Dissertation

Potential of GLP-1 Receptor Agonist in Type-2 Diabetes Mellitus in US

Submitted by:
Nivreti Pandit

Table Of Contents

Diabetes Mellitus: Is a Chronic Disease Caused By Ineffectiveness Of Insulin Produced By Pancreas

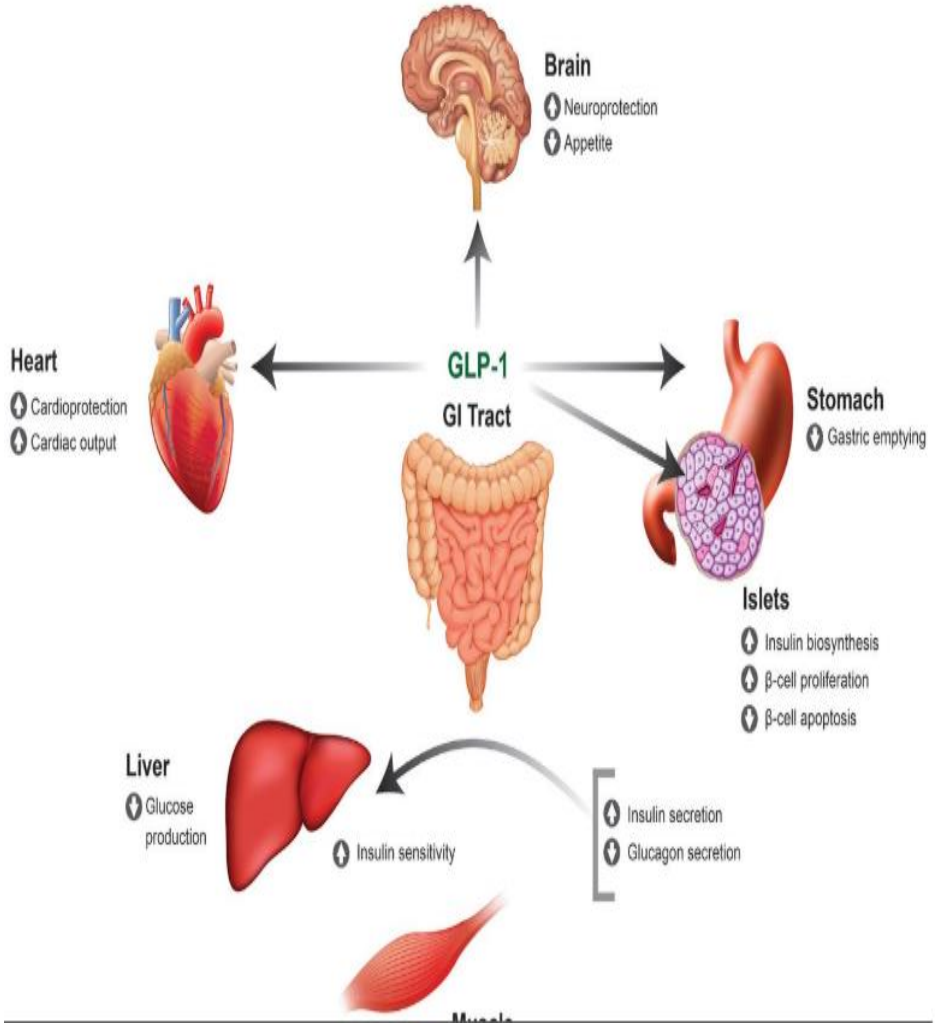
Definition

Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced

Symptoms

- Excessive thirst and dry mouth
- Recurrent fungal infections in the skin
- Frequent and abundant urination
- Slow healing wounds
- Lack of energy, extreme tiredness
- Blurred vision
- Tingling in hands and feet

Mechanism Of GLP-1 Agonist In Diabetes



Methodology- A Descriptive and Exploratory Study Involving Data From Different Databases

Research Question

What is the market potential of GLP-1 in Type-2 Diabetes Mellitus In US?

Objectives

- To study the competitive landscape of GLP-1 in diabetes market
- To determine the key products and players in the diabetes market
- To estimate the market value and market volume of GLP-1 in Type-2 Diabetes Mellitus

Materials And Methods

Study Design: Descriptive and exploratory study
Data Collection Technique: Review of relevant documents was done, and qualitative information was collected based on resource input provided.
Data Analysis: MS Excel
Data Source: Different databanks, research papers, journals and websites

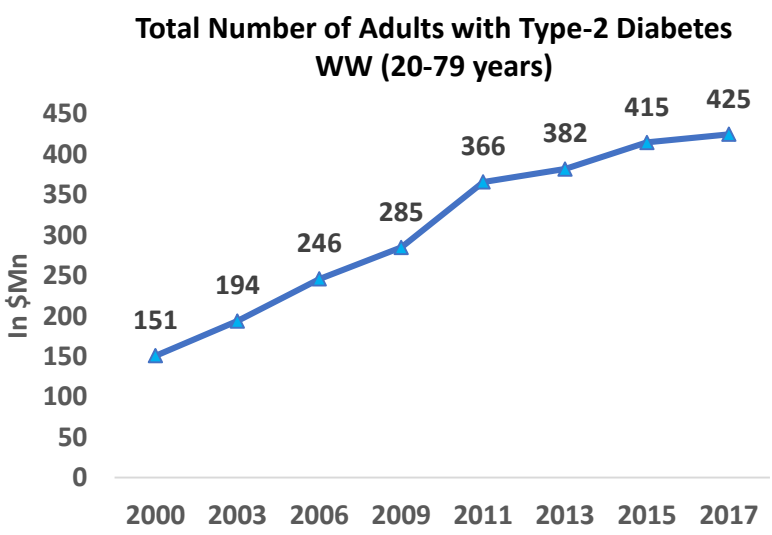
Duration of the Study

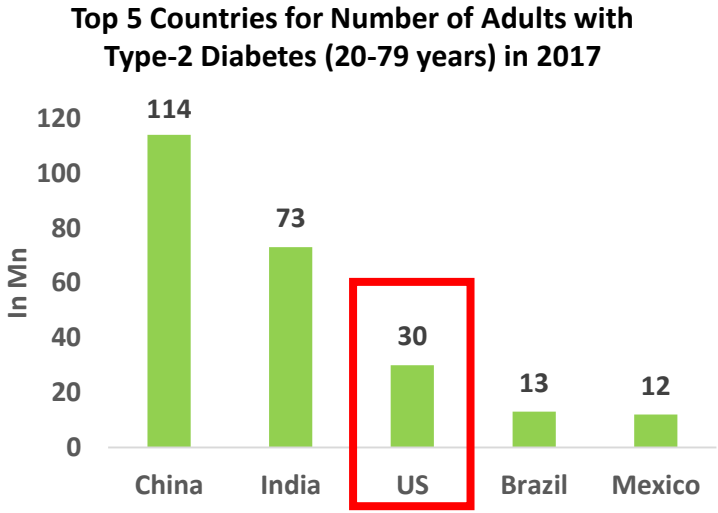
The study was done for a period of three months i.e. from 4th February 2019 to 3rd May 2019

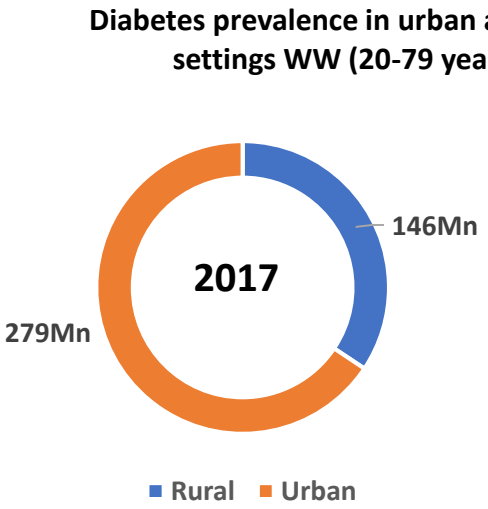
Literature Review

Title	Study	Sample Size	Year	Link
Predictors of Effectiveness of Glucagon-Like Peptide-1 Receptor Agonist Therapy in Patients with Type 2 Diabetes and Obesity	Identification of simple and accessible predictors of the response to aGLP-1 therapy will optimize the selection of patients for this therapy and improve not only glycemic control, but also the control of metabolic parameters which are cardiovascular risk factors	40 patients with type 2 DM (T2DM) and obesity who were treated with GLP-1	Dec 2018	https://www.hindawi.com/journals/jdr/2019/1365162/ref/
GLP-1 Receptor Agonists: An Alternative for Rapid-Acting Insulin- A US Pharmacist Report	GLP-1 RAs demonstrated a beneficial effect on weight loss as opposed to weight gain seen with insulin	566 patients suffering from diabetes mellitus since 11 years	Oct 2016	https://www.uspharmacist.com/article/glp1-receptor-agonists-an-alternative-for-rapidacting-insulin

Diabetes Prevalence Is On The Rise Across The Globe With ~425Mn People Living With The Disease



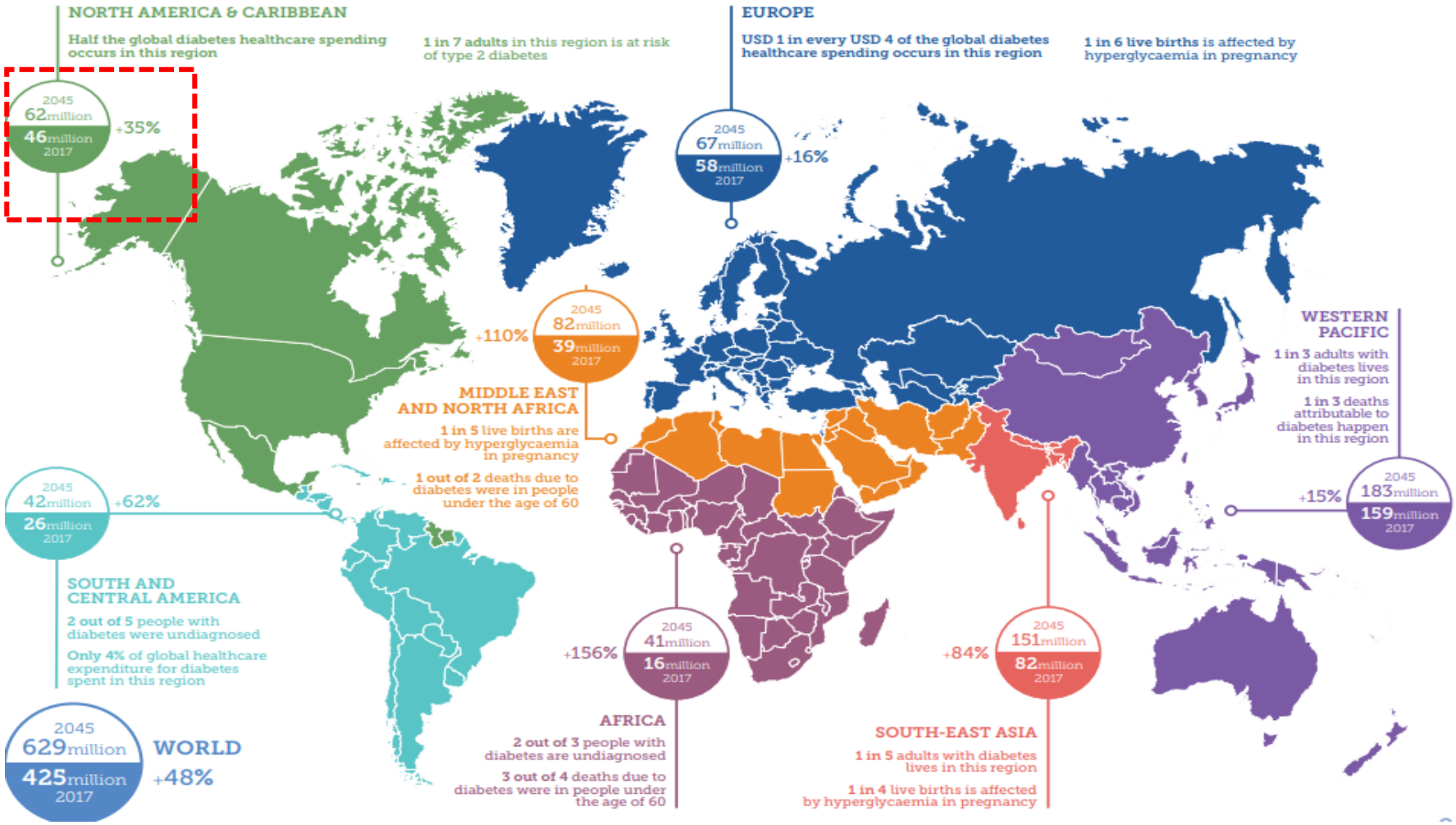




- Diabetes is a global emergency with approx. 425 million people (**8.8% of adults 20-79 years)** living with the disease worldwide
- There are **327Mn** people of working age(20-64 years) with diabetes, and 122.8 million people (65-99 years) with diabetes
- In 2017, there are more people 20-79 years with diabetes in urban (**279Mn**) versus rural (**146Mn**) settings, and the prevalence is higher in urban(10.2%) than in rural areas(6.9%)
- Diabetes accounted for **10.7%** of global all-cause mortality among people in this age group
- Approximately **4.0Mn** people aged between 20 and 79 years are estimated to die from diabetes in 2017
- Approx. **54.4Mn** people, or **15.4%** of adults aged 20-79 years in NAC have impaired glucose tolerance (IGT), putting them at high risk of developing type 2 diabetes

NAC- North America And Caribbean Region , Source: IDF-International Diabetes Federation

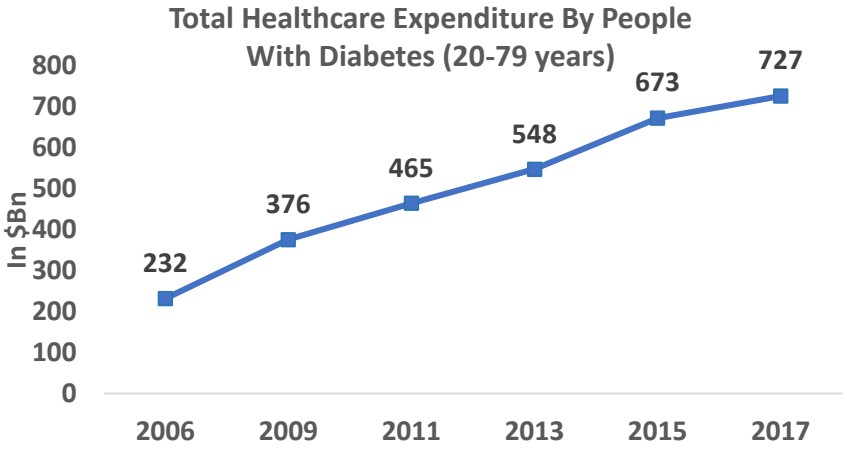
Number Of People With Diabetes Worldwide And Per Region In 2017 And 2045 (20-79years)

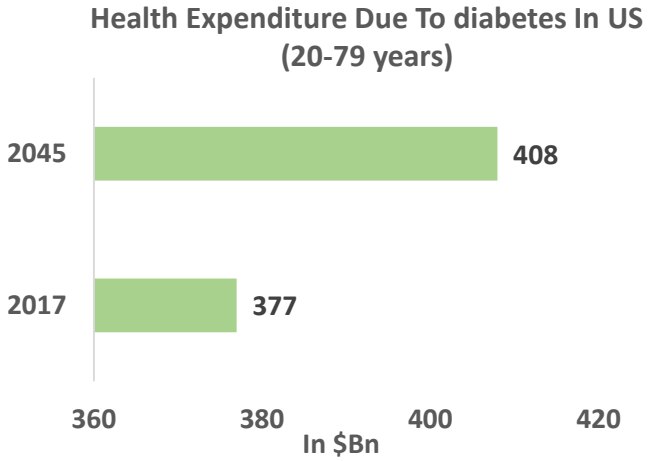


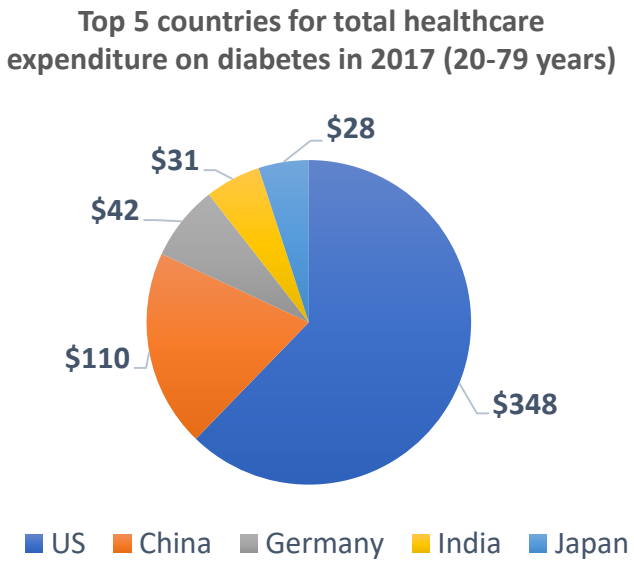
- With 13.0% (10.8-14.5%) of adults aged 20-79 years affected, NAC has the highest prevalence of diabetes among all the regions
- An estimated 46(38.2-51.3) million people with diabetes aged 20-79 years live in the region in 2017, of whom 17.3 million (37.6%) are undiagnosed
- In the USA, more than **176,700people** are estimated to die from diabetes in 2017, one of the highest numbers of deaths due to diabetes of any country in the world

Source: IDF-International Diabetes Federation

Diabetes Imposes A Significant Economic Impact On Healthcare Systems With Nearly ~$348Bn Spent In The US Alone



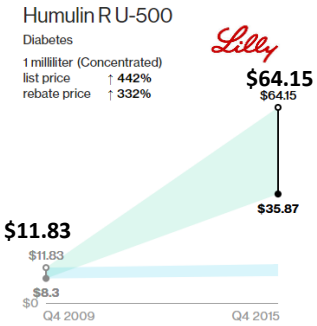


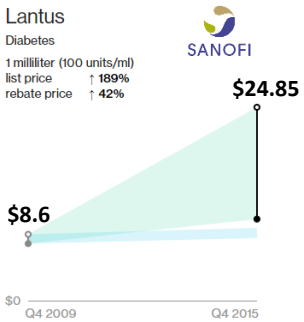


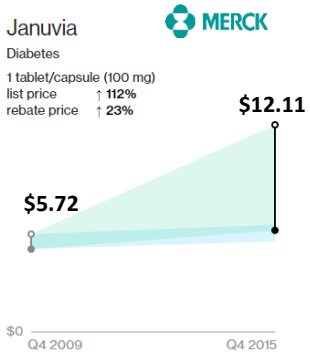
- In 2017, the total healthcare expenditure on diabetes is estimated to be ~ $727 Bn (20-79 years), which represents an 8% increase compared to the 2015
- When using the expanded age group of 18 to 99 years, the costs estimates up to USD 850 billion
- It is projected that the healthcare expenditure on diabetes will reach USD 776 billion by 2045
- The highest expenditures on diabetes were observed in the US with ID 348 billion, followed by China, and Germany, with ID 110 billion, and ID 42 billion respectively
- US has the highest yearly cost per person with diabetes with ID 11,638 spent in 2017

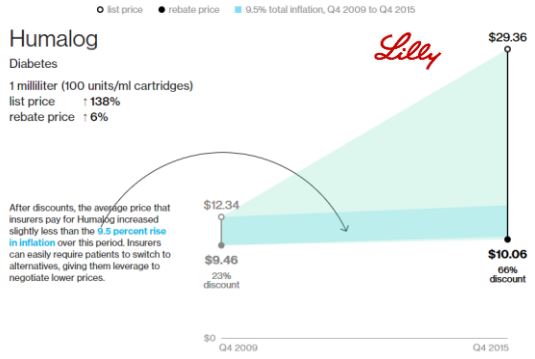
NAC- North America And Caribbean Region , Source: IDF-International Diabetes Federation

Diabetes Drug Pricing Practice For Medicines With Global Sales Of More Than $1 Billion A Year





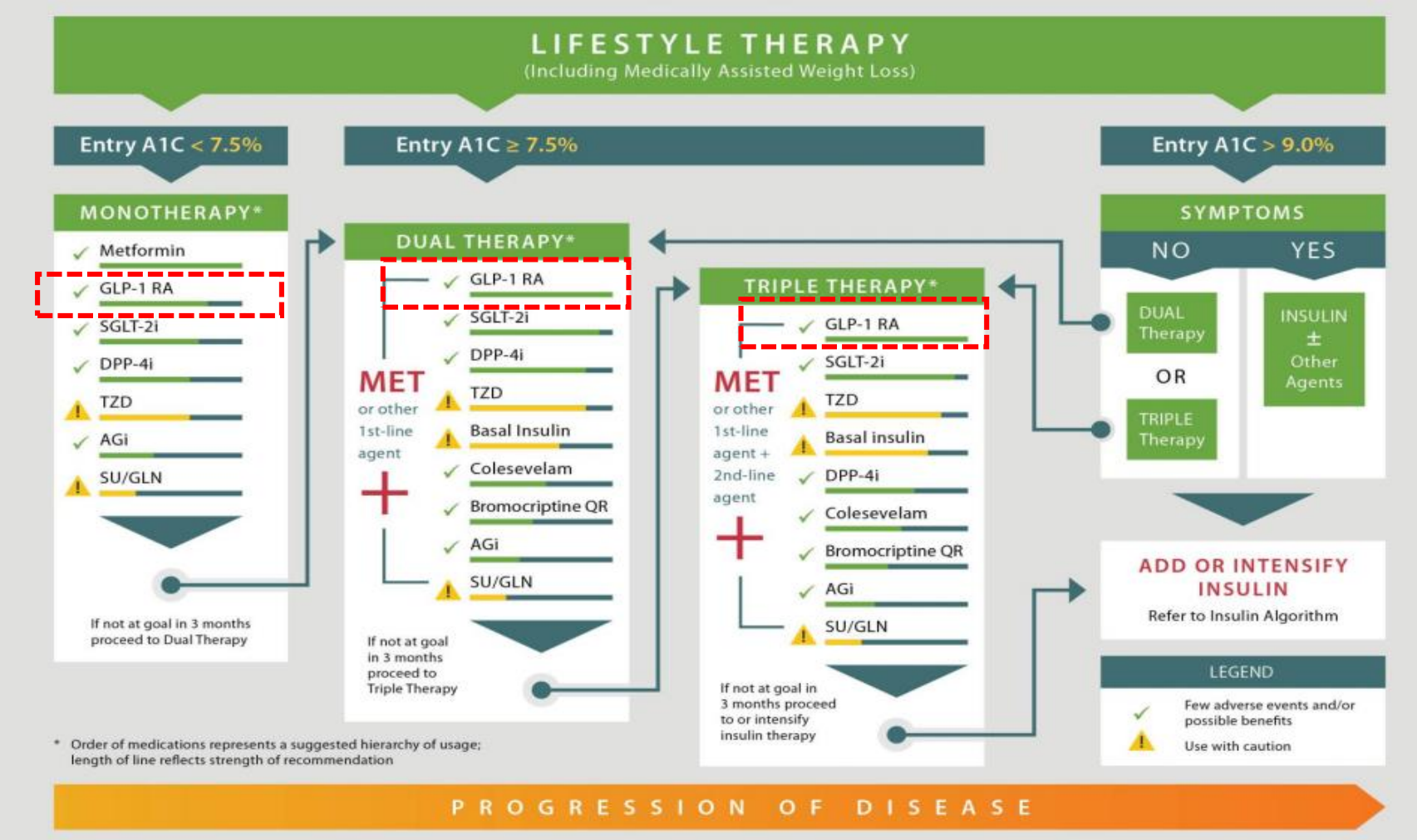




- Discounts vary dramatically, depending on disease type and how much competition exists
- Humalog, (a short-acting insulin made by Eli Lilly & Co.) list price increases were wiped out by ever-bigger discounts
- Lilly offered discounts of 66 percent on Humalog last year, up from 23 percent in 2009, according to SSR Health estimates
- Lilly provides on an average 35 percent discount for commercial insurance plans and 80 percent for government plans
- Novo Nordisk offered over 50 percent discount in for all its medicines, compared with about 35 percent in 2010
- Januvia's after discount price rose by 23% when the inflation was about 9.3% suggesting a price increase slightly above the inflation price
- Humulin R U-500 after discount price rose by 332% compared to an inflation of 9.5 percent suggesting pricing practice well above inflation
- Lantus price after discount rose by 42% in Q42015 compared to a price of $8.6 in Q42009 suggesting pricing practice well above inflation

- Humalog had a price increase from $12.34 in Q4 2009 to $29.36 in Q42015
- After discounts, the average price that insurers pay for Humalog increased slightly less than the 9.5 percent rise in inflation over this period
- Insurers can easily require patients to switch to alternatives, giving them leverage to negotiate lower prices
- Humalog faces competition from a very similar drug: Novolog, from Novo Nordisk A/S
- Discounts for Novolog have risen in a parallel fashion since 2012

Glycemic Management of Type 2 Diabetes Involves Lowering Of A1C Levels And Preventing Hypoglycemia



- Monotherapy may be effective when the baseline A1C levels are between 6.5%-7.5%(Metformin is the first choice for monotherapy if no contraindications)
- Dual therapy with metformin provides superior glycemic control over metformin alone (Baseline A1C 7.6% - 9.0%)
- If patient is asymptomatic with recent onset of disease and drug naïve, may consider starting with dual or triple oral regimens (Baseline A1C > 9.0%), If symptomatic, start insulin

Pipeline GLP-1

BPI-3016
(Beta Pharma

PGC-GLP-1
(Pharma IN)

PB-119
Peg Bio Co., Ltd.
(NCT03059719- Oct 2016)

TTP-273
vTv Therapeutics
(NCT02653599- Jan 2017)

Taspoglutide
Hoffmann-La Roche
NCT00909597- Nov 2010

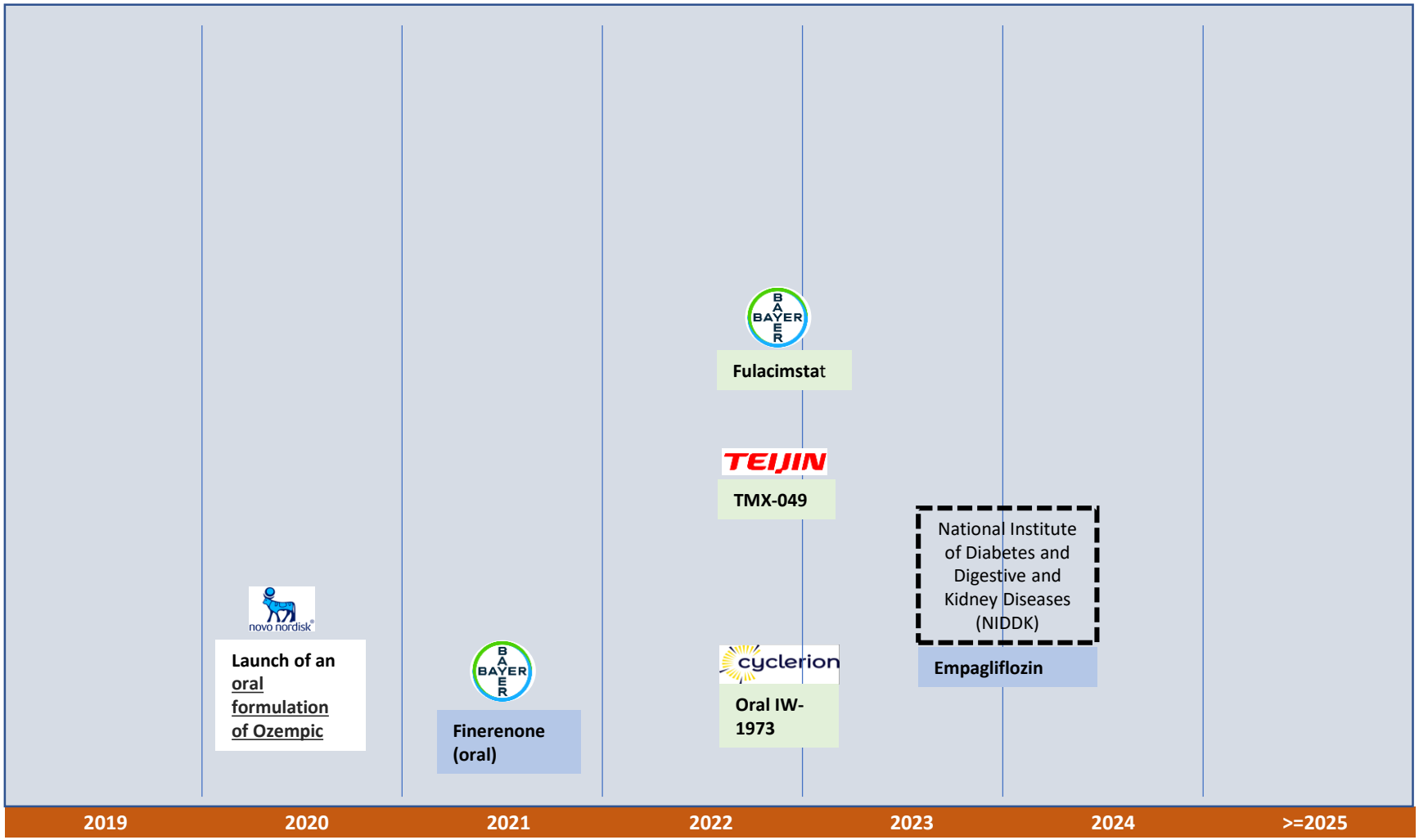
Efpeglenatide
Sanofi pharmaceuticals
(NCT03684642**-Dec 2020)**

Bexagliflozin
Theracos
(NCT02390050- June 2016)

- Includes 2 Asset in Preclinical Stage
- PB-119 is in Phase 1 for diabetes
- Efpeglenatide is in phase 3 for diabetes

Preclinical | Phase-1 | Phase-2 | **Phase-3**

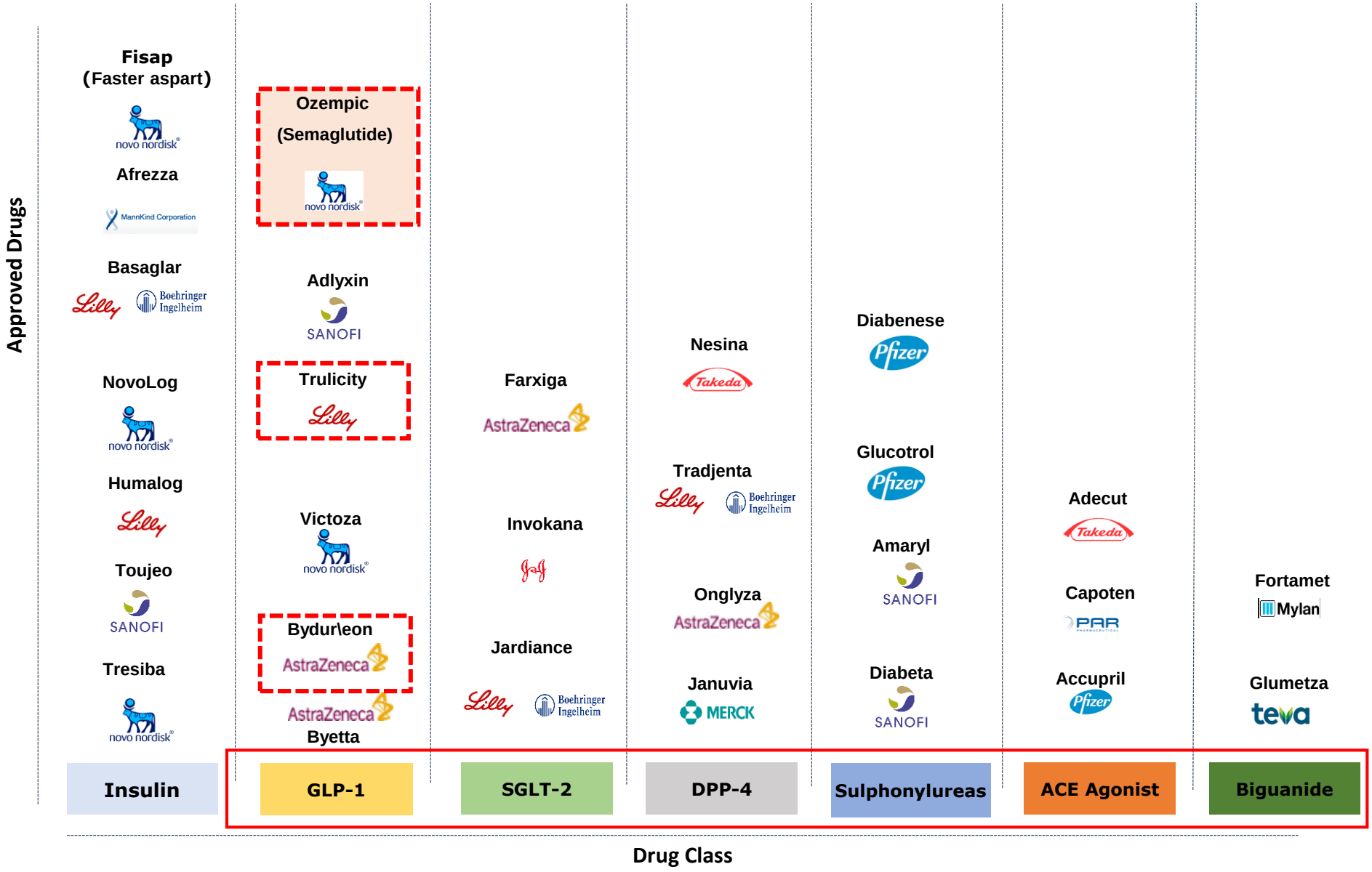
Pipeline Type 2 Diabetes Mellitus



- There are currently 5 assests in Pipeline for Diabetic Nephropathy
- There is one non-industry sponsored assest in pipeline for Diabetic Nephropathy

Phase 2 | Phase 3 | Non-Industry Sponsored

The Treatment Landscape Itself Is Crowded, With Multiple Classes And Multiple Agents Within Each Class With No Novel Treatments in Pipeline



GLP-1: Glucagon-like peptide 1, SGLT-2: Sodium-glucose co-transporter-2, DPP-4: dipeptidyl peptidase 4, ARB- Angiotensin Receptor Blockers, ACE- Angiotensin Converting Enzyme

Once Weekly

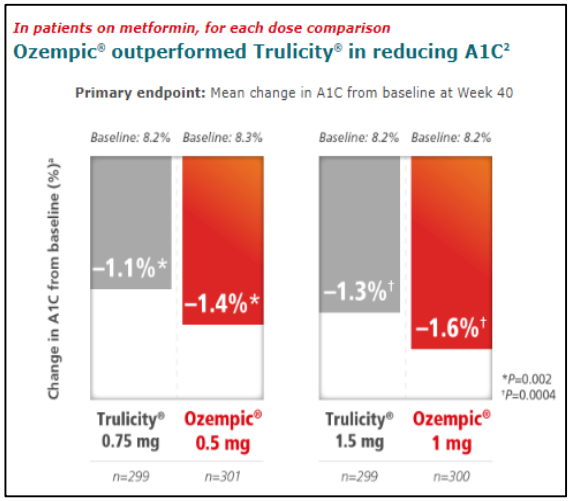
Diabetes Products Forecast 2024

		Annual Sales WW ($B)	($B)	($B)	
Product	**Company**	**Description**	**2018e**	**2021e**	**2024e**
Trulicity	Eli Lilly	GLP 1 agonist (once-weekly injection)	3.07	4.48	4.89
Ozempic	Novo Nordisk	GLP 1 agonist (once-weekly injection)	0.21	2.71	4.25
Jardiance	Boehringer Ingelheim	SGLT 2 inhibitor (once-daily pill)	1.45	2.28	2.9
Tresiba	Novo Nordisk	Insulin analogue	1.36	2.24	2.9
Farxiga	AstraZeneca	SGLT 2 inhibitor (once-daily pill)	1.39	2.1	2.49
NovoRapid	Novo Nordisk	Insulin analogue	3.01	2.65	2.41
Semaglutide Oral	Novo Nordisk	GLP 1 agonist (once-daily pill)	-	0.66	2.23
Lantus	Sanofi	Insulin analogue	4.24	2.82	2.14
Humalog	Eli Lilly	Insulin analogue	3.04	2.35	1.79
Glyxambi	Boehringer Ingelheim	DPP IV & SGLT 2 inhibitor (once-daily pill)	0.53	1.38	1.67
		Total diabetes market	49.12	56.2	56.3

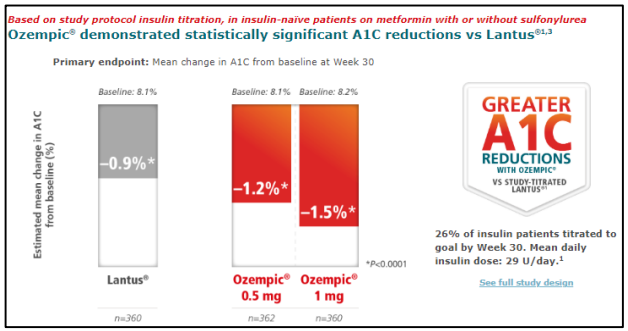
Source: EvaluatePharma

GLP-1 Agonist Efficacy- Market Value

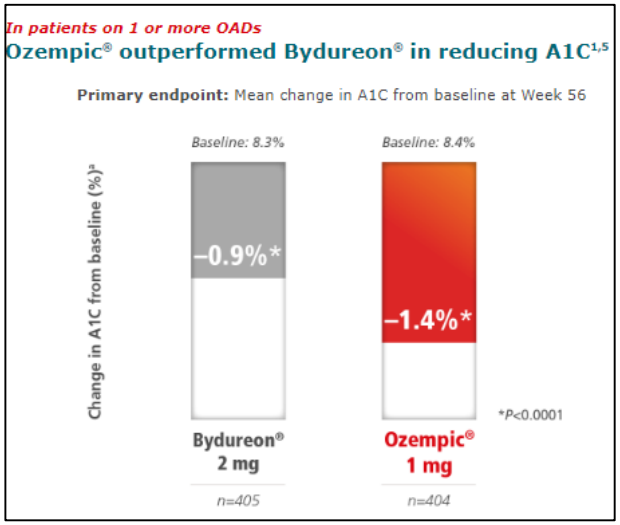
- Semaglutide (GLP-1) is a next generation long-acting glucagon-like peptide-1 (GLP-1) analogue with 94% homology to human GLP-1 (once weekly dosing)
- Semaglutide exhibits GLP-1 receptor mediated effects, leading to lowering of glucose and decreased appetite through physiologically relevant mechanisms
- As a result, semaglutide provides strong glycaemic control and weight loss (In addition, the cardiovascular safety of semaglutide has been confirmed)
- Ozempic was approved by the US FDA on 5 December 2017 (Launched in Feb 2018)
- **New or worsening nephropathy was lower with both doses of Ozempic (semaglutide) vs. placebo** (The SUSTAIN-6 clinical trial in patients with T2DM and high cardiovascular risk showed that once-weekly semaglutide **0.5 mg or 1 mg** in addition to standard care was non-inferior and superior to placebo with regard to a reduction in major adverse cardiovascular events after 105 weeks of therapy. In this study, there was also a significant 23% absolute reduction in the risk of new or worsening nephropathy with semaglutide compared with placebo)



Vs Trulicuty

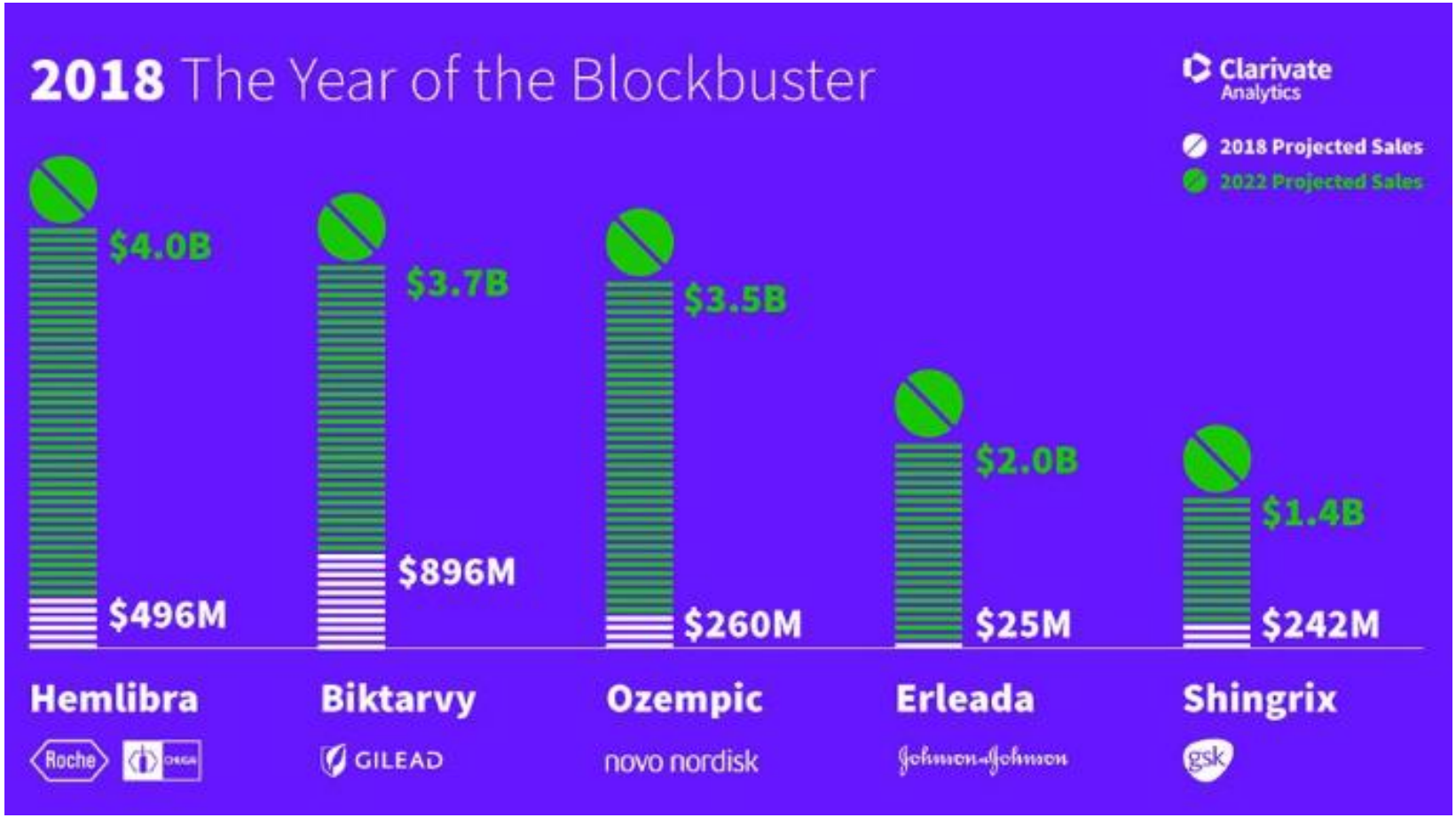


Vs Lantus



Vs Bydureon

Ozempic Sales Are Forecasted To Reach $3.5Bn By 2022 And Was In The 2018 Blockbuster Drugs



- The Cortellis Consensus Forecast data for the semaglutide, including Ozempic and oral semaglutide, currently stand at $4 billion for 2022

In The Increasingly Tough Diabetes Space GLP-1 Agonists Represent The Fastest-growing Category, And Once-daily Victoza Is Currently The King Of This Castle

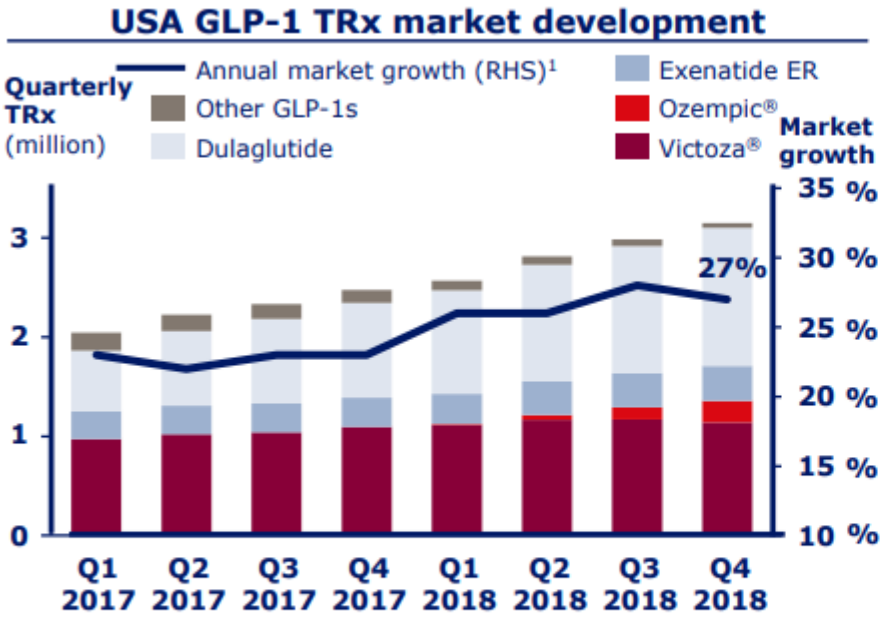
Once-weekly Ozempic launched in February, has put Novo on an equal footing with Lilly in terms of convenience, and Novo hopes to gain more ground with an oral version of semaglutide which could reach the market in 2020

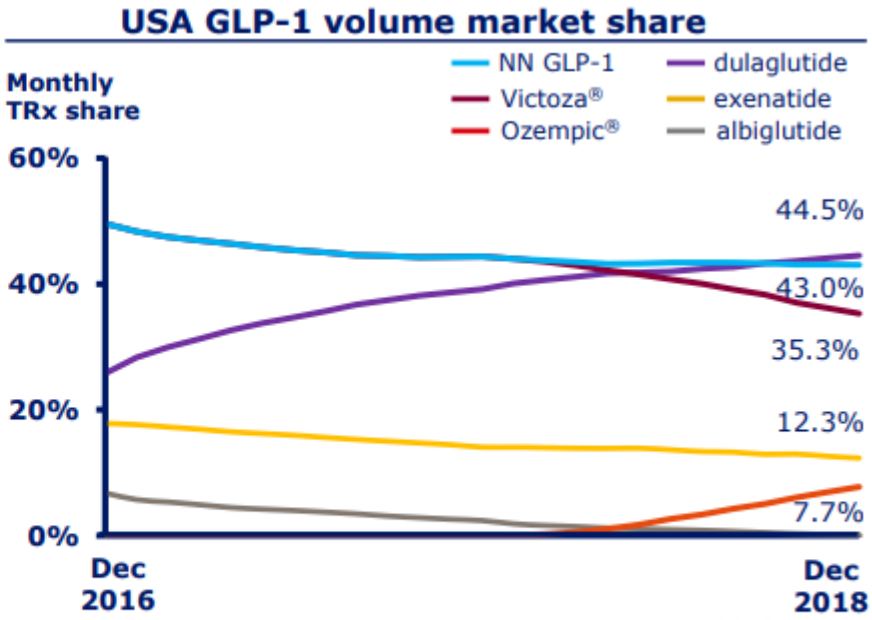
Battle of the GLP1 agonists

			Annual sales ($m)				
Product	**Company**	**Status**	**2018e**	**2020e**	**2022e**	**2024e**	**12-mth change in 2022 forecast ($m)**
Trulicity	Lilly	Marketed	2,872	3,858	4,407	4,726	+769
Ozempic	Novo Nordisk	Marketed	209	1,819	3,407	4,652	+1,497
Oral semaglutide	Novo Nordisk	Phase III	-	171	1,211	2,087	+399
Victoza	Novo Nordisk	Marketed	3,975	3,573	2,793	1,195	-963

Source: EvaluatePharma.

Ozempic Launch Contributed To 27% GLP-1 Market Growth





Source: IQVIA weekly NPA, week ending 4 Jan 2019 for Q4 2018; monthly NPA dated Nov 2018 TRx
Script Count for prior quarters
CV: Cardiovascular
[1] Growth rate three months year over year
RHS: Right hand side

Source: IQVIA monthly NPA, Nov 2018; weekly NPA for Dec, week ending 4 Jan 2019

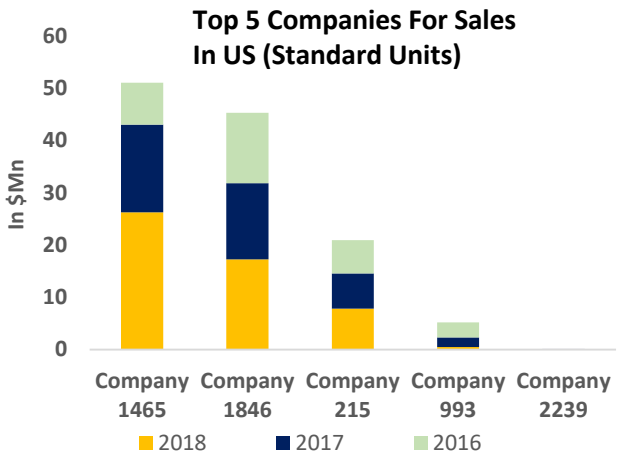
Ozempic carved out **a 5.6% share** for the GLP-1 non-insulin antidiabetics market and secured **nearly 5,000 new prescriptions** for the week of July 20, 2018 (Source: Data compiled by Iqvia and cited by Cowen & Co.)

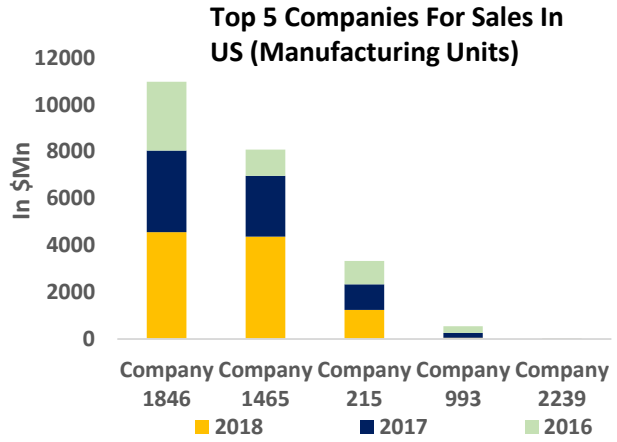
Ozempic's GLP-1 NRx market share grows, but rivals remain daunting

	Week of: March 2	April 6	May 4	June 1	July 6	July 13	July 20
Ozempic	717	1,418	2,297	2,603	3,763	4,611	4,898
Trulicity	32,899	32,116	34,408	30,241	29,927	35,153	35,364
Victoza	36,771	34,589	35,812	32,251	32,191	35,691	34,685
Bydureon	10,653	10,324	10,760	9,214	8,962	10,527	10,714

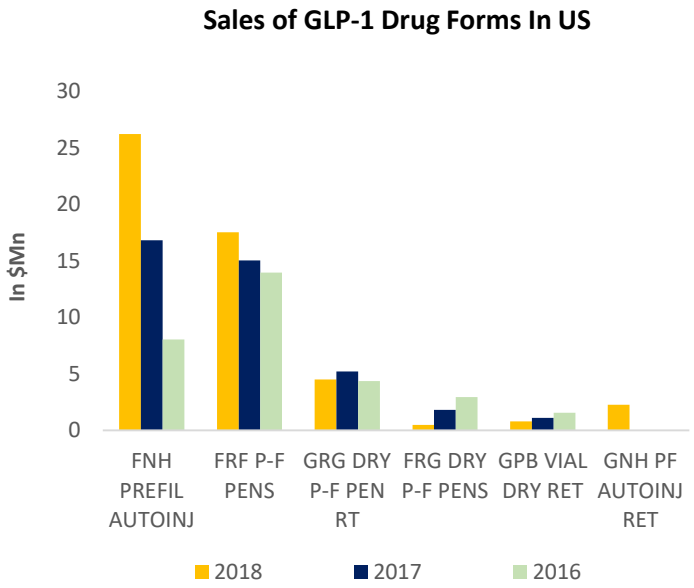
SOURCE: Cowen & Co., Iqvia

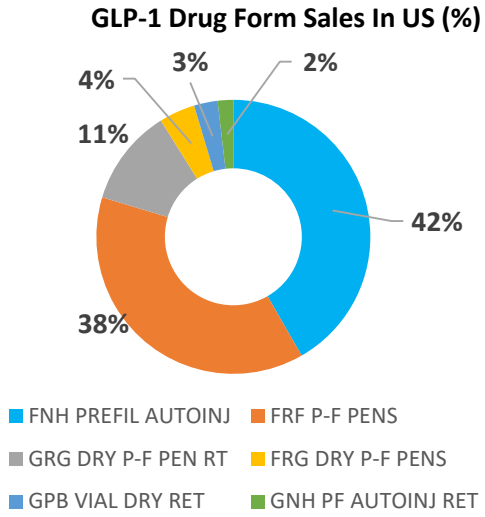
Market Analysis Of GLP-1 Agonist In US





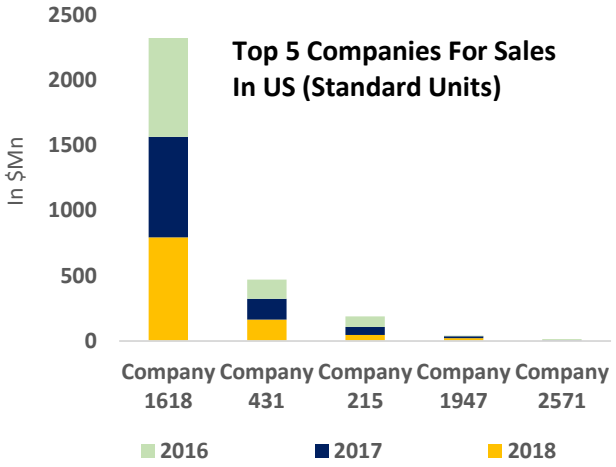
- The top five companies In GLP-1 Market Include- Company1465, Company 1846, Company 215, Company 993, Company 2239
- Company 1465 showed the highest sales of ~$22Mn in 2018
- Company 1846 has the highest sales of ~$4Bn (in terms of manufacturing units) for the year 2016-2018
- Company 993 had had a negative growth of -52%and - for the year 2016-17

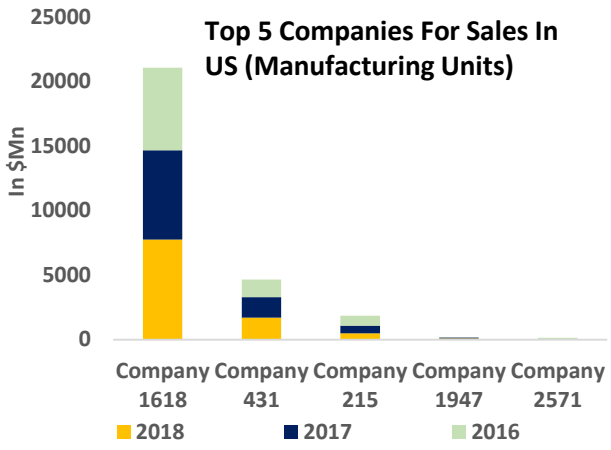




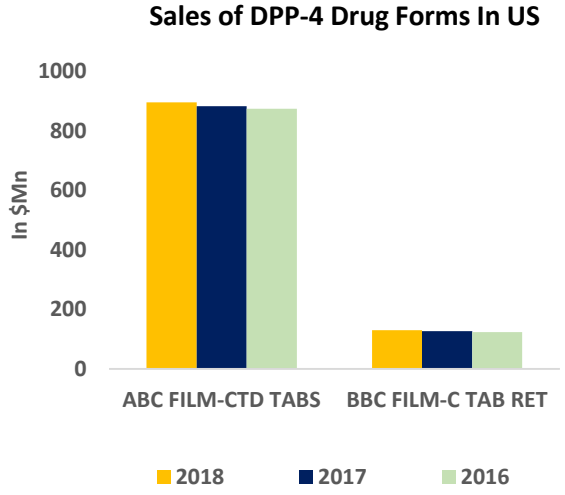
- GLP-1 Agonist are dispensed in 6 forms i.e. Pre-filled Auto-injection, FRF Pens, GRG Dry P-F Pens, FRG Dry Pens, GPB Vial and GNH PF Auto-injection
- The FNH Pre-filled Auto-injector had the highest sales of 42% followed by FRF P-F Pens for the year 2016-18
- Sales of FNH Pre-filled Auto-injector was highest for all the year with sales of ~$26Mn in 2018
- FRF P-F Pens had sales of ~$17 Mn in 2018

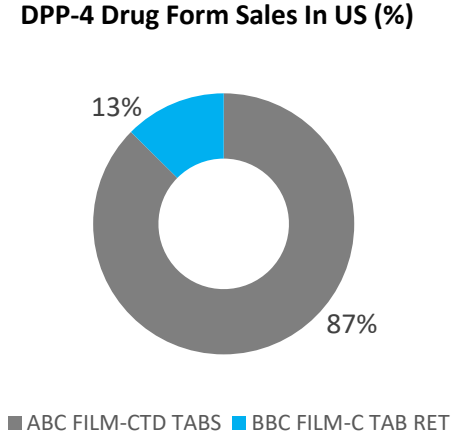
Market Analysis Of DPP-4 Agonist In US





- The YOY growth for company1618 was 2% in 2016-17 and 3% in the year 2017-18(SU)
- Company 1618 has the highest sales of ~$1Bn (in terms of standard units) for the year 2016-2018(SU)
- Company 2571 experienced a negative growth of -106% and -97% for the year 2016-17 and 2017-18 respectively(SU)

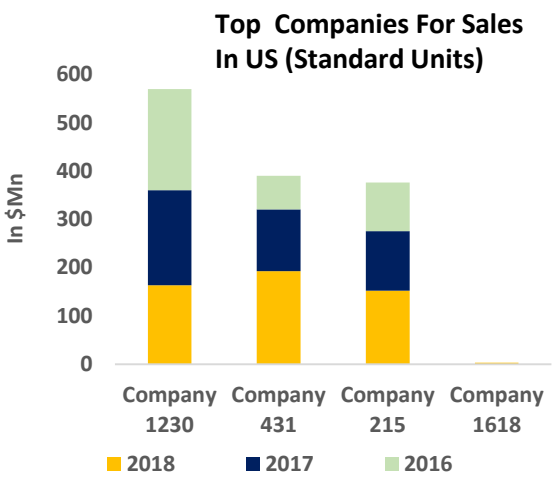


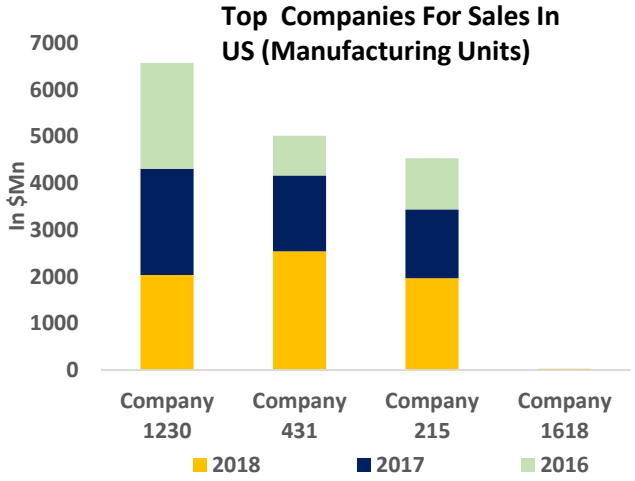


- DPP-4 Agonist are dispensed in 2 forms i.e. ABC Film Coated Tablets and BBC Film-C Tablets
- The BBC Film C- Tab had the highest sales of 87% compared to 13% sales of the BBC Film-C Tab for the year 2016-18
- Sales for ABC Film-CTD tablets was more than than BBC tablets with ~$895Mn sales in 2018
- BBC Film-C Tab Ret had sales of ~$130 Mn in 2018

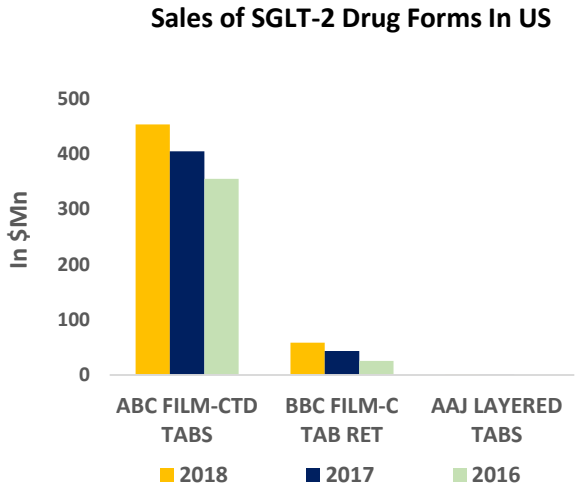
SU- Standard Units, MnF- Manufacturing Units

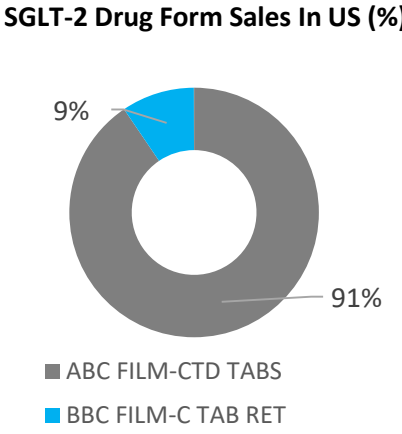
Market Analysis Of SGLT-2 Agonist In US





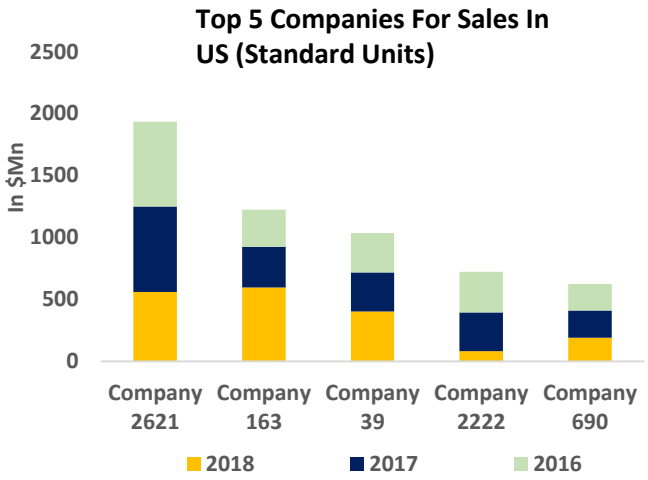
- The YOY growth for company 1230 was -7% for the year 2016-17 and -20% in the year 2017-18 suggesting a decrease in the sales per year
- Company 1230 has the highest sales of ~$163Mn (in terms of standard units) for the year 2016-2018 (SU)
- Company 431 had a negative growth of -106% and -97% for the year 2016-17 and 2017-18 respectively(SU)

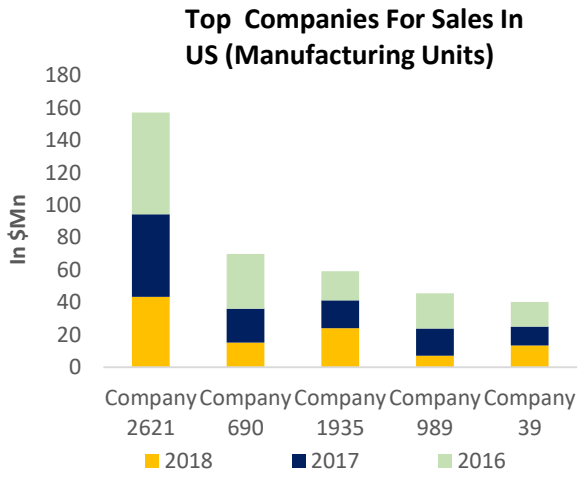




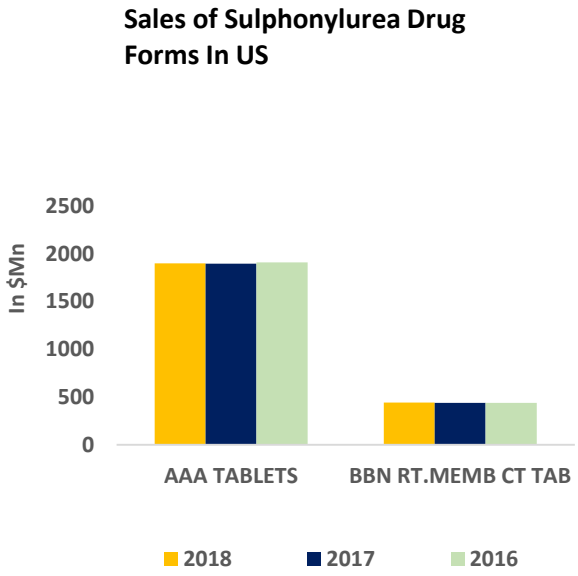
- SGLT-2 Agonist are dispensed in 3 forms i.e. ABC Film Coated Tablets, BBC Film-C Tablets and AAI Layered Tabs
- The ABC FILM-C Tab had the highest sales of 91% compared to 9% sales of the BBC Film-C Tab for the year 2016-18
- Sales for ABC Film-CTD tablets was highest for all the year with sales of ~$453Mn in 2018
- BBC Film-C Tab Ret had sales of ~$58 Mn in 2018

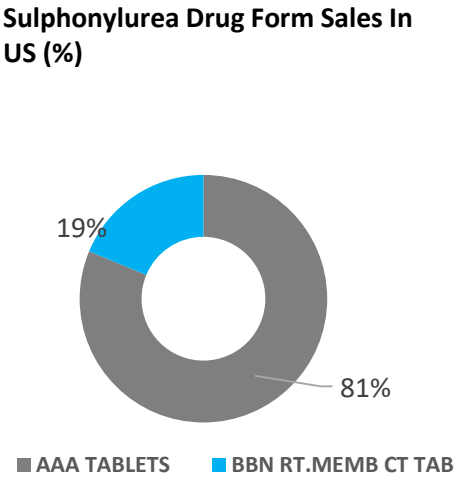
Market Analysis Of Sulphonylureas In US





- The top five companies In Sulphonylurea market includes - Company2621, Company 163, Company 39, Company 2222 and Company 690
- Company 2621 showed the highest sales of ~$561Mn in 2018
- Company 2621 has the highest sales of ~$4Bn (in terms of manufacturing units) for the year 2016-2018
- Company 2222had a negative YOY growth of -5%and for the year 2016-17





- Sulphonylureas are dispensed in 2 oral forms i.e. AAA Tablets, BBN RT Memb. CT Tabs
- The AAA Tablets had the highest sales of 81% followed by 19% sales for the BBN RT Memb. CT Tablets for the year 2016-18
- Sales of AAA Tablets was highest for all the year with sales of ~$1Bn in 2018
- BBN RT memb. CT Tabs had sales of ~$442Mn in 2018

Key Trends In Diabetes Market

Artificial Pancreas

- Bigfoot Biomedical is building an artificial pancreas for diabetes
- The market is projected to rise in 2018 as more patients demand the technology and more insurers reimburse for the systems

- Bigfoot bought an insulin pump company, partnered with continuous glucose monitor company Dexcom, to work on building an artificial pancreas system
- This system can also be connected to the patient's phone
- The first trial for the device got underway in July, and the company hopes to get the device in the market in the next few years
- It uses computer algorithms to automatically and continuously deliver an adequate supply of insulin to the body
- Approved by the FDA, it enables direct communication between a glucose monitoring device and an insulin pump to stabilize a person's blood glucose level

Glucose Meters/ Smart Pens

Glucose meters will offer non-invasive methods to monitor blood glucose

- Novo Nordisk's Novo Pen Echo Plus reusable insulin pen boasts several features designed to make dosing easier
- While its predecessor, the NovoPen Echo, records only the most recent dose, the Echo Plus stores three months of injections—up to 800 doses
- The company anticipates a US release in 2019
- Dario makes a personalized, pocket-sized, all-in-one glucose meter coupled with a real-time mobile app to track, monitor and manage diabetes from a smartphone

Insulin Pumps

- Tandem is expected to launch insulin T:slim X2 insulin pump in 2019
- If approved by the FDA, it will be the first system to correct elevated blood glucose levels by automatically delivering a correction bolus dose of insulin

Ready to use Glucagon Therapy

Glucagon is used to treat severe hypoglycemia in a diabetes patient

Rescue Pen

Nasal Spray

- Currently, glucagon must be mixed right before it's injected
- Ready-to-use glucagon solutions may be on the way: Xeris Pharmaceutical's Rescue Pen and a nasal spray from Eli Lilly are both under review by the FDA with approval expected in mid-2019

Replacing insulin-producing cells

- Although islet cell transplants are commercially available in many countries, the procedure is still experimental in the US due to concerns about effectiveness and about the short supply of human islet cells available for transplant

Conclusion And Suggestions

- The branded GLP-1 is facing stiff competition from the other drugs and generics in the market. Hence future market strategy should come up to address this problem
- GLP-1Agonist have shown superior and statistically significant reduction in diabetes market relative to standard of care with sales forecasted to reach $3.5Bn by 2022 [2018 sales were ~$276Mn].
- Ozempic (a GLP-1 analog) gained 25% market share when it was launched in US in 2018. (Ozempic is direct to consumer product, which carved out a 5.6% share for the GLP-1 non-insulin antidiabetics market and secured nearly 5,000 new prescriptions by mid-July (within 4 months of launch)
- At the end of January 2019, GLP-1 analogue held a 24% share of weekly new-to-brand prescriptions in the diabetes market at the time of its launch, according to Iqvia sales estimates cited by Credit Suisse
- The main GLP-1 Agonist grabbing the diabetes market include- Trulicity (Lilly) and Ozempic (Novo Nordisk). Once-weekly launch of GLP-1 inhibitor-Ozempic in 2018 has put Novo on an equal footing with Lilly in terms of convenience and hopes to gain more ground with sales expected to reach $4.7Bn by 2024[slide 14 for more details]
- Another oral GLP-1 is expected to launch in 2020 with greater efficacy results in the clinical trials which is expected to boost up the sales of GLP-1 Agonist in the diabetes market space
- Thus, GLP-1 Agonist with its potential anti-hyperglycemic effect and weight loss reductions in diabetes mellitus patients holds a greater scope in the treatment of Type-2 diabetes mellitus patients