COWEN
AND COMPANY

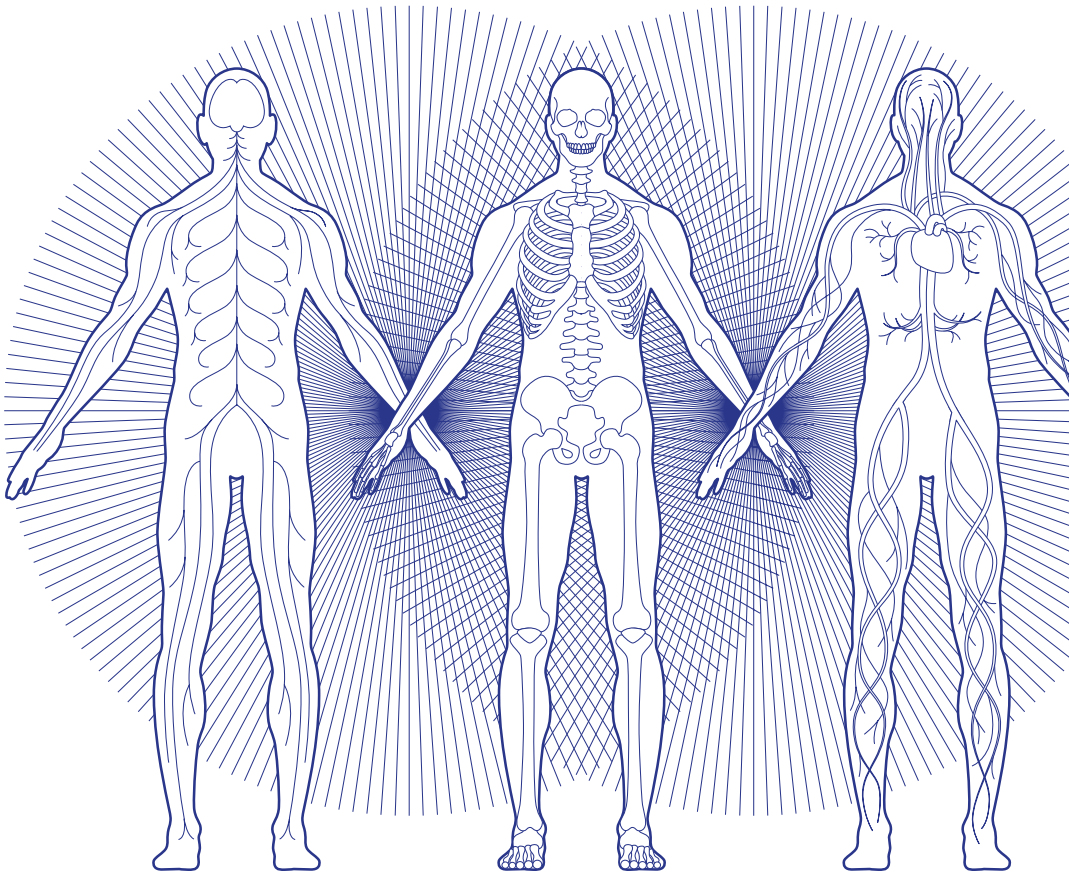
Equity Research
Health Care

Therapeutic Categories Outlook

Comprehensive Study

February 2015

Alzheimer's Disease
Bone Diseases
Cardiovascular
Central Nervous System
Dermatology
Diabetes
Epilepsy
Gastrointestinal/Ulcer
Hepatitis B Virus/Hepatitis C Virus
Infectious Disease
Multiple Sclerosis
Obesity
Oncology/Hematology
Ophthalmology
Orphan Diseases
Pain Management
Respiratory
Rheumatology
Sleep Disorders
Urinary Incontinence
Women's Health



Please see addendum of this report for important disclosures.

+9% CGR 2014-19E

Diabetes

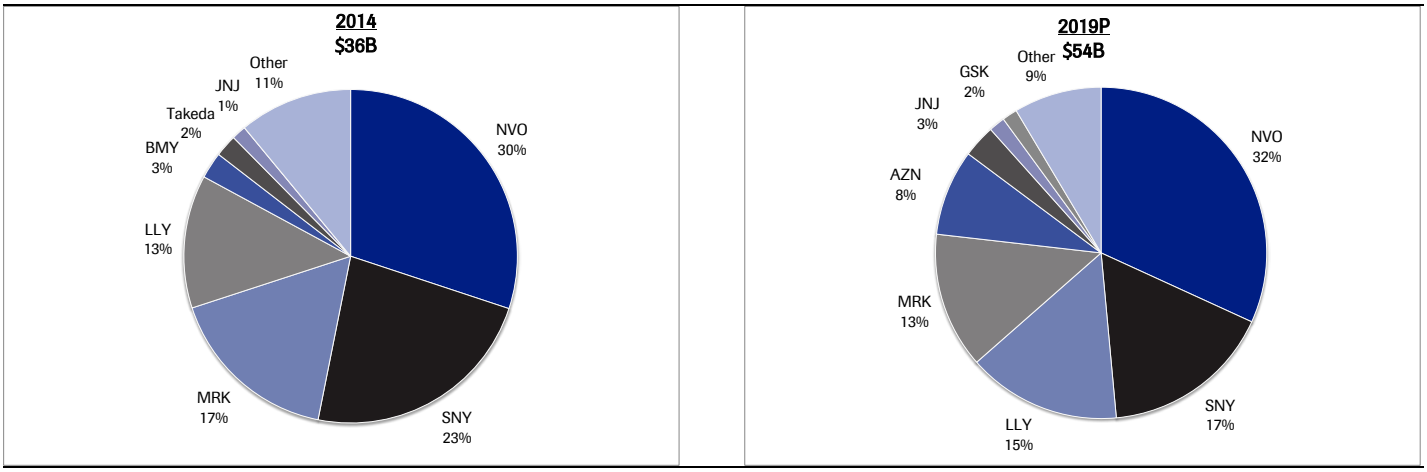
Diabetes: Many New Drugs, But Insulin Still Dominant

Diabetes is characterized by the inability to produce insulin and/or a dysregulated response to insulin. Insulin is a hormone that regulates metabolic substrate utilization and promotes the cellular uptake and conversion of sugars and starches into biochemical energy. The cause of diabetes is not fully understood, although both genetics and environmental factors such as obesity and physical inactivity appear to play roles. If left unregulated, diabetes-related metabolic sequela can result in organ damage involving the nervous system, kidneys, eyes, immune system, and cardiovascular system.

There are an estimated 382MM people worldwide with diabetes. There are 24MM children and adults in the United States, or 8% of the population, who have diabetes. An estimated 17.9MM (75%) have been diagnosed with the disease, approximately 90% with type 2 diabetes. While the pathogenesis of type 2 diabetes is not completely understood, early stages are associated with euglycemia (normal blood sugar levels) maintained by compensatory hyperinsulinemia in the setting of peripheral insulin resistance (metabolic syndrome). Prolonged elevations in circulating insulin result in the down-regulation of insulin receptors in muscle and adipose, increasing insulin resistance and hyperglycemia, and further increasing insulin secretion (non-insulin dependent diabetes mellitus). In the latter stages of type 2 diabetes, the pancreas is no longer able to produce enough insulin to compensate for extreme insulin resistance and beta-cells begin to die. At this stage patients often require exogenous insulin to maintain appropriate blood glucose concentrations (insulin-dependent diabetes mellitus). Type 2 diabetics are currently managed with diet, exercise, oral antidiabetes agents, and insulin when necessary. The use of insulin is increasing among type 2 patients as oral agents fail to get patients to goal (HbA1c <7%) and insulin becomes easier to administer. It is estimated that by 2030 the worldwide type 2 prevalence will have grown from 190MM to 330MM patients.

Five to ten percent of diabetics have type 1 diabetes, which is a state of absolute insulin deficiency stemming from autoimmune destruction of the insulin-producing beta-cells in the pancreas. Patients with type 1 diabetes produce little or no insulin and are dependent on insulin injections for survival. A small percentage of diabetics who appear to have type 2 diabetes actually have a slowly progressing form of type 1 diabetes and require insulin therapy.

Diabetes Category Market Share By $ Sales



Source: Cowen and Company

MAJOR TRENDS & ISSUES

In 2014, Novo Nordisk, Sanofi, Merck, and Eli Lilly led the $36B diabetes category. In 2019, we forecast that these same four companies plus AstraZeneca (post its January 2014 acquisition of Bristol's diabetes assets) will dominate a projected $54B market, driven by growth of their insulins and GLP-1 products.

- Insulin remains the cornerstone of diabetes treatment with an estimated 2014 WW market of $20B. Sales growth will be driven by increased penetration of insulin analogs resulting in an estimated market of $25B by 2019 (5% CAGR). Sanofi's Lantus is the leading basal insulin but competitive basal insulins and biosimilar glargine may be available by 2015-16. In August 2014 the FDA issued a tentative approval of BI/LLY insulin glargine (Basaglar). The approval is subject to an automatic hold as a result of a litigation filed by Sanofi that claims patents infringement. Merck is also stepping up its biosimilar glargine efforts by running two Phase III non-inferiority studies versus Lantus (both type 1 and 2 diabetes) with estimated primary completions in March and May 2015. A number of novel long acting basal insulins are in development; Novo's degludec (Tresiba) is rolling out in the E.U., Japan and may file in the U.S. H1:15 if DEVOTE (CV study) interim analysis is positive. Filing of Lilly's novel basal insulin (Peglispro) has been delayed to after 2016 as new clinical data is required to clear hepatotoxicity concerns. Sanofi's Toujeo concentrated glargine formulation allows for smaller volumes of administration and awaits regulatory approval in Q1:15. Sanofi hopes to expand the Lantus market opportunity. Eli Lilly's Humalog and Novo's Novalog split the short-acting market; new competitors have had very little impact.

- Oral DPP-IV inhibitors reduce the breakdown of GLP-1 and have become successful as add-on therapies, usually with metformin. 2014 WW market is valued $8.8B and is estimated to grow to $12.6B by 2019 (CAGR 7%). Merck's Januvia (sitagliptin) has performed well, but faces competition from AstraZeneca's Onglyza (saxagliptin), BI/Lilly's Tradjenta (linagliptin), and Takeda's Nesina (alogliptin). Novartis' Galvus (vildagliptin) has done well OUS. Takeda and Merck have once weekly oral compound (trelagliptin and omarigliptin) that were filed in Japan in March and November 2014.

- Our physician consultants view the oral DPP-IVs as less efficacious than GLP-1 analogs given their inability to engage GLP-1 in a wide variety of tissues. Head-to-

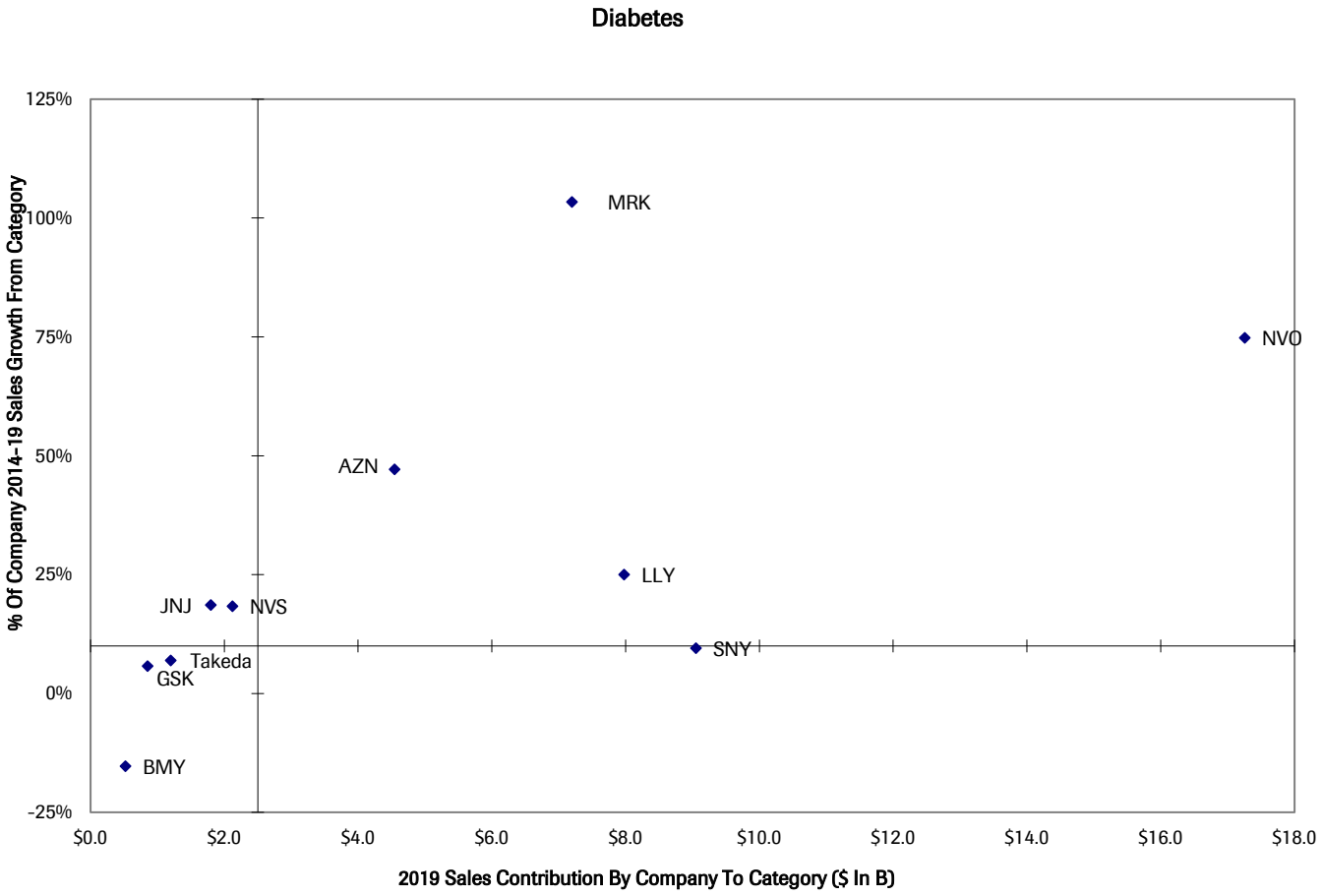
head studies vs. GLP-1 have shown DPP-IVs to produce inferior lowering of HbA1c. Despite their limited efficacy, DPP-IV success has been driven by their ease of use. Onglyza's SAVOR CV outcomes trial met its primary safety endpoint, but failed to improve CV outcomes; Januvia's TECOS CV trial is expected to have data available for presentation at ADA 2015. Our physician experts give DPP-IV inhibitors only a 10-15% chance of meeting CV endpoints.

- GLP-1 receptor agonist enhance pancreatic insulin secretion and reduce hepatic glucose production. 2014 WW market is valued $3B and is estimated to grow to $9B by 2019 (CAGR 24%). Sales growth of Astra's GLP-1s Byetta and Bydureon remains sluggish. Safety concerns have emerged for the class including drug-induced pancreatitis and a possible link to pancreatic neoplasms. FDA and EMA have largely dismissed a causal relationship between GLP-1 agonist and pancreatic cancer, although safety data from CV outcome trials will be key. Scrip data suggest endocrinologists are putting more new patients on Novo's Victoza, but that it has grown the GLP-1 market only modestly. Sanofi's Lyxumia (lixisenatide), has been launched in the E.U. but submission was pulled in the U.S. until Phase III trial complete which is expected for Q3:15; its differentiation will be in combo with Lantus. Lilly's Trulicity (dulaglutide), approved in late 2014 appears to have very good efficacy and acceptable safety. Glaxo's Tanzeum/Eperzan (albiglutide) appears to offer no differentiating features.

- Latest entrants to the oral diabetes treatment portfolio are the SGLT-2s. 2014 WW market is valued $574MM and is estimated to grow to $3.6B by 2019 (CAGR 44%). JNJ's Invokana, approved March 2013, has enjoyed first to market advantage. AZN's Farxiga, which was approved in January 2014, provides competition. Lilly/BI's Jardiance (empagliflozin) was approved in the U.S. and E.U. in late 2014. Merck/Pfizer's ertugliflozin is in Phase III. In early 2015 BI/Lilly first-in-class SGLT-2/DPP-4 combination (Glyxambi) was approved by the FDA and AZN is expected to file a similar combination (saxagliptin+dapagliflozin) in early 2015.

- Our scatter plot shows that, through 2019, we expect the diabetes therapies of Novo Nordisk, Sanofi, Eli Lilly, AstraZeneca and Merck will contribute significantly to sales.

Diabetes Scatter Plot



Source: Company data; Cowen and Company

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