled over-the-counter or provided as samples by the physician cannot be observed in the claims data. The presence of a diagnosis code on a medical claim does not necessarily indicate a positive presence of disease, as the diagnosis code may be incorrect or included as rule-out criteria rather than actual disease. And certain information that is not readily available in claims could influence study outcomes, such as clinical and disease-specific parameters.

5.3. Study Population

5.3.1 Selection Criteria

U-500R Syringe Initiators [Index Event **a**]

Inclusion Criteria

Patient will be included if they:

- had ≥1 prescription claim for U-500R vial during the identification period (VHA: 01JAN2014–30JUN2017; Truven: 01JUL2014–30JUN2017), with the first prescription claim for U-500R vial designated as index Event a (U-500R syringe initiation), and the date designated as the index date;
- had ≥2 claims with an ICD-9/10-CM code (Appendix 1) for T2DM in any position (primary/secondary) at any time prior to the index date;
- were aged ≥18 years on the index date;
- had continuous health plan enrollment with medical and pharmacy benefits for ≥9 months pre- and post-index event;
- had ≥1 prescription claim for any insulin other than U-500R in the pre-index period;
- had ≥1 HbA1c measurement within 90 days pre-index or 30 days post-index event;
- had ≥1 HbA1c measurement after the 30-day post-index period at any time in the 9-month post-index period;

- had claims indicating TDD >180 in the post-index period;
- had claims indicating TDD >180 in the pre-index period; and

Exclusion Criteria

Patient will be excluded if they:

- had both T1DM and T2DM, had no oral anti-diabetic drug (OADs; Appendix 1) other than metformin, and the ratio between the number of T1DM and T2DM claims >0.5 at any time in the study period (VHA: 01APR2013–31MAR2018; Truven: 01JUL2013–30JUN2018);
- had previous use of U-500R in the 9-month pre-index period;
- had ≥1 claim with an ICD-9/10-CM code (Appendix 1) for secondary diabetes, gestational diabetes, diabetes complicating pregnancy, childbirth, puerperium, or non-clinical diabetes at any time during the 9-month pre-index period;
- had claims indicating pump use (Appendix 2) in the 9-month post-index (follow-up) period;
- had claims indicating TDD above 2000 units/day at any time in the pre-index or post-index periods; or
- had claims indicating insulin use other than U-500R in the post-index period.

U-500R Kwikpen Initiators [Index Event **b**]

Inclusion Criteria

Patient will be included if they:

- had ≥1 prescription claim for U-500R Kwikpen administration during the identification period (VHA: 01JAN2014–30JUN2017; Truven: 01JUL2014–30JUN2017), with the first prescription claim for U-500R Kwikpen administration designated as Index Event **b**, and the date designated as the index date;
- had ≥2 claim with an ICD-9/10-CM code (Appendix 1) for T2DM in any position (primary/secondary) at any time prior to the index date;
- were aged ≥18 years on the index date;
- had continuous health plan enrollment with medical and pharmacy benefits for ≥9 months pre- and post-index event;
- had ≥1 prescription claim for any insulin other than U-500R (Table 1) in the pre-index period;
- had ≥1 HbA1c measurement within 90 days pre-index or 30 days post-index event;
- had ≥1 HbA1c measurement after the 30-day post-index period at any time in the follow-up period;
- had claims indicating TDD >180 in the post-index period;

- had claims indicating TDD >180 in the pre-index period; and

Exclusion Criteria

Patient will be excluded if they:

- had both T1DM and T2DM, had no OADs (Appendix 1) other than metformin, with the ratio between the number of T1DM and T2DM claims >0.5 at any time in the study period (VHA: 01APR2013–31MAR2018; Truven: 01JUL2013–30JUN2018);
- had previous use of U-500R in the 9-month pre-index period;
- had ≥1 claim with a ICD-9/10-CM code (Appendix 1) for secondary diabetes, gestational diabetes, diabetes complicating pregnancy, childbirth, puerperium, or non-clinical diabetes at any time during the pre-index period;
- had evidence of pump use (Appendix 2) in the post-index period;
- had claims indicating TDD above 2000 units/day at any time in the pre-index or post-index periods; or
- had claims indicating insulin use other than U-500R in the post-index period.

Sample selection criteria for any U-500R Initiators [Index Event **c**]

Inclusion Criteria

Patient will be included if they:

- had ≥1 prescription claim for U-500R syringe or Kwikpen administration during the identification period (VHA: 01JAN2014–30JUN2017; Truven: 01JUL2014–30JUN2017), with the first prescription claim for U-500R syringe or Kwikpen administration designated as Index Event **c**, and the date designated as the index date;
- had ≥2 claim with an ICD-9/10-CM code (Appendix 1) for T2DM in any position (primary/secondary) at any time prior to the index date;
- were aged ≥18 years on the index date;
- had continuous health plan enrollment with medical and pharmacy benefits for ≥9 months pre- and post-index event;
- had ≥1 prescription claim for any insulin other than U-500R (Table 1) in the pre-index period ;
- had ≥1 HbA1c measurement within 90 days pre-index or 30 days post-index event;
- had ≥1 HbA1c measurement after the 30-day post-index period at any time in the follow-up period;
- had claims indicating TDD >180 in the post-index period; and
- had claims indicating TDD >180 in the pre-index period

Exclusion Criteria

Patient will be excluded if they:

- had both T1DM and T2DM, had no OADs (Appendix 1) other than metformin, with the ratio between the number of T1DM and T2DM claims >0.5 at any time in the study period (VHA: 01APR2013–31MAR2018; Truven: 01JUL2013–30JUN2018);
- had previous use of U-500R in the 9-month pre-index period;
- had ≥1 claim with a ICD-9/10-CM code (Appendix 1) for secondary diabetes, gestational diabetes, diabetes complicating pregnancy, childbirth, or puerperium, or non-clinical diabetes at any time during the pre-index period;
- had evidence of pump use (Appendix 2) in the follow-up period;
- had claims indicating TDD above 2000 units/day at any time in the pre-index or post-index periods; or
- had claims indicating insulin use other than U-500R in the post-index period.

Note:

- All high-dose U-500R patients will be defined by having an average TDD of >180 units per day, with no additional insulin used concomitantly or no U-500R pump use.
- Since the Truven claims database does not include lab data, the ≥1 HbA1c criterion will be removed from the selection criteria while using this database.
- For analysis conducted using the Truven claims database, the pre-index period and the post-index period will be 12 months instead of 9 months.
- The corresponding ICD-9/10 codes for all the diagnoses and the NDC codes for the insulin treatments are provided in Appendix 1.

Subgroup analysis:

- Elderly (≥65 years) patients among each of the high-dose U-500R Kwikpen, high-dose U-500R syringe, and any high-dose U-500R initiator cohorts will be flagged, and a subgroup analysis will be performed comparing the treatment patterns and outcomes (HbA1c and hypoglycemia) before and after U-500R initiation.
- Patients with a TDD of 201-300 units in the post-index period among each of the high-dose U-500R Kwikpen, high-dose U-500R syringe, and any high-dose U-500R initiator cohorts will be flagged, and a subgroup analysis will be performed comparing the treatment patterns and outcomes (HbA1c and hypoglycemia) before and after U-500R initiation.
- (Optional): Patients with a TDD of >300 units in the post-index period among each of the high-dose U-500R Kwikpen, high-dose U-500R syringe, and any high-dose U-500R initiator cohorts, and a subgroup analysis will be performed comparing the treatment patterns and outcomes (HbA1c and hypoglycemia) before and after U-500R initiation.

Table 1. Classification of Insulin Products

Insulin Class	Generic Name	Product Name
Inhaled Insulin	Insulin Human Inhaled	AFREZZA
		EXUBERA
		EXUBERA COMBINATION PACK 12
		EXUBERA COMBINATION PACK 15
		EXUBERA KIT
Intermediate-acting Insulin	Insulin Human Zinc (lente)	HUMULIN L
	Insulin Human Isophane (nph)	HUMULIN N (NPH)
		HUMULIN N (NPH) KWIKPEN
		HUMULIN N PEN
		INSULATARD HUMAN INSULIN
		MIXTARD HUMAN INSULIN 70/30
		NOVOLIN N
		NOVOLIN N (NPH)
		NOVOLIN N INNOLET
		NOVOLIN N PENFILL
		RELION HUMULIN N
		RELION NOVOLIN N INNOLET
Long-acting Insulin	Insulin Glargine Soln Pen-Injector	Basaglar KwikPen
	Insulin Glargine, Recombinant	LANTUS
		LANTUS SOLOSTAR
	Insulin Detemir	LEVEMIR
		LEVEMIR FLEXPEN
		LEVEMIR FLEXTOUCH
	Insulin Glargine, Recombinant	TOUJEO
	Insulin Degludec	TRESIBA
Pre-mixed Insulin	Insulin Lispro Protamine/Insulin Lispro	HUMALOG MIX 50/50
		HUMALOG MIX 75/25
		HUMALOG MIX 75/25 PEN
	Insulin Human Isophane (nph)/Insulin Human Regular	HUMULIN
		HUMULIN 50/50
		HUMULIN 70/30
		HUMULIN 70/30 KWIKPEN
		HUMULIN 70/30 PEN

Insulin Class	Generic Name	Product Name
	Insulin Beef Regular/Insulin Pork Isophane (nph)	ILETIN NPH I
	Insulin Human Isophane (nph)/Insulin Human Regular	NOVOLIN 70/30
		NOVOLIN 70/30 INNOLET
		NOVOLIN 70/30 PENFILL
	Insulin Aspart Protamine/Insulin Aspart	NOVOLOG MIX 70/30
		NOVOLOG MIX 70/30 FLEXPEN
	Insulin Human Isophane (nph)/Insulin Human Regular	RELION HUMULIN 70/30
		RELION NOVOLIN 70/30
		RELION NOVOLIN 70/30 INNOLET
Rapid-acting Insulin	Insulin Glulisine	APIDRA
		APIDRA SOLOSTAR
	Insulin Lispro, Recombinant	HUMALOG
		HUMALOG KWIKPEN
		HUMALOG PEN
		LISPRO-PFC
	Insulin Aspart, Recombinant	NOVOLOG
		NOVOLOG FLEXPEN
		NOVOLOG PENFILL
Short-acting Insulin	Insulin Human Regular, Buffered	HUMULIN BR
	Insulin Human Regular	HUMULIN R
		INSULIN HUMAN REGULAR
		NOVOLIN 70/30 PENFILL
		NOVOLIN N PENFILL
		NOVOLIN R
		NOVOLIN R INNOLET
		NOVOLIN R PENFILL
		RELION HUMULIN R
		RELION NOVOLIN R
	Insulin Human Regular, Buffered	VELOSULIN BR
U-500R	Insulin Human Regular	HUMULIN R CONCENTRATED U-500
		HUMULIN R CONCENTRATED U-500 KWIKPEN
	INSULIN REGULAR (HUMAN)	HUMULIN R U-500 KWIKPEN

5.3.2 Subject Groups

After applying the selection criteria, our analysis will focus on the following cohorts.

Index Event a

- high-dose U-500R Syringe Initiators Cohort: Patients who initiated U-500R syringe administration (Index Event **a**) on their index date.

Index Event b

- High-dose U-500R Kwikpen Initiators Cohort: Patients who initiated U-500R Kwikpen administration (Index Event **b**) on their index date.

Index Event c

- Any high-dose U-500R Initiators Cohort: Patients who initiated U-500R (vial or Kwikpen; Index Event **c**) on their index date. The first prescription claim for vial or Kwikpen will be defined as the index date.

Note: In each of the abovementioned cohorts, subgroups of elderly patients (≥65 years), patients with TDD 201-300 units/day and (optional) those who had TDD >300 units/day will be identified for the subgroup analysis.

5.4 Time Periods

The study period will range from 01APR2013–31MAR2018 for VHA, and 01JUL2013–30JUN2018 for Truven MarketScan claims. The identification period will be 01JAN2014–30JUN2017 for VHA, and 01JUL2014–30JUN2017 for Truven MarketScan claims. The pre-index and post-index periods will be 9 months for the VHA and 12 months for the Truven MarketScan database, respectively (Figures 1-3).

5.5 Variables/Measures

Table 2 presents the study variables and operational definitions.

Table 2 Variables and Definitions

Variable	Source	Definition
Exposure		
Insulin use	Truven: Outpatient pharmacy claims table VHA: Pharmacy file	Index Event **a**: any insulin use other than U-500R in the pre-index and high-dose U-500R syringe use in the post-index period Index Event **b**: any insulin use other than U-500R in the pre-index and high-dose U-500R Kwikpen use in the post-index period Index Event **c**: any insulin use other than U-500R in the pre-index and high-dose U-500R Kwikpen/syringe use in the post-index period
Patient Characteristics*		

Variable	Source	Definition
Age	Truven: Inpatient service table, outpatient service table, outpatient pharmacy claims table VHA: Enrollment file	Age will be retained in the dataset as a continuous variable for groups aged 18-25, 26-35, 36-45, 46-55, 56-64, and ≥65 years.
Sex	Truven: Inpatient service table, outpatient service table, outpatient pharmacy claims table VHA: Enrollment file	A flag will be created for male and female patients.
Race (only VHA)	VHA: Enrollment file	A flag will be created for white, black, and other race patients.
US Region (only Truven)	Truven: Inpatient service table, outpatient service table, outpatient pharmacy claims table	A flag will be created for patients residing in the Northeast, Northcentral, South, and West US regions.
Medicare eligibility (only Truven)	From Truven	A flag will be created for patients who are enrolled in Truven Medicare.
Body mass index (BMI)	VHA: Vital Status file	BMI on the index date will be calculated and reported as a continuous variable.
Quan-Charlson comorbidity index (CCI) score[26]	Truven: Inpatient service table, outpatient service table VHA: Inpatient and outpatient files	Quan-CCI score will be constructed using enhanced ICD-9/10-CM codes for 17 different comorbid conditions.
Individual Comorbidities[27]	Truven: Inpatient service table, outpatient service table VHA: Inpatient and outpatient files	A flag will be created using ICD-9/10-CM codes (Appendix 1) for patients diagnosed in the pre-index period with any of the following individual comorbidities: retinopathy, nephropathy, neuropathy, coronary artery disease, peripheral vascular disease, congestive heart failure, hypertension, depression, obesity, or malignant tumor.
Health Economics Outcomes Research (HEOR) Outcomes		

Variable	Source	Definition
Observed TDD in claims	Truven: Outpatient pharmacy claims table VHA: Pharmacy file	The observed insulin TDD will be calculated as the total number of insulin units/total unique days of supply as recorded in claims and will be calculated both in the pre-and post-index periods among the high-dose U-500R Kwikpen initiators, high-dose U-500R syringe initiators, and any high-dose U-500R initiators. TDD will be reported as both a continuous and categorical variable. <u>For high-dose U-500R syringe initiators (Index Event **a**):</u> Total insulin units correspond to all the insulin units in pre-index and post-index periods, respectively. <u>For high-dose U-500R Kwikpen initiators (Index Event **b**):</u> Total insulin units correspond to all the insulin units in pre-index and post-index periods, respectively. <u>For any high-dose U-500R initiators (Index Event **c**):</u> Total insulin units correspond to all the insulin units in pre-index and post-index periods, respectively. <u>Note:</u> For the unique days supply in patients with evidence of a basal-bolus regimen, or basal/bolus-pre-mixed or basal/bolus-U-500R, the overlap days will be adjusted for the concomitant use of basal and bolus insulin products, but will not be adjusted within basal and within bolus insulins.
Change in observed TDD		The change in observed TDD will be defined as the difference between the pre- and post-index observed TDD.

Variable	Source	Definition
Observed average daily dose (ADD) in claims	Truven: Outpatient pharmacy claims table VHA: Pharmacy file	The observed insulin ADD will be calculated both in the pre-and post-index periods among the high-dose U-500R Kwikpen initiators, high-dose U-500R syringe initiators, and any high-dose U-500R initiators. ADD will be reported as both a continuous and categorical variable. <u>Pre-index ADD:</u> the total number of insulin units/the total number of days in the pre-index period. <u>Post-index ADD:</u> the total number of insulin units/ the total number of days in the post-index period <u>Note:</u> Total insulin units calculation in based on the similar approach as described in TDD.
Adherence	Truven: Outpatient pharmacy claims table VHA: Pharmacy file	Adherence to insulin will be assessed using the proportion of days covered (PDC), and reported in categories of 0-20%, 20-40%, 40-60%, 60-80%, and 80%-100%. PDC will be calculated both in the pre-and post-index periods among the U-500R Kwikpen initiators, U-500R syringe initiators, and any U-500R initiators. <u>For high-dose U-500R syringe initiators (Index Event **a**):</u> PDC before U-500R initiation will be calculated as the number of days covered by the prescription claims of insulin (any insulin)/total days in the pre-index period. PDC after U-500R initiation will be calculated as the number of days covered by the prescription claims of insulin /total days in the post-index period. <u>For high-dose U-500R Kwikpen initiators (Index Event **b**):</u>

Variable	Source	Definition
		PDC before U-500R initiation will be calculated as the number of days covered by the prescription claims of insulin (any insulin)/total days in the pre-index period. PDC after U-500R initiation will be calculated as the number of days covered by the prescription claims of insulin /total days in the post-index period. <u>For any high-dose U-500R initiators (Index Event **c**):</u> PDC before U-500R initiation will be calculated as the number of days covered by the prescription claims of insulin (any insulin)/total days in the pre-index period. PDC after U-500R initiation will be calculated as the number of days covered by the prescription claims of insulin /total days in the post-index period. <u>Note:</u> For the calculation of PDC in patients with evidence of a basal-bolus regimen, basal/bolus-premixed, or basal/bolus-U-500R, the overlap days will be adjusted for the concomitant use of basal and bolus insulins, but will not be adjusted within basal and within bolus insulins.
Abandonment/fill rates	Truven: Outpatient pharmacy claims table VHA: Pharmacy file	The average number of insulin prescription fills will be calculated in the follow-up period among all the study cohorts.
Claim gaps	Truven: Outpatient pharmacy claims table VHA: Pharmacy file	The average gap between prescription fills of insulins will be calculated in the pre- and post-index periods among all the study cohorts.
Concomitant medications [28,29,30]	Truven: Outpatient pharmacy claims table VHA: Pharmacy file	A flag will be created for patients prescribed the following antihyperglycemic agents (AHA):

Variable	Source	Definition
		thiazolidinediones, sulfonylureas, biguanides, meglitinides, alpha-glucosidase inhibitors, DPP-4 inhibitors, SGLT-2 inhibitors, bile acid sequestrants, fixed-dose combinations, GLP-1 receptor agonists, and amylin agonists (Appendix 1).
HbA1c [31]	VHA: Lab file	The HbA1c value in the pre-index and post-index period for each index event will be reported. Pre-index HbA1c will be the HbA1c measurement -90/+30 days of the index date. For patients with multiple HbA1c measurements within this period, the measurement taken closest to the index event date will be reported as the pre-index HbA1c value. The post-index HbA1c value will be the farthest HbA1c measurement taken in the time period after the 30 day-post index event date.
Change in HbA1c		The change in HbA1c will be defined as the difference in the pre-index and post-index HbA1c values.
Hypoglycemic events	Truven: Inpatient service table, outpatient service table VHA: Inpatient and outpatient files, Lab file and Pharmacy file	Hypoglycemia events in the pre- and post-index periods will be evaluated using the ICD-9 codes from the Ginde algorithm (Appendix 1),[32] the presence of a cutoff of blood glucose ≤70 mg/dL, or any evidence of intramuscular glucagon administration (Appendix 1). Hypoglycemia events that occurred on or after the index date will be considered the follow-up hypoglycemia event; and hypoglycemia event occurred on or prior to - 1 day of the index date will be considered as the pre-index hypoglycemia event. The number of hypoglycaemia events per patient per year (PPPY) will be reported in both the pre-and post-index periods.

Variable	Source	Definition
Out-of-pocket costs	Truven: Inpatient service table, outpatient service table, outpatient pharmacy claims table	Out-of-pocket pharmacy costs will be computed among T2DM patients before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and any high-dose U-500R initiation. Out-of-pocket pharmacy costs will be further classified into: • Diabetes-related out-of-pocket pharmacy costs (i.e., the costs associated with any insulins and AHAs [sulfonylureas, TZD, biguanides, meglitinides, alpha-glucosidase inhibitors, DPP-4 inhibitors, SGLT-2, bile acid sequestrant, fixed-dose combination, GLP-1, pramlintide) • Insulin-related out-of-pocket pharmacy costs • All-cause out-of-pocket pharmacy costs (i.e., all the pharmacy costs in the 12 months period) Costs will be adjusted to 2018 US dollars using the annual medical care and drug costs components of the Consumer Price Index (CPI) to reflect inflation.

Note: Treatment pattern in the Truven database will be conducted using the 12-month pre- and post-index period.

6. Sample Size and Statistical Methods

6.1 Determination of Sample Size

The preliminary sample sizes for the VHA databases from 2013–2018 are shown below. This study will use the most recent 5 years of data available.

Table 3. Preliminary Sample Size

Database	Counts
VHA (01APRIL2013–31MARCH2018)	
Kwikpen:	
Evidence of U-500R Kwikpen during the identification period	2,596
Evidence of T2DM	2,536
≥1 HbA1c in the pre-index and post-index periods	741
After applying other inclusion/exclusion criteria and excluding patients with pump use along with U-500R Kwikpen	647
Syringe Use:	
Evidence of U-500R syringe use during the identification period	5,162
Evidence of T2DM	4,956
≥1 HbA1c in the pre-index and post-index periods	1,930
After applying other inclusion/exclusion criteria and excluding patients with pump use along with U-500R syringe	1,766

6.2 Missing Data

Patients with missing demographic information (including age, sex, and race) will be excluded from the study.

6.3 Significance Levels

Two-sided hypothesis testing will be applied to test statistical significance, but multiple testing adjustment for controlling type I error rates will not be applied. A p-value of <0.05 will be considered statistically significant. SAS for Windows Version 9.4 (Cary, NC) will be used for all statistical analyses.

6.4 Other Analyses

6.4.1 Outcomes Analyses

All the analyses will be performed separately in VHA and Truven claims database.

Research Objective 1: Primary Objective 1

Descriptive Analysis

All study variables including demographics, clinical characteristics, and treatment patterns of insulin (i.e., TDD, adherence, prescription fill rate, claim gaps, and concomitant medication use)

will be analyzed descriptively before and after high-dose U-500R Kwikpen initiation, high-dose U-500R syringe initiation, and any high-dose U-500R initiation.

Numbers and percentages will be provided for dichotomous and polychotomous variables. Means and standard deviations (SDs) will be provided for continuous variables. To determine the statistical significance of before and after values, McNemar's test will be used for categorical variables, and the paired t-test will be used for continuous variables.

Multivariate Analysis

A mixed linear model will be used to evaluate factors associated with insulin adherence in the pre- and post-index periods among high-dose U-500R Kwikpen initiators, high-dose U-500R syringe initiators, and any high-dose U-500R initiators. Mixed linear models are used for studies with a longitudinal feature in which a continuous outcome variable is measured for the same subject repeatedly over the time period. Based on the distribution of the data, observations measured for the same subject are likely to be correlated over the study period, and these measurements are considered *multilevel* data. In addition, mixed linear models have a mixed effect consisting of both fixed and random effects. Time-varying and time-invariant variables can both be included in the model. In the current model, adherence (measured at 2 time intervals [before and after the index event: U-500R initiation]) will be considered the dependent variable. Observed TDD will be designated as the time varying covariate in the model (measured both before and after the index event), and the time-independent covariates will include the demographic and clinical characteristics.

The complete list of time varying and time-independent covariates will include:

- age;
- sex;
- race;
- BMI;
- Pre-index CCI score;
- observed TDD from claims; and
- time (pre/post).

Note:

- Age, sex, race, BMI, and CCI score will be assessed during pre-index period. Adherence (PDC) and observed TDD will be calculated during the entire pre-index and post-index periods, respectively.
- The abovementioned statistical approach for Primary Objective 1 will be repeated in the subgroup analyses for elderly population and other subgroup high-dose cohorts (i.e., TDD =201-300 units and TDD >300 units [optional]).

Research Objective 2: Primary Objective 2

Descriptive Analysis

HbA1c will be analyzed descriptively before and after high-dose U-500R Kwikpen initiation, high-dose U-500R syringe initiation, and before and after any high-dose U-500R initiation.

Numbers and percentages will be provided for dichotomous and polychotomous variables. Means and SDs will be provided for continuous variables. McNemar's test will be used to determine statistical significance of before and after values for categorical variables, and the paired t-test will be used to assess the statistical significance of before and after values in continuous variables.

Multivariate Analysis: HbA1c

Mixed Linear Model

A mixed linear model (see details above) will be used to evaluate factors associated with HbA1c level in the pre-and post-index periods among high-dose U-500R Kwikpen initiators, high-dose U-500R syringe initiators, and any high-dose U-500R initiators. For this objective, the mixed linear model will help to evaluate the effect of both time-varying and time-independent variables on the HbA1c, while taking into account for correlation due to multiple assessments from the same individual. In the current model, HbA1c level, (measured at 2 time intervals [before and after the index event: U-500R initiation]), will be considered the dependent variable. Observed TDD will be designated as the time-varying covariate in the model (measured both before and after the index event), and the time-independent covariates include the demographic and clinical characteristics. The complete list of covariates will include:

- age;
- sex;
- race;
- BMI;
- Pre-index CCI score;
- observed TDD from claims; and
- time (pre/post).

Note:

- Age, sex, race, BMI, and CCI score will be assessed during the pre-index period. Observed TDD will be calculated during the entire pre-and post-index periods, respectively. Pre-index HbA1c will be defined as the HbA1c measurement -90/+30 days of the index date. For patients with multiple HbA1c measurements within this period, the measurement taken closest to the index event date will be reported as the pre-index HbA1c value. Post-index HbA1c will be defined as the last HbA1c in the follow-up period.
- The abovementioned statistical approach for Primary Objective 2 will be repeated in the subgroup analyses for the elderly population and other subgroup high-dose cohorts (i.e., post-index TDD =201-300 units and post-index TDD >300 units [optional]).

Research Objective 2: Secondary Objective 2a

Descriptive Analysis

The number of hypoglycemia events will be analyzed descriptively before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and before and after any high-dose U-500R initiation.

Numbers and percentages will be provided for dichotomous and polychotomous variables. Means and SDs will be provided for continuous variables. To determine the statistical significance of before and after values, McNemar's test will be used for categorical variables, and the paired t-test will be used for continuous variables.

Multivariate Analysis: Hypoglycemia Event

Zero-inflated negative binomial mixed model

A zero-inflated negative binomial mixed model will be used to evaluate factors associated with the number of hypoglycemia events PPPY in the pre-and post-index periods among high-dose U-500R Kwikpen initiators, high-dose U-500R syringe initiators, and any high-dose U-500R initiators cohorts. Zero-inflated negative binomial distribution is a mixture of a binary distribution that is degenerate at zero and an ordinary count distribution such as a negative binomial. In cases of outcome variables being repeatedly measured from the individual subjects, zero-inflated models are extended to include random effects to account for the correlation among the repeated measures within a subject. In the current model, the number of hypoglycemia events that might have more zeroes (for example, some patients might not have a lab visit for glucose) and is measured at 2 time intervals (before and after the index event: U-500R initiation), will be considered the dependent variable. Observed TDD and HbA1c will be designated as the time-varying covariates in the model (measured both before and after the index date), and the time-independent covariates will include the demographic and clinical characteristics.

The complete list of covariates will include:

- age;
- sex;
- race;
- BMI;
- Pre-index CCI score;
- observed TDD from claims;
- HbA1c; and
- time (pre/post).

Note:

- Age, sex, race, BMI, and CCI score will be assessed during the pre-index period. Observed TDD and HbA1c will be calculated during the entire pre-index and post-index periods, respectively. Pre-index HbA1c will be defined as the HbA1c measurement -90/+30 days of the index date. For patients with multiple HbA1c measurements within this period, the measurement taken closest to the index event date will be reported as the pre-index HbA1c value. Post-index HbA1c will be defined as the last HbA1c in the follow-up period.
- The abovementioned statistical approach for Primary Objective 2a will be repeated in the subgroup analyses for the elderly population and other subgroup high-dose cohorts (i.e., TDD =201-300 units and TDD >300 units [optional]).

Research Objective 3: Exporatory Objective 3

Descriptive Analysis

Out-of-pocket pharmacy costs will be analyzed descriptively before and after high-dose U-500R syringe initiation, high-dose U-500R Kwikpen initiation, and any high-dose U-500R initiation. Numbers and percentages will be provided for dichotomous and polychotomous variables. Means and SDs, along with the median, minimum and maximum will be provided for continuous variables. To determine the statistical significance of before and after values, McNemar's test will be used for categorical variables, and the paired t-test will be used for continuous variables.

Multivariate Analysis

A generalized linear mixed model (details above) with log link will be used to evaluate factors associated with insulin-related out-of-pocket pharmacy costs in the pre-and post-index periods among high-dose U-500R syringe initiators, high-dose U-500R Kwikpen initiators, and any high-dose U-500R initiation. For this objective, the mixed linear model will help to evaluate the effect of both time-varying and time-independent variables on the costs, while taking into account for correlation due to multiple assessments from the same individual. In the current model, costs (measured at 2 time intervals [before and after the index event; U-500R initiation]) will be designated as the dependent variable. Observed TDD will be designated as the time-varying covariate in the model (measured both before and after the index date), and the time-independent covariates will include the demographic and clinical characteristics.
The complete list of covariates will include:

- age;
- sex;
- region;
- pre-index CCI score;
- observed TDD from claims ;
- Medicare (yes/no); and
- time (pre/post).

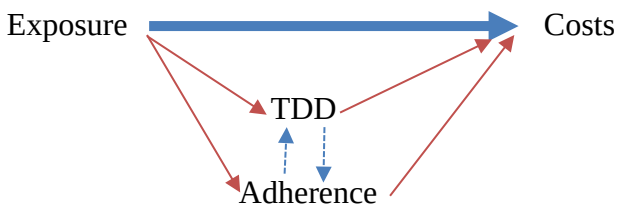
Note:

- Age, sex, region, Medicare (yes/no), and CCI score will be assessed during the pre-index period. Observed TDD will be calculated during both the entire pre-index and post-index periods.
- Adherence will not be included as a covariate here due to the high collinearity between time and adherence.

Exploratory Analysis: Mediator Effect of Adherence (PDC) and Observed Total Daily Dose (TDD) on Insulin-related Pharmacy Costs

Mediation analysis is a collection of methodologies designed to formalize and quantify possible mechanisms (i.e., causal pathways) linking a cause to an effect[35, 36]. The total effect of an exposure on an outcome is decomposed into direct (blue thick arrow) and indirect effects (red arrows) through mediators. Causal mediation analysis further defines both direct and indirect effects based on counterfactual models and is able to provide a causal interpretation. Causal mediation analysis is becoming an important tool for investigating pathways or mechanisms that explains the treatment effect and the underlying mechanism in epidemiology and in the social sciences.

In contrast to non-U-500R insulin therapies that are mostly basal-bolus regiment that requires more than one insulin use at a time, U-500R is an insulin-monotherapy. It is expected that, if the insulin requirement of patients and their adherence behavior were to remain the same, the out-of-pocket costs for purchasing insulins would be lower for the period when patients were exposed to U-500R treatment than for the period when patients are exposed to other insulins. However, from a previous study, it is observed that the observed total daily dose and PDC were different before and after patients were exposed to U-500R. While patients' underlying insulin requirement may or may not have changed, the changes in the observed total daily dose using claims data may reflect more of the compliance behavior (i.e. using the right amount of insulin). Similarly, PDC, another aspect of treatment compliance, may change due to the different insulin treatment characteristics. Changes in obtained insulins quantity (reflected in TDD) as well as changes in number of days with insulins (reflected in PDC) will impact number of insulin purchases (i.e. number of claims filed) and therefore the amount of out-of-pocket costs. As a result, the observed insulin-related out-of-pocket costs may be impacted by the change in the copay needed (direct effect of the exposure to different insulins) as well as the changes in TDD and PDC (indirect effect of the exposure to different insulins)



Confounder
(age, gender, CCI, weight, HbA1c, etc.)

Mediation analysis following the below modeling steps will be considered to understand the impact of index event (time: pre-index indicates use of other non-U-500R insulins and post-index indicates exposure to U-500R use) on insulin-related out-of-pocket costs through potential mediators. Adherence (measured by PDC) and Observed Total Daily Dose (TDD) are considered as potential mediators between costs and treatment period (i.e. exposure). The key steps in mediation analysis include a model of the outcome (costs) as a function of both the mediators (PDC, and TDD) and the predictor (treatment period) and a model of the mediators (PDC and TDD) as functions of the predictor (treatment period). Confounders will be included in the models. Unfortunately, certain confounding variables are unobserved in claims data, e.g., weight, HbA1c.

1.) Suppose the dataset consists of n patients. For patient i ($i = 1,\ldots,n$), denote by Y_{ik} the outcome variable of interest, e.g. costs, during the period k ($k = 0, 1$), where $k = 0$ refers to pre-index period and $k = 1$ refers to the post-index period.
2.) Let M_{ijk} be the mediators at period k, and $j=1,2$ denotes the different mediators PDC and TDD
3.) Let A_{ik} be a binary indicator of treatment during period k. Write $\mathbf{A}_i = \{A_{ik}\}_k$. According to the design, all the patients did not take the U-500R during the pre-index period, but they took the U-500R during the post-index period, thus $A_{ik} = k$ for $k = 0, 1$.
4.) A set of covariates as potential confounding variables, including age, sex, region, pre-index CCI score.

$$Y_{ik} = \beta_0 + \beta_A A_{ik} + \beta_{M1} M_{i1k} + \beta_1 Age + \beta_2 Sex + \beta_3 Region + \beta_4 CCI + \beta_5 M_{i1k} + \beta_6 M_{i2k} + d_i + \varepsilon_{ik,}$$
$$M_{ijk} = \alpha_0 + \alpha_{Aj} A_{ik} + \alpha_{1j} Age + \alpha_{2j} Sex + \alpha_{3j} Region + \alpha_{4j} CCI + b_{0i} + b_{Mij} + b_{Ai} A_{ik} + \eta_{ijk},$$

where random errors ε_{ik} and η_{ijk} along with random effects d_i, b_{0i} and b_{Ai} are mutually independent over i, j, k. The random effects b_{i0} and b_{iA} capture the dependence among M_{ijk}'s. The random effects d_i's, ontrol the dependence between the outcome variable between the pre-index and post-index periods given the mediators and confounders,

Once the coefficient estimates from the models fitting are obstained, the mediation effects will be estimated following standard decomposition approach using counterfactural framework. The confidence intervals will be provided by using parametric bootstrap approach.

7. Safety Evaluations

7.1. Adverse Events

This is a non-interventional study based on secondary data use, and therefore no ICSR reporting is required. The study protocol-defined adverse events (AEs) include hypoglycaemia. Hypoglycemia events in the pre-index and post-index period will be evaluated using the ICD-9 codes from the Ginde algorithm (Appendix 1). All protocol-defined adverse events collected will be summarized in the final study report. No other AEs will be collected.

8. Subject Consent to Release Information, Ethical Review, and Regulatory Considerations

8.1. Subject Consent to Release Information

As this is an observational study that uses data previously collected and does not impose any form of intervention, the data has been de-identified to protect subject privacy. Therefore, a formal Consent to Release Information form is not required.

8.2. Ethical Review and Regulatory Considerations

Observational studies will be submitted to ethical review boards (ERBs) for approval or waivers sought whenever required by local law. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and that are consistent with Good Pharmacoepidemology Practices (GPPs) and applicable laws and regulations of the country or countries where the study is being conducted, as appropriate.

9. Record Keeping, Data Reporting, Data Quality Assurance, and Publications

Subject data are recorded on data forms. Investigators are responsible for the integrity of the data reported to Lilly (accuracy, completeness, legibility, and timeliness). The investigators will follow local laws and regulations or institutional practices for document retention.

All information about this observational study and individual subject medical information resulting from this study are considered confidential, and disclosure to third parties is prohibited except for regulatory authorities and as applicable by law. Publications may result from this study.

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Attachment 1. Observational Study Protocol

Table Shells

On-label cohort Table Shells_01NC

Appendix 1. Tables for ICD 9/10 and NDC Codes

Appen_08072109.xlsx

Appendix 2. Tables for List of Codes for Pump Use

Pump-Pump Supp_08072019.xlsx

Summary of Study Design

This will be a retrospective cohort study with secondary use of claims data from the VHA and Truven databases. The study is designed to use real-world data to evaluate treatment patterns,

treatment outcomes, and out-of-pocket pharmacy costs among T2DM patients who initiated U-500R whose TDD were on-label. The study period will range from 01APR2013–31MAR2018 for VHA; and 01JUL2013–30JUN2018 for Truven MarketScan data. The first prescription claim date for U-500R syringe or U-500R Kwikpen administration will be considered the on-label U-500R initiation and designated as Index Event (syringe: Index Event **a**; Kwikpen:Index Event **b**; any U-500R use: Index Event **c**). For on-label U-500R syringe initiation, on-label U-500R Kwikpen initiation and any on-label U-500R initiation, the identification period will be 01JAN2014–30JUN2017 for VHA, and 01JUL2014–30JUN2017 for Truven, and the pre-index and post-index periods will be 9 months and 12 month for the VHA and Truven database, respectively. The study outcomes will be reported in the periods before and after on-label U-500R syringe initiation, on-label U-500R Kwikpen initiation, and any on-label U-500R initiation.