AdverseEvents
REDEFINING DRUG SAFETY

SPECIAL REPORT

The Comparative Safety of Type 2 Diabetes Medications:

An Analysis Utilizing AdverseEvents Explorer

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Contents

The importance of post-marketing safety surveillance

The pre-approval clinical trial process suffers from many limitations including: homogenous groups of patients, limited drug exposure times, ever-increasing exclusion criteria, lack of gender-specific analyses, inadequate testing of the elderly and different races, etc. All of these restrictions can result in very different reactions, especially with regard to side effects, in clinical trial subjects versus real-world consumer populations[1]. Accordingly, the true side effect profile of a drug is almost never realized until many months, or even years, after Food and Drug Administration (FDA) approval[2, 3]. As a consequence, all FDA approved drugs have the potential to trigger various side effects not revealed during pre-approval investigations. For more detail please see a White Paper we recently produced, "Post FDA-approval drug safety data: why they are vital and how they can be made accessible, actionable, and predictable."

Adverse events (AEs) from FDA approved drugs are a major public safety concern. In fact, almost one million new AE reports are currently reported to the FDA each year, across ~2,000 approved drugs[4].

Because of the noted limits of pre-approval safety processes, AdverseEvents believes that post-marketing side effect analysis can supply our clients with the real-world data they need to make informed coverage, formulary, and prescribing decisions.

Careful and continuous post-approval monitoring is therefore vital to the evaluation of a drug's safety profile. That is exactly what we specialize in here at AdverseEvents.

To obtain such data, we leverage the FDA's Adverse Event Reporting System (FAERS), a centralized, computerized information database that is broadly used by the FDA and other pharmacovigilance experts for post-marketing drug safety surveillance[1, 5-20]. The FDA uses FAERS analyses to make post-marketing regulatory decisions such as the issuance of warnings, label changes, and/or market removal[21]. International government and related organizations (Australia's "Therapeutic Goods Administration," Canada's "Vigilance Adverse Reaction Online Database," Europe's "EudraVigilance," Japan's "Pharmaceuticals and Medical Devices Agency," The United Kingdom's "Yellow Card Scheme," and The World Health Organization's "VigiBase") also use spontaneous AE

databases to identify post-approval drug safety concerns.

Challenges to using FAERS data, however, have been reported to include "underreporting," the "Weber Effect"[22, 23], and "stimulated reporting"[24-28]. With regard to underreporting, recent efforts by both FDA and the healthcare industry are helping to increase AE reporting rates. Indeed, almost one million AE reports will be added to FAERS this year alone[4], and the database now has a total of over seven million reports. With regard to the "Weber effect," a recent study has demonstrated that it may be of less concern than it was in the past, likely due to the aforementioned modern focus on the importance and utility of post-approval AE reporting by both the FDA and key health care players[29].

We have recently examined modern FAERS trends to determine the magnitude of "stimulated reporting" after an FDA-issued AE warning. We analyzed over 100 recent FDA Alerts and found little evidence to support the hypothesis that "stimulated reporting" is widespread within FAERS (*article in progress*).

FAERS data (after extensive organization and cleanup via algorithms and our analysts) forms the cornerstone of our product offerings. At the time of this analysis, publicly available FAERS data were only current through Q1 2013. To provide our clients with the most up to date information, we obtained non-publicly available FAERS data via Freedom of Information Act inquiries in order to be current to March 2014.

Our analyses of Type 2 Diabetes Mellitus drugs suggest that:

1) **Both GLP-1 and DPP-4 inhibitors (especially sitagliptin) have elevated associations with pancreatitis and pancreatic cancer, but neither class appears to have strong links to presumed renal and hepatic complications.**

2) **Bydureon and Byetta may be safer choices than Victoza within the GLP-1 inhibitor class.**

3) **DPP-4 inhibitors may be linked to more serious side effects than is widely believed, with Nesina of particular concern.**

4) **SLGT2 inhibitors are, as expected, associated with elevated urinary infection risks but may also be linked to more serious events.**

Type 2 Diabetes Drugs

Type 2 Diabetes Mellitus (T2DM) is a chronic and progressive disorder characterized by high blood glucose levels (hyperglycemia) and elevated glycated hemoglobin (A1c) levels. It affects approximately 230 million people worldwide and incidence is growing at an alarming rate. It has been projected that, by the year 2050, one in three Americans may suffer from diabetes[30].

Hyperglycemia associated with T2DM drives both insulin resistance and beta-cell death (i.e. "glucotoxicity") and is the main risk factor for microvascular and other complications (stroke, peripheral artery disease, myocardial infarction, kidney problems, nerve issues, eye disorders, etc.) that plague subjects with the disease. Every 1% decrease in A1c level is associated with an approximately 30% reduction in microvascular risks and, accordingly, medications to control hyperglycemia represent a huge healthcare priority.

T2DM is characterized by a progressive dysfunction in the beta cells of the pancreas as well resistance to the glucose storage and utilization effects normally mediated by insulin. Optimal glucose control reduces the occurrence of the complications discussed above.

While the modification of lifestyle and diet are the first step in combating the disease, they are seldom sufficient. Medications, therefore, are almost always needed, even in the early steps in the progression of the disease. The first line of defense against hyperglycemia is usually the drug metformin (a biguanide that decreases glucose output from the liver, lowers fasting glycemia, and increases insulin responsiveness). Unfortunately, however, just 3 years after a patient's diagnosis of diabetes there is a 50% chance that they will need to supplement metformin monotherapy with other drugs to achieve desired glycemic control[31]. In such subjects, the addition of exogenous insulin administration and/or a sulfonylurea (or related medication) is then indicated. For many T2DM patients, even these approaches fail to result in acceptable glycemia. Additionally, some of these drugs cause weight gain, fluid retention, and have been linked to both increased cardiovascular risk and dangerous episodes of hypoglycemia.

To address these shortcomings, newer drug classes are in development such as: glucagon-like peptide-1 receptor (**GLP-1**) agonists (incretin pathway), dipeptidyl peptidase-4 (**DPP-4**) inhibitors (incretin pathway), and sodium-glucose co-transporter 2 (**SGLT2**) inhibitors (glucuretics). These drugs classes are discussed below.

Glucagon-like peptide-1 agonists

The "incretin effect" describes the phenomenon wherein the intake of oral glucose produces a larger insulin response, in a healthy subject, than the injection of glucose[32, 33]. It was the discovery of this effect that lead to the detection of Glucagon-like peptide-1 (GLP-1), which is a hormone secreted in the intestine in response to nutrient intake. The incretin effect is impaired in subjects with T2DM[34].

GLP-1, and like hormones, induce insulin secretion in response to food intake in a glucose-dependent manner. This linkage to glucose levels in an important one, especially from a drug development perspective, as pharmacologically enhanced GLP-1 activity should pose less *hypo*glycemic risks when compared to other diabetes drugs that are not coupled to glucose concentrations. GLP-1 triggers insulin secretion, suppresses glucagon secretion, and delays gastric emptying. This endogenous peptide, however, has a very short half-life due to rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4). It is because of these characteristics that drug development efforts have focused on producing 1) long half-life **GLP-1 agonists** and 2) inhibitors of DPP-4 activity.

GLP-1 agonists have been developed that are either short- or long-acting. As previously mentioned, they act in a glucose-dependent manner and can be used in combination with insulin treatment(s). Not only are they thought to effectively control glycemia, but they are also believed to reduce blood pressure, promote weight loss, enhance satiety, and have a low risk of hypoglycemia. The use of these drugs appears to results in greater reductions in glycated hemoglobin levels than the administration of DPP-4 inhibitors (discussed below). GLP-1 agonists include both the "short acting" **Byetta (exenatide)** and the "long acting" **Bydureon (exenatide)** and **liraglutide (Victoza)**. By targeting both pancreatic beta (insulin) and alpha (glucagon) cell dysfunctions, as well as exerting non-pancreatic effects, these medications are believed to have lower risks of hypoglycemia and weight gain.

Liraglutide differs from the exenatides in that it is not metabolized/eliminated by the kidneys or liver, so it may be a preferred choice for the significant percent of T2DM patients that have either renal or hepatic impairment[35]. This characteristic may also affect its post-marketing side effect profile, a question we will address here.

Adverse events linked to these medications include: nausea and vomiting (believed to be less common in long-acting verse short-acting GLP-1 agonists),

injection site reactions, gastrointestinal issues, kidney injury, neoplasms (including specific ones like medullary thyroid cancer), hypoglycemia, and pancreatitis. For a review of links between GLP-1 agonist use and renal functioning please see Filippatos and Elisaf[36]. For a discussion of potential evidence linking liraglutide to cancer please see Alves et al.[37].

Controversy surrounds the links between these drugs and pancreatitis and pancreatic cancer. On the one hand, a survey of the FAERS database was conducted which indicated a significantly increased risk for pancreatitis and both pancreas and thyroid cancer[38]. A related study[39] and two recent meta-analysis of pre-approval clinical trials, however, did not find plausible evidence of increased risk of pancreatitis with use of GLP-1 inhibitors[37, 40]. Additionally, with regard to the risks of pancreatitis and pancreatic cancer, these are already known to be elevated in both the obese and subjects with T2DM.

In summary, *current opinion* is that GLP-1 drugs are well tolerated[32], and there does not appear to be any safety differences between members of the class[41]. Our post-marketing analysis detailed here, in part, is intended to address the merits of that opinion.

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 inhibitors also affect the incretin pathway by blocking the action of DPP-4 (the enzyme which cleaves and therefore inactivates GLP-1). Accordingly, these inhibitors increase the effective half-life of endogenous GLP-1. As with the GLP-1 agonists, DPP-4 inhibitors act in a glucose-dependent manner and are therefore thought to trigger fewer hypoglycemic episodes when compared with the administration of insulin, sulfonylureas, etc. As outlined in table 1, their effect on A1c levels is generally thought to be less potent than GLP-1 agonists. Some have also noted that DPP-4 inhibitors are not specific, and they only modestly increase GLP-1 activity[35]. In contrast to GLP-1 agonists, they do not appear to affect gastric emptying or cause decreases in body weight. However, both their mode of administration (oral) and gastrointestinal tolerability are likely to be more desirable than current, injectable, GLP-1 agonists[42]. DPP-4 inhibitors include: **alogliptin (Nesina), linagliptin (Tradjenta), linagliptin** plus **metformin (Jentadueto), saxagliptin (Onglyza), sitagliptin (Januvia),** and **sitagliptin** plus **metformin (Janumet)**.

Adverse events commonly linked to these medications include those listed above for GLP-1 inhibitors, such as renal issues, pancreatitis, as well as nasopharyngitis, upper respiratory infections, and urinary tract infections. Generally, however, these side effects are believed to be of lower severity and frequency when compared with metformin or GLP-1 agonists[43]. A recent meta-analysis of pre-approval clinical trials, however, did not find evidence of increased risk of pancreatitis with use of DDP-4 inhibitors[44]. Finally, linagliptin (Tradjenta) is the only member of the class that does not require dosage adjustments for patients with either renal or hepatic impairment. It will be of interest to see if such dosing guidelines are supported by the post-marketing analysis conducted here.

Sodium-glucose co-transporter 2 inhibitors

Sodium-glucose co-transporter 2 inhibitors (SLGT2) include **canagliflozin (Invokana)** and **dapagliflozin (Farxiga)**. These compounds act upon receptors in the kidney that normally mediate the high-efficiency reabsorption of glucose from plasma. Normally, only a ~1% concentration of glucose remains in the urine after the kidney reabsorption process. When these SLGT2 receptors are blocked, however, glucose reabsorption is stopped and is therefore excreted in the urine. Both lower blood glucose levels and weight loss, due to calorie elimination, result. Since these inhibitors operate in a non-insulin manner, they can be readily combined with insulin-acting treatments to hopefully increase glycemic control[45].

Like the DPP-4 inhibitors, these drugs offer slightly less glycemic control when compared to the GLP-1 agonists. However, given that their mechanism of action is insulin-independent and that they do not interact with the incretin pathway (like GLP-1s and DPP-4s), these drugs may be a good fit for add-on medications to those not responding to first and second line T2DM medications. Additionally, part of the disease progression in T2DM is that drugs used to enhance insulin secretion or improve sensitivity to it begin to lose their effectiveness over time. Accordingly, SLGT2s could provide a solution to that part of T2DM treatment progression. They, like the other drug classes mentioned in this report, are also believed to pose a low risk of hypoglycemia. The efficacy of SLGT2 inhibitors, however, is dependent on how much glucose is filtered through the kidneys[46]. Therefore, in patients with renal impairment (common in those suffering from T2DM) these drugs might have limited efficacy.

The downside of increased sugar content in urine is that both yeasts and bacteria thrive in glucose-rich environments, so the use of these drugs increases the propensity for genital and urinary tract infections, especially in women. Adverse events commonly linked to these medications include genital and urinary tract infections (both possibly as high as 10% of those treated)[47, 48]. Possible links to breast and bladder cancer have also been noted[49]. Finally, some SGLT2 inhibitors require dose adjustment in patients with low creatinine clearance[50], indicating that kidney-related adverse events might be of concern.

Summary of the three T2DM medication classes discussed above:

	GLP-1 Receptor Agonists	DPP-4 Inhibitors	SLGT-2 Inhibitors
A1c reduction	~0.5% to 1.0+%	~0.5 to 0.8%	~0.5% to 1.0%
Gastric slowing?	Yes	No	No
Weight loss?	Yes	No	Yes
Route of administration	Injection	Oral	Oral

While the efficacy traits of the three drug classes discussed above are well known from their respective clinical trial programs, the compounds within each class all have differing half-lives, metabolites, molecular sizes, non-specific binding sites, and pharmacokinetic characteristics. Oftentimes it is these differences that can result in varied adverse event profiles after the drugs are granted FDA approval and are then introduced into heterogeneous consumer patient populations.

Accordingly, we used our multiple analytic platforms to analyze post-marketing safety signals across these three separate classes of T2DM medications.

Methods & Results

In order to better understand the post-approval safety data available on three major classes of Type 2 Diabetes drugs, we conducted a detailed review of FAERS.

We subdivided the drugs into three main classes: GLP-1's (Bydureon, Byetta, and Victoza); DPP-4s (Nesina, Tradjenta, Jentadueto, Onglyza, Januvia, Janumet); and SGLT2's (Invokana and Farxiga). For additional details on each of these drugs please see the Appendix.

To import and filter data from FAERS, data pre-processing techniques were used to normalize and qualify textual data, such as removal of non-alphanumeric characters, whitespace and line breaks. Filtering processes included: i) a system for automated name matching which corrected for drug name misspellings and incorrect data within major fields (i.e., the inclusion of dosages or routes of administration as part of the drug name field); ii) aggregation of generic and non-U.S. brand name drugs under a single brand name; iii) separation of "primary suspect" and "all suspect" designations, iv) removal of duplicate case reports; and v) identification of common adverse event and condition types.

Automated data pre-processing and scrubbing workflow provided an initial assignment of a 'raw' FDA FAERS drug names. The automated matching process was accomplished by a combination of fuzzy string matching, string distance, and phonetic matching algorithms.

Drug name text-mapping was accomplished as previously described[51]. Textual drug name data were validated by text-mapping of brand drug names and active ingredient names to the RxNorm database[52], and manual curation.

Utilizing the AdverseEvents Explorer platform, we analyzed the drugs with: 1) RxFilter (a big data analytic that optimizes FAERS and makes it user-friendly and fully searchable)[51], 2) a disproportionality measure (mathematical analysis that compares "expected" versus "unexpected" rates of adverse events)[53], and 3) the RxScore system (a proprietary algorithmic drug-safety ranking analytic).

RxFilter™ Analysis

In order to make FAERS data accessible to broad groups of healthcare professionals, AdverseEvents analyzes and categorizes the extensive database by using a combination of computer algorithms and in-house data analysis, called **RxFilter**. Our **AdverseEvents Explorer** platform makes FAERS data easy to search and understand[51] and feeds clean data into our other analytics. It accurately standardizes and normalizes all reported side effects (from 1997 on) linked to over ~2,000 FDA approved drugs, enabling health plan administrators, health systems analysts, and pharmaceutical companies rapid access to FAERS information in order to supplement their own sources of drug safety data.

FAERS data was queried from a drug's approval through the most recently available date. All drugs included in the current analysis have data through March 28, 2014 because we had previously petitioned FDA, via a Freedom of

Information Act (FOIA) request, for updated case reports on those specific drugs. FOIA requests are a routine service we provide for our clients, and our latest update on the process is detailed in a special report, "Expediting Drug Safety Using FOIA: An Analysis of 57,000 New Unreleased FAERS Reports."

Top-level analysis of each of the major classes of T2DM medications showed:

Table 1: GLP-1 agonists

Drug Name	Approval Date	Primary Suspect Cases	Life-Threatening Cases (%)	Hospitalization Cases (%)	Disability Cases (%)	Death Cases (%)
Bydureon (exenatide)	1/27/2012	3,087	31 (1.00%)	298 (9.65%)	15 (0.49%)	17 (0.55%)
Byetta (exenatide)	4/28/2005	38,223	378 (0.99%)	4,840 (12.66%)	188 (0.49%)	577 (1.51%)
Victoza (liraglutide)	1/25/2010	13,454	258 (1.92%)	1,914 (14.23%)	80 (0.59%)	221 (1.64%)

Table 2: DPP-4 inhibitors

Drug Name	Approval Date	Primary Suspect Cases	Life-Threatening Cases (%)	Hospitalization Cases (%)	Disability Cases (%)	Death Cases (%)
Janumet (sitagliptin, metformin)	3/30/2007	1,958	173 (8.84%)	694 (35.44%)	121 (6.18%)	205 (10.47%)
Januvia (sitagliptin)	10/16/2006	12,668	650 (5.13%)	2,665 (21.04%)	525 (4.14%)	523 (4.13%)
Jentadueto (linagliptin, metformin)	1/30/2012	120	0	13 (10.83%)	2 (1.67%)	1 (0.83%)
Nesina (alogliptin)	1/25/2013	218	22 (10.09%)	121 (55.50%)	6 (2.75%)	35 (16.06%)
Onglyza (saxagliptin)	7/31/2009	2,000	55 (2.75%)	411 (20.55%)	14 (0.70%)	56 (2.80%)
Tradjenta (linagliptin)	5/2/2011	1,892	49 (2.59%)	382 (20.19%)	25 (1.32%)	86 (4.55%)

Table 3: SGLT2 inhibitors

Drug Name	Approval Date	Primary Suspect Cases	Life-Threatening Cases (%)	Hospitalization Cases (%)	Disability Cases (%)	Death Cases (%)
Farxiga (dapagliflozin)	1/8/2014	24	2 (8.33%)	14 (58.33%)	2 (8.33%)	1 (4.17%)
Invokana (canagliflozin)	3/29/2013	307	15 (4.89%)	106 (34.53%)	8 (2.61%)	6 (1.95%)

Disproportionality Analysis

Data mining algorithms based on disproportionality can be used to estimate the relative frequency of an AE associated with the use of specific drug. The Reporting Odds Ratio (ROR) is a disproportionality measure commonly used by drug safety professionals to help identify drug-associated AEs that are reported more frequently than expected. The method compares expected reporting frequencies (based upon all drugs and all AEs in the FAERS database) with the amount of a given AE reported for a specific drug.

An ROR score of ≥ 1.0 indicates that there is a higher than normal reporting rate for a given AE / drug combination. While there is no widely accepted benchmark regarding the numerical level at which disproportionality analysis yields a "safety signal," many in the drug industry assume that results above 1.5-2.0 warrant attention. We derived ROR and Confidence Intervals (CI) by the use of standard formulas[53], with the additional step of correlating the starting date of our calculations to each drug's FDA approval date.

The tables below list the number of "primary suspect" case reports for each drug and how many of those reports fall into corresponding Medical Dictionary for Regulatory Activities (MedDRA) "Preferred Term" (PT), "High-Level Term" (HLT), and "Standardized MedDRA Queries" (SMQ) adverse event categories. With regard to the latter, MedDRA and the Council for International Organization of Medical Sciences (CIOMS) created and validated categories of related AEs known as "Standardized MedDRA Queries" (SMQ). SMQs are standardized sets of MedDRA terms that are commonly used to support both safety signal detection and monitoring. SMQs contain either "narrow" or "broad" concept terms. Narrow terms are defined by MedDRA as being "cases highly likely to be the condition of interest" and are therefore the SMQ terms we analyze.

For **GLP-1 agonists**, the following SMQs were queried: "Gastro" (includes two SMQs ("Gastrointestinal Nonspecific Symptoms And Therapeutic Procedures" and "Gastrointestinal Nonspecific Dysfunction"); "Fluid" ("Hemodynamic Edema, Effusions and Fluid Overload"); "Hemo" (Hemorrhage Terms (excl Laboratory Terms)); "Renal" ("Acute renal failure"); "Hepatic" ("Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions"); "Gall" ("Gallbladder related disorders"); "Cancer" ("Malignant Tumors"). One HLT was searched, "Pancreatitis" ("Acute And Chronic Pancreatitis"). Two HLT's were combined into one group, "Pancr Cancer" ("Pancreatic neoplasms malignant (excl islet cell and carcinoid" and "Pancreatic neoplasms"). Three HLT's were combined into one group, "Thyroid neoplasms" ("Thyroid neoplasms benign," "Thyroid

neoplasms malignant," and "Thyroid neoplasms").

RORs and CIs were calculated for "primary suspect" cases reported from the drug's approval date to the most recent FAERS data we have access to.

Table 4: GLP-1 agonists

Drug Name	SMQs: Gastro	SMQ: Fluid	SMQ: Hemo	SMQ: Renal	SMQ: Hepatic	SMQ: Gall	SMQ: Cancer	HLT: Pancreatitis	HLTs: Pancr Cancer	HLTs: Thyroid neoplasms
Bydureon (exenatide)	1.9 (1.7-2.0)	2.0 (1.8-2.3)	2.8 (2.5-3.0)	0.5 (0.4-0.7)	0.2 (0.1-0.4)	0.6 (0.4-1.0)	0.4 (0.3-0.5)	8.5 (7.1-10.1)	2.9 (1.8-4.7)	2.4 (1.2-4.6)
Byetta (exenatide)	4.3 (4.2-4.4)	0.4 (0.4-0.5)	1.2 (1.15-1.24)	0.82 (0.76-0.9)	0.4 (0.3-0.4)	1.6 (1.5-1.8)	0.7 (0.6-0.7)	10.8 (10.3-11.2)	13.2 (12.0-14.5)	4.8 (4.2-5.6)
Victoza (liraglutide)	4.7 (4.5-4.9)	0.3 (0.3-0.4)	0.8 (0.7-0.8)	0.5 (0.5-0.6)	0.4 (0.3-0.5)	1.3 (1.1-1.5)	0.8 (0.7-0.9)	17.9 (16.9-19.0)	15.0 (13.1-17.0)	8.8 (7.3-10.5)

For **DPP-4 inhibitors**, the same categories that were run for GLP-1 agonists were used: "Gastro"; "Fluid"; "Hemo"; "Renal"; "Hepatic"; "Gall"; "Cancer"; "Pancreatitis"; and "Pancr Cancer". In addition, two High Level Terms (HLTs) were searched, "Urinary" ("Genitourinary tract infections and inflammations NEC") and "Respir" (Upper respiratory tract infections NEC)." One PT was searched, "Gastric Cancer."

Table 5: DPP-4 inhibitors

Drug Name	SMQs: Gastro	SMQ: Fluid	SMQ: Hemo	SMQ: Renal	SMQ: Hepatic	SMQ: Gall	SMQ: Cancer	HLT: Urinary	HLT: Pancreatitis	HLTs: Pancr Cancer	HLT: Respir	PT: Gastric Cancer
Janumet (sitagliptin, metformin)	1.8 (1.6-2.0)	0.6 (0.5-0.8)	0.7 (0.3-0.5)	2.7 (2.2-3.2)	1.4 (1.0-1.9)	2.0 (1.4-2.8)	2.0 (1.7-2.3)	0.8 (0.5-1.4)	25.6 (22.6-28.9)	43.7 (35.6-53.7)	0.4 (0.3-0.7)	6.9 (3.1-15.3)
Januvia (sitagliptin)	1.2 (1.1-1.2)	1.0 (0.9-1.0)	0.3 (0.3-0.4)	1.2 (1.1-1.3)	0.9 (0.7-1.0)	1.1 (0.9-1.3)	1.1 (1.0-1.2)	0.4 (0.3-0.6)	16.8 (15.9-17.9)	27.5 (24.7-30.6)	1.4 (1.3-1.6)	2.1 (1.2-3.7)
Jentadueto (linagliptin, metformin)	4.4 (3.0-6.4)	0.6 (0.2-1.7)	0.1 (0.0-0.8)	0.4 (0.1-3.0)	0.7 (0.1-4.8)	0	0.2 (0.0-1.5)	0.8 (0.1-5.4)	7.7 (3.1-18.8)	4.5 (0.6-32.5)	0.8 (0.2-3.0)	0
Nesina (alogliptin)	0.4 (0.3-0.8)	0.2 (0.1-0.8)	0.8 (0.5-1.4)	2.4 (1.2-4.9)	4.2 (2.2-8.2)	5.6 (2.5-12.7)	4.9 (3.4-7.1)	0.4 (0.1-2.7)	19.5 (12.8-29.9)	15.4 (8.1-29.1)	0.2 (0.0-1.1)	80.9 (35.2-185.6)
Onglyza (saxagliptin)	1.3 (1.1-1.4)	1.7 (1.4-2.0)	0.3 (0.2-0.4)	1.5 (1.2-1.9)	0.7 (0.4-1.1)	1.5 (1.0-2.5)	0.7 (0.5-0.9)	1.6 (1.1-2.2)	11.5 (9.8-13.6)	11.5 (8.1-16.5)	0.9 (0.6-1.2)	1.1 (0.2-8.1)
Tradjenta (linagliptin)	1.6 (1.5-1.8)	0.7 (0.5-0.9)	0.3 (0.2-0.4)	1.5 (1.2-2.0)	1.0 (0.7-1.5)	0.6 (0.4-1.1)	0.7 (0.5-0.9)	0.4 (0.2-0.8)	17.4 (14.9-20.2)	8.4 (5.7-12.5)	0.5 (0.3-0.7)	1.2 (0.2-8.8)

For **SGLT2 inhibitors**, we used the categories that were run for GLP-1 agonists and DDP-4 inhibitors: "Gastro"; "Fluid"; "Hemo"; "Renal"; "Hepatic"; "Gall"; "Cancer"; "Pancreatitis"; and "Pancr Cancer." In addition, one High Level Term (HLT) was searched, "Urinary" ("Genitourinary tract infections and inflammations NEC"), and two PTs were searched, "Breast Cancer" and "Bladder Cancer."

Table 6: SGLT2 inhibitors

Drug Name	SMQs: Gastro	SMQ: Fluid	SMQ: Hemo	SMQ: Renal	SMQ: Hepatic	SMQ: Gall	SMQ: Cancer	HLT: Urinary	HLT: Pancreatitis	PT: Breast Cancer	PT: Bladder Cancer
Farxiga (dapagliflozin)	0.5 (0.1-2.1)	0	1.0 (0.2-4.1)	1.8 (0.2-13.6)	0	0	0	3.7 (0.8-16.1)	0	0	0
Invokana (canagliflozin)	0.5 (0.3-0.8)	0.3 (0.1-0.8)	0.6 (0.4-1.0)	9.9 (7.1-14.0)	1.0 (0.3-3.1)	3.4 (1.4-8.2)	0.6 (0.3-1.3)	4.9 (3.1-7.8)	0.8 (0.2-3.1)	0	5.9 (0.8-42.5)

RxScore™

People are accustomed to counting on objective product ranking and scoring platforms such as Consumer Reports to guide their purchasing decisions. Drugs, however, have no similar platform, for either efficacy or safety.

Determining the overall safety risk of a drug necessarily involves the simultaneous assessment of several safety-related parameters. Choosing these factors, and determining how to weigh their individual contribution within a ranking platform, needs careful consideration. To paint a fair picture of the damage done by an AE, it would also need to factor in existing comorbidities that a patient was suffering from *before* a given drug was administered.

To meet these needs, we developed the "RxScore," a proprietary algorithmic scoring model based predominantly on post-marketed safety data from over five million FDA Adverse Event Reporting System (FAERS) reports. RxScore is presented on a 100-point scale meant to reflect both the breadth and seriousness of side effect(s) by incorporating differentially weighted categories including FAERS fields such as "Outcome," "Event Seriousness," "Report Type," "Reporter Type," and a disproportionality measure. The score is also negatively adjusted by factoring in both "Indication Seriousness" and a patient's existing comorbidities. A score of 100 indicates the highest potential adverse event risks. In order to highlight differences between the drugs in a class, the tables below list the total score as well as the "percent of maximum" that each drug had across individual components of the total RxScore.

Our RxScore analysis of T2DM drugs yielded the following:

Table 7: GLP-1 agonists: RxScores and % of Maximum for Key components

Drug	RxScore	Outcome	Event Seriousness	Disproportionality
Bydureon (exenatide)	29.56	22.07%	21.77%	22.03%
Byetta (exenatide)	23.49	24.05%	22.97%	17.29%
Victoza (liraglutide)	36.52	25.69%	29.96%	13.62%

Table 8: DPP-4 inhibitors: RxScores and % of Maximum for Key components

Drug	RxScore	Outcome	Event Seriousness	Disproportionality
Janumet (sitagliptin, metformin)	54.05	40.58%	38.09%	10.41%
Januvia (sitagliptin)	31.81	32.09%	34.35%	9.21%
Jentadueto (linagliptin, metformin)	34.43	22.57%	22.37%	5.34%
Nesina (alogliptin)	59.04	55.83%	63.54%	6.94%
Onglyza (saxagliptin)	31.72	30.53%	35.15%	7.41%
Tradjenta (linagliptin)	30.83	29.43%	31.35%	9.21%

Table 9: SGLT2 inhibitors: RxScores and % of Maximum for Key components

Drug	RxScore	Outcome	Event Seriousness	Disproportionality
Invokana (canagliflozin)	25.69	33.65%	35.80%	0.00%

Note: Farxiga (dapagliflozin) did not receive an RxScore as it did not meet the minimum requirement for 100 primary suspect cases.

Results Summary

RxFilter Analysis

For the **GLP-1 agonists**, Bydureon had lower percentages of its case reports listed as "Hospitalization" (~10%) and "Death" (~0.5%) than both Byetta (~13% and ~1.5%) and Victoza (~14% and ~1.6%), respectively. Interestingly, **DPP-4 inhibitors**, in general, had a higher percentage of their case

reports listed as “Life-threatening,” “Hospitalization,” “Disability,” and “Death” when compared to the **GLP-1 agonists**. The **DPP-4 inhibitors** showed a wide range for percentage of case reports listed as “Death,” with the highest amounts (~16% and ~10%) linked to Nesina and Janumet, while the lowest percentages were seen for Jentadueto and Onglyza (~1% and ~3%). Nesina was also an outlier in the class for both “Life-threatening” (~10%) and “Hospitalization” (~64%). While we do not yet have a large amount of case counts for the new **SGLT2 inhibitors** their percentages show relatively high “Hospitalization” (~35-58%) and “Death” (~2-4%) totals.

Disproportionality

As a group, the **GLP-1 agonists** showed elevated disproportionality results for gastrointestinal, pancreatitis, pancreatic cancer, and thyroid neoplasm categories. It was mentioned earlier that Victoza was not metabolized by the kidney or liver and therefore could possibly have less hepatic and renal AEs compared to its’ peers. This assumption was not confirmed by these data simply because none of the GLP-1’s showed elevated disproportionality for renal or hepatic AEs. With regard to gastrointestinal AEs, Bydureon had much lower disproportionality results than both Byetta and Victoza. Bydureon, however, had higher results than its’ peers for both fluid overload and hemorrhage categories. All three GLP-1 agonists showed high disproportionality for pancreatitis, pancreatic cancer, and thyroid neoplasms. Bydureon, however, had much lower totals than its’ peers in those three categories.

The **DPP-4 inhibitors**, as a group, had high disproportionality results for both pancreatitis and pancreatic cancer. The highest totals for those categories were seen with Janumet (sitagliptin combined with metformin) and Januvia (sitagliptin). Nesina has the third highest total, while Jentadueto (linagliptin with metformin) had the lowest. Jentadueto, however, was the only DPP-4 to register an elevated gastrointestinal signal. Even though the disproportionally ranges were sizeable for the gastric cancer category, two results are worth mentioning: Janumet had a results of ~7 while Nesina had the highest disproportionally result recorded in this study, an ~81 (note, however, that Nesina had significantly fewer total case reports when compared to other drugs in this analysis. Therefore, Nesina's disproportionality calculations had a very broad range that lowered our confidence in these figures. We await the next round of FAERS data to better calculate potential associations). Nesina also had the highest results, when compared with its’ peer group, for hepatic, gallbladder, and cancer categories.

While we do not yet have a large amount of case reports to analyze, the **SGLT2 inhibitors** both showed, as expected, elevated disproportionality for the urinary category. Invokana also had a high renal result (~9) as well as elevated totals for both gallbladder (~3) and bladder cancer (~6) categories.

RxScore Analysis

Our RxScore analysis of the **GLP-1 agonists** showed that Bydureon and Byetta had similar scores and that Victoza was higher than both of its' peers due mainly to higher totals in the two important categories of Outcome and Event Seriousness. As a group, the **DPP-4 inhibitors** showed higher scores than the **GLP-1 inhibitors**, with Janumet and Nesina having the highest totals, driven by elevated Outcome and Event Seriousness components, with Nesina having an especially elevated total for the latter.

Conclusion

Pre-marketing clinical trials are the established means for determining a drug's safety and efficacy during the approval process, but they are by no means perfect. When a new drug comes to market a more heterogeneous population uses it and, accordingly, real-world side effects begin to appear.

Accordingly, healthcare decision makers need safety tools that reflect a given medications effects in these real-life populations. We believe that the use of the platforms discussed here meet such needs.

Using the methods outlined here we were able to detail real-world side effect data across three classes of T2DM medications.

Our review of post-approval AE data suggest disproportionally elevated reporting of gastrointestinal issues, pancreatitis, and both pancreatic and thyroid cancers linked to the **GLP-1 agonists**, with **Bydureon** having consistently lower associations with these side effects when compared to **Victoza** and **Byetta**. **DPP-4 inhibitors** had far lower associations with gastrointestinal issues than the **GLP-1s**, but also showed elevated signals for both pancreatitis and pancreatic cancer. Within the class, **Janumet** and **Januvia** (both containing sitagliptin) had the highest associations with these side effects. Somewhat surprisingly the **DPP-4's** had higher percentages of their case reports as "hospitalization" and "death," when compared to the **GLP-1's**. **Nesina** showed the highest signals of any **DPP-4's** for hepatic, gallbladder, and cancer categories. While we await

more data on the new **SLGT2 inhibitor** class, the data we analyzed confirmed the known linkage to urinary infections. Our preliminary results with this class also suggested possible concerns for renal and gallbladder issues, as well as bladder cancer.

Our RxFilter, disproportionality, and RxScore analyses suggest that:

1) **Both GLP-1 and DPP-4 inhibitors (especially sitagliptin) have elevated associations with pancreatitis and pancreatic cancer, but neither class appears to have strong links to presumed renal and hepatic complications.**

2) **Bydureon and Byetta may be safer choices than Victoza within the GLP-1 inhibitor class.**

3) **DPP-4 inhibitors may be linked to more serious side effects than is widely believed, with Nesina of particular concern.**

4) **SLGT2 inhibitors are, as expected, associated with elevated urinary infection risks but may also be linked to more serious events.**

Additionally, these data show specific post-marketing AE results that differ within each of the T2DM drug sub-classes, and therefore may be important for healthcare providers, especially for those who prescribe these medications.

These results are based upon publicly available FAERS data (last update Q1 2013) supplemented with more recent FAERS data obtained via our Freedom of Information Act inquiries (current to March 28, 2014). These efforts to obtain and analyze the most current, non-public, FAERS data underscore our policy of providing clients with the most up to date and relevant post-marketing safety information.

Disclaimers

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In general, post-marketing data may be subject to biases such as underreporting, stimulated reporting, and confounding by comorbidities. An adverse event report does not definitively ascertain causality.

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Appendix – FDA-Approved Indications for each Drug

Glucagon-like peptide-1 (GLP-1) receptor agonists

Drug Name	Approval Date	Approved Indications
Bydureon (exenatide)	1/27/2012	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Byetta (exenatide)	4/28/2005	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Victoza (liraglutide)	1/25/2010	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Dipeptidyl peptidase-4 (DPP-4) inhibitors

Drug Name	Approval Date	Approved Indications
Janumet (sitagliptin, metformin)	3/30/2007	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate.
Januvia (sitagliptin)	10/16/2006	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Jentadueto (linagliptin, metformin)	1/30/2012	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate,
Nesina (alogliptin)	1/25/2013	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.
Onglyza (saxagliptin)	7/31/2009	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.
Tradjenta (linagliptin)	5/2/2011	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Drug Name	Approval Date	Approved Indications
Farxiga (dapagliflozin)	1/8/2014	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Invokana (canagliflozin)	3/29/2013	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.