BRYAN, GARNIER & CO

INDEPENDENT RESEARCH

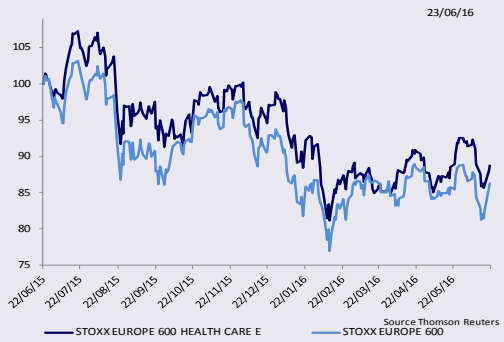
24th June 2016

Pharmaceuticals

Back from ADA 2016: Update on T2D treatments

Pharmaceuticals

ADOCIA		**BUY**	**FV EUR100 vs. 93**
Bloomberg	ADOC FP	Reuters	ADOC.FR
Price	EUR48.44	High/Low	93.65/44.43
Market cap.	EUR332m	Enterprise Val	EUR-51,959m
PE (2016e)	37.3x	EV/EBIT (2016e)	-3.7x
NOVO NORDISK		**NEUTRAL**	**FV DKK400**
Bloomberg	NOVOB DC	Reuters	NOVOB.CO
Price	DKK348.2	High/Low	410.7/306.4
Market cap.	DKK700,775m	Enterprise Val	DKK675,624m
PE (2016e)	22.9x	EV/EBIT (2016e)	13.7x
SANOFI		**NEUTRAL**	**FV EUR83**
Bloomberg	SAN FP	Reuters	SASY.PA
Price	EUR72	High/Low	100.65/67.27
Market Cap.	EUR92,662m	Enterprise Val	EUR100,058m
PE (2016e)	13.2x	EV/EBIT (2016e)	10.4x
ZEALAND		**BUY**	**FV DKK176**
Bloomberg	ZEAL DC	Reuters	22Z.F
Price	DKK121	High/Low	168.5/92.5
Market Cap.	DKK2,969m	Enterprise Val	DKK3,079m
PE (2016e)	NS	EV/EBIT (2016e)	NS



We thought it might be useful to provide some feedback from the 2016 ADA congress in New Orleans since it is very illustrative of the current trends in the diabetes field and as such is informative for companies working in the space which are under our coverage, like Novo-Nordisk, Sanofi, Zealand and Adocia.

- Of course, the main point was to gain a better feel of how the clinical results were received by attendees of the presentations. From this perspective, CV outcome studies were very much in focus, testifying to the increasing relevance of morbidity-mortality trials when approving drugs to treat diabetes. Henceforth the aim is no longer just to say there is no harm but to prove a benefit.
- Although the final LEADER results appeared disappointing to some investors, liraglutide is the first GLP-1 analogue to show CV benefit and we found the data very compelling across the board, including safety-wise. We know that SUSTAIN-6 also met the same primary endpoint and so we expect Novo-Nordisk to remain a solid leader in the GLP-1 class.
- Moving to the combination of GLP-1 with basal insulins, they were also the subject of much excitement because of clear positive efficacy results together with simple daily administration. Although price can be an issue, the point is now to see how Sanofi and Novo-Nordisk will leverage their respective opportunities in the category. The next step is to get both iGlarLixi and Xultophy approved by the FDA in the coming months.
- In terms of summarizing ADA 2016 for the different companies involved in diabetes, we would say that (i) overall it was positive for Novo-Nordisk which is the most innovative and science-driven player in the field with the largest range of promising product opportunities. The issue might be to drive this value-based strategy in an increasing difficult market price-wise; (ii) Sanofi is doing the best it can with its glargine-based portfolio and iGlarLixi is key to remaining in the loop and maintaining positive momentum; (iii) obviously, this is even more the case for Zealand since it is highly dependent on iGlarLixi which represents more than two-thirds of the total valuation; (iv) no direct read-out for Adocia but a lot of indirect ones that are very positive overall. This is the only FV change in this report.

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1. Background to Diabetes Mellitus

The prevalence of diabetes increases with age, obesity and lack of physical activity.

1.1. Epidemiology and market

1.1.1. An epidemic

Between 1980 and 2014, the number of people affected by diabetes in the world quadrupled from 108 million to 422 million. The global prevalence of diabetes in adults aged over 18 years old reached 8.5% in 2014. As yet, this increasing prevalence is uneven globally: low- and middle-income countries are more affected as a result of the higher prevalence of obesity and sedentary lifestyles. Diabetes is increasing most rapidly in Asia, Africa and South America. Ethnic minorities, such as American Indians/Alaskan natives, non-Hispanic blacks, and Hispanics are more affected by diabetes than non-Hispanic white people in the US. In non-Western countries, diets contain fewer calories and daily expenditure is higher, thus type 2 diabetes is less common. Note that, in 2015, one in three adults aged over 18 years were overweight and one in ten were obese in the world (World Health Organization (WHO), s.d.).

In 2014, 29.1 million Americans had diabetes (one in eleven) and, more dangerously, 86 million had prediabetes (more than one in three), of whom nine in ten were not aware that they had the condition. The prevalence is 9.3% and 1.4 million Americans are newly diagnosed every year (American Diabetes Association (ADA), s.d.). In France, 3.3 million adults aged from 20 to 79 years were living with diabetes in 2015, with a prevalence of 7.4% (International Diabetes Federation -IDF, s.d.).

In a 2001 study, Boyle, et al. predicted that there would be 29 million Americans with diagnosed diabetes by 2050, a 165% increase from the 2000 level (Boyle, et al., 2001). As diabetes has progressed more rapidly than expected, this projection was reached in 2014 (36 years earlier than initially forecast). Without taking any undue risks we can assume that since: 1/the population is ageing; 2/and current sedentary lifestyles are leading to less physical activity and a higher sugar/fat diet, diabetes prevalence rates and incidence are likely to continue to progress over time.

1.1.2. A leading cause of death in the world

People living with diabetes can also suffer from various short- and long-term complications, including blindness, kidney failure, heart attacks, stroke and lower limb amputation, leading to their premature death. Since Type 2 is the more common type of diabetes, in addition to its insidious onset and late recognition in particular in resource-poor developing countries (Africa), morbidity and mortality have been increasing (Olokoba & Obateru, 2012).

In 2012, it was estimated that 1.5 million people had died due to diabetes and another 2.2 million due to high blood glucose (leading to cardiovascular and other diseases), with half the deaths occurring before the age of 70. By 2030, WHO predicts that diabetes will be the seventh leading cause of death.

1.1.3. Type 2 diabetes is more common than Type 1

There are two distinct types of diabetes: Type 1 and Type 2. Type 1 diabetes is caused by a lack of insulin production (β cells in the pancreas do not produce any insulin) whereas Type 2 diabetes is characterized by insulin resistance (the body does not respond to insulin effectively) and by insufficient insulin production (β cells are also affected). A third type of diabetes is gestational diabetes, and women are at increased risk of complications during pregnancy and delivery.

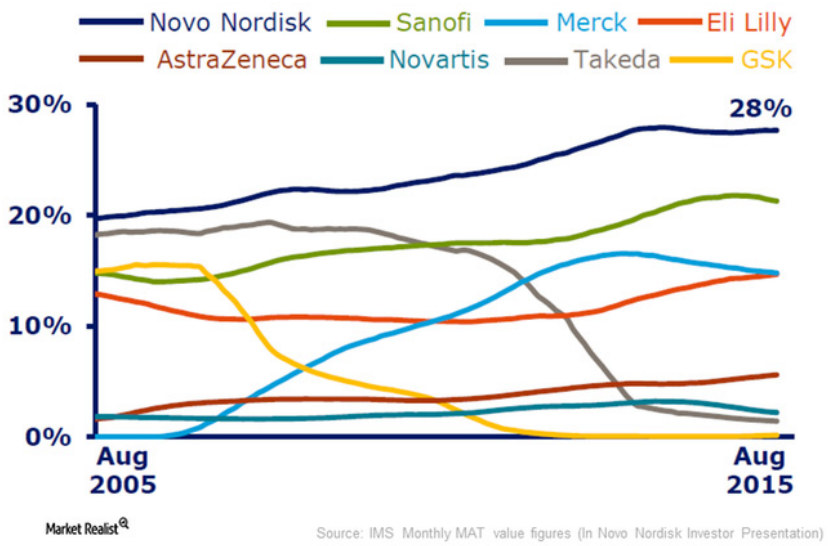
1.1.4. A growing and dynamic market

The global Type 2 Diabetes market is expected to grow at a CAGR of 7.28% over the 2016-2020 period (MedGadget, 2016). Estimtes show sales of Type 2 diabetes drugs worldwide increasing from USD23.5 billion in 2014 to USD39 billion in 2021 as a result of an increased prevalence along with the development of innovative drugs (Chisholm, 2015). The two main markets are the US and the EU, but sales to the Rest of the World are growing.

The Top ten companies present on the anti-diabetic drugs market are: Novo Nordisk, Sanofi, Merck & Co, Eli Lilly, AstraZeneca, Boehringer Ingelheim, JNJ, Novartis, Takeda and Merck KGaA. By contrast, in the following chart, we can see that GSK and Takeda's active Diabetes franchise was not as strong as the position they enjoyed in 2005.

The Top five anti-diabetic products in 2015 included Januvia/Janumet (Merck & Co), Lantus (Sanofi), NovoRapid (Novo Nordisk), Victoza (Novo Nordisk) and Humalog (Eli Lilly) (Market Realist, s.d.).

Fig. 1: Global diabetes care market value (2015)



Novo Nordisk is still the largest player in the diabetes market.

Source: (Market Realist, s.d.)

1.2. Pathophysiology

1.2.1. How the body processes sugar

- **Two main opposing hormones: Insulin and Glucagon**

  - When the blood glucose level is low (overnight or between meals)

Glucagon is secreted by pancreatic α-cells and converts: 1/glycogen (chain of connected glucose) into glucose units in the liver (glycogenolysis); 2/fatty acids from fat cells into ketones (ketogenesis); 3/amino acids, waste products and fat by-products to manufacture new glucose (gluconeogenesis) for energy, preventing hypoglycaemia.

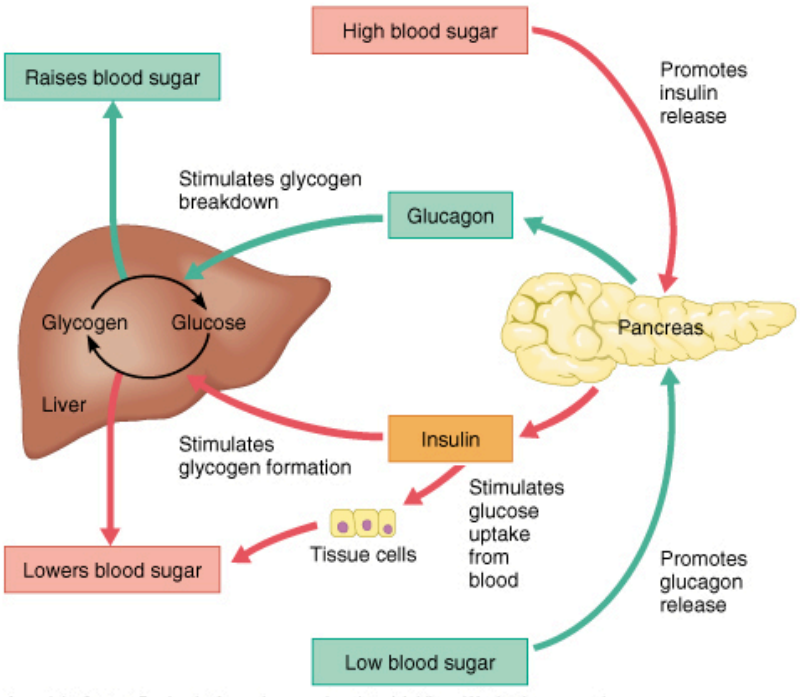
⇨ The liver not only stores ingested glucose but also manufactures new glucose

When glycogen storage in the body is not sufficient and when the body needs to conserve some glucose for vital organs including the brain, red blood cells and kidney, the liver uses the ketogenesis process to produce energy (ketones not glucose) from fat. This also happens when the body lacks insulin and blood glucose is abnormally high, or during a low carb diet. Ketones are used as alternative fuels for muscles and body organs. However, ketones are produced along with ketoacids, and elevated ketoacid levels make the blood pH too acidic, leading to ketoacidosis (DKA). This acidic blood leads to serious illness and death within a short time span (*American Diabetes Association* (ADA), 2015).

- When the blood glucose is elevated (after a meal)

Insulin is secreted by pancreatic β-cells and stores glucose from the bloodstream in muscle, fat and liver cells for future use. The insulin, an anabolic hormone, promotes the conversion of simple energy units (glucose, amino acids) into more complex macromolecules (glycogen, triglycerides) in the liver, muscle and fat cells (Leto & Saltiel, 2012).

Fig. 2: The pancreas: a key hormone factory to control blood sugar



Glucagon is secreted by α-cells to increase blood glucose levels while insulin is produced by pancreatic β-cells to lower the glycaemia index. When the blood sugar is elevated, insulin secretion is activated and glucagon secretion is suppressed. Inversely, when blood sugar is low, glucagon secretion is stimulated while insulin secretion is cancelled.

Source: Fresh Holistics, 2014

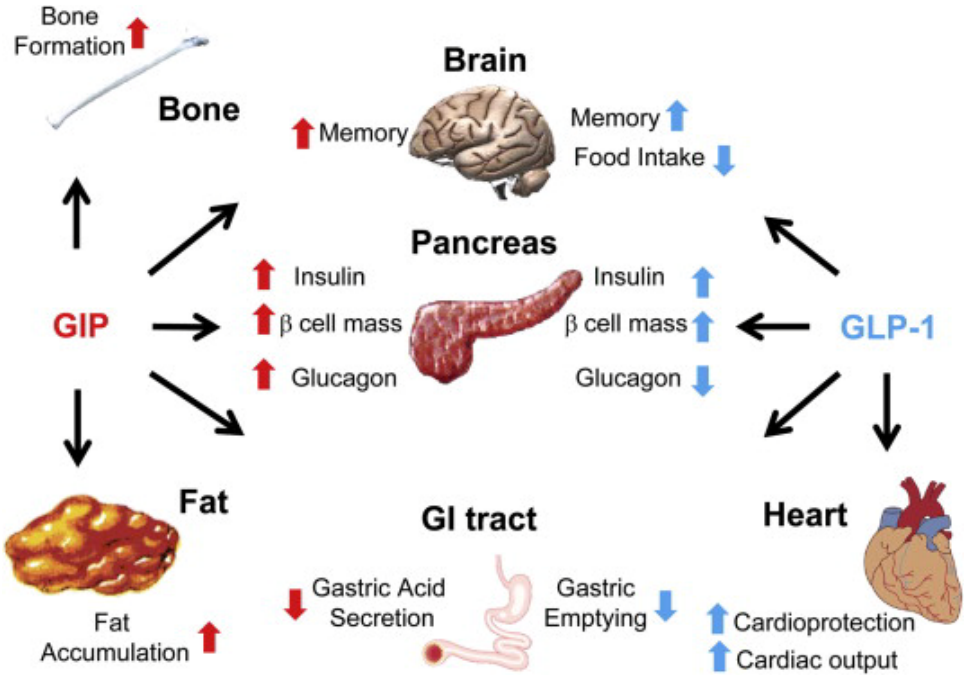
Incretin hormones: GLP-1 & GIP

Upon glucose ingestion, Gastric Inhibitory Polypeptide (GIP) and Glucagon-Like Peptide-1 (GLP-1) hormones are produced by intestine cells and have been found to stimulate insulin secretion from pancreatic β-cells. They are called INtestine seCRETion INsulin (incretin) hormones. Both incretin hormones' receptors (GIPR, GLP-1R) belong to the G-protein coupled receptor family and are expressed on pancreatic cells.

Incretin hormones demonstrated various biological actions. Not only do they stimulate insulin production (insulinotropic effect), but they also inhibit pancreatic β-cell apoptosis and enhance their proliferation, thus preserving the pancreatic β-cell mass which is crucial for insulin production. The main difference is that GIP stimulates glucagon production while the GLP-1 hormone reduces glucagon levels.

Importantly, incretin hormones undergo rapid proteolytic degradation catalysed by the Dipeptidyl Peptidase-4 (DPP-4) and consequently their insulinotropic effect is inactivated (Yabe & Seino, 2011). In other words, GLP-1 is downgraded by the DPP-IV enzyme meaning that inhibition of DPP-IV has an indirect influence on GLP-1 levels.

Fig. 3: Incretin hormones increase insulin secretion and β-cell mass



GIP and GLP-1 incretin hormones have various biological functions on the endocrine pancreas, bone, fat, GI tract, heart and brain.

Source: Yabe & Seino, 2011

- **Other hormones involved in blood glucose regulation**

  - Amylin

On a carbohydrate-rich diet (containing or convertible into glucose), amylin, an islet amyloid polypeptide (IAPP), is secreted together with insulin from pancreatic β-cells in a 1:20 ratio (amylin:insulin). Similarly to GLP-1, amylin suppresses glucagon release from the pancreas preventing glucose release from the liver, decreases gastric emptying and, eventually, stimulates the satiety centre located in the brain to avoid overeating. Across several studies, it has been observed that amylin could aggregate into toxic amyloid fibers (protein misfolding), leading to loss of pancreatic β-cells in Type 2 diabetes (Schmitz, Brock, & Rungby, 2004) (Pillay & Govender, 2013).

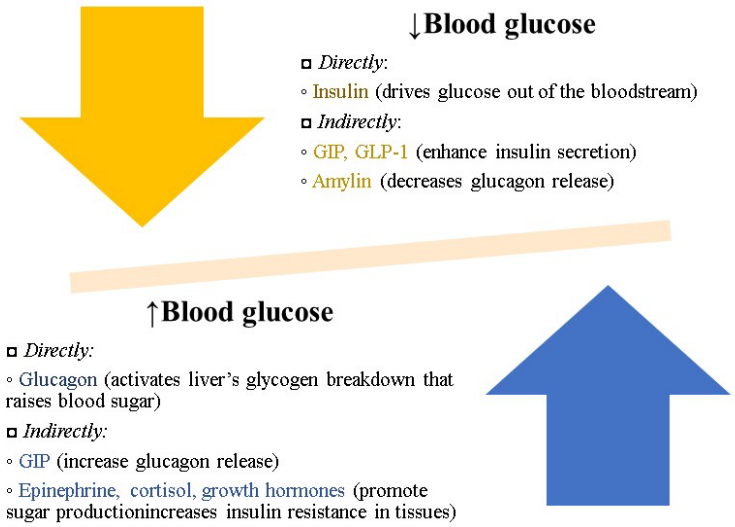
  - Glucose counter-regulatory hormones: "stress" hormones

Growth hormones, epinephrine (also known as adrenaline) and cortisol are counter-regulatory hormones responsible for increasing blood glucose levels, countering the action of insulin.

Located in the brain, the pituitary gland releases growth hormone that can lead to insulin resistance. Epinephrine, secreted from the adrenal gland and nerve endings, promotes: 1/glycogenolysis (sugar production in the liver from glycogen); 2/the use of fat nutrients to manufacture sugar and ketones also in the liver. Lastly, cortisol, which is also secreted from the adrenal gland, leads to insulin resistance (fat and muscle tissues do not respond effectively to insulin and the glucose entry into these tissues is limited) and promotes glycogenolysis in the liver.

The purpose of these mechanisms is to defend the body against hypoglycaemia. While the glucagon and epinephrine have a rapid effect, cortisol and growth hormones have a delayed action on glucose regulation (Sprague & Arbeláez, 2011).

Fig. 4: Various hormones regulate our blood sugar levels



Source: Bryan, Garnier & Co

1.2.2. Hallmarks of Type 2 Diabetes

Diabetes is a chronic progressive metabolic disorder characterized by poor glucose control. This report will focus mainly on Type 2 diabetes which accounts for around 90% of diabetic patients.

- **T2D dysfunctions**

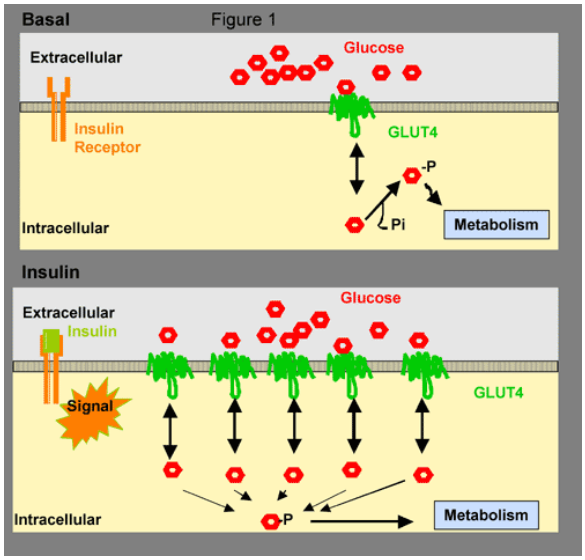
Type 2 diabetes (T2D), which is characterized by hyperglycaemia, is the result of a combination of three dysfunctions:

1/Resistance to insulin action (implying pancreatic β-cells are still functioning)

Despite the presence of insulin receptors on muscle and fat tissue, the insulin signalling cascade is affected resulting in lower glucose uptake via the GLUT4 (glucose transporter carrying glucose into

the cells) (Leto & Saltiel, 2012). Our cells thus cannot get all the glucose they need for the appropriate tissue development, growth and maintenance, irrespective of how much insulin has been secreted by the pancreas. Insulin resistance cannot be explained by a single etiological pathway as it is a complex metabolic disorder.

Fig. 5: Insulin-signalling increases GLUT4 glucose transporter



Insulin increases glucose uptake into fat and skeletal muscle cells through the glucose transporter type 4 (GLUT4). When there is no insulin (basal condition), only a few glucose units enter the cell via the GLUT4 transporter. On a rise in blood glucose, insulin is secreted and stimulates the glucose transfer from blood to inside cells by increasing the number of GLUT4 transporters. In the insulin-resistant condition, despite the presence of insulin, the insulin-signalling cascade is affected and does not facilitate glucose storage in tissues.

Source: McGraw Lab, s.d.

2/Inadequate insulin production

When the insulin receptors are relatively insensitive to insulin, the β-cells are forced to compensate for this resistance by increasing their insulin output to meet the tissues' needs. There are two possible ways to increase insulin secretion: 1/individual β-cells can secrete more insulin by multiplying insulin secretory granules; 2/β-cell mass increases and the pancreas then becomes atrophied. As long as the β-cells are working normally, obese individuals who tend to have insulin resistance manage to maintain glucose homeostasis by increasing insulin secretion.

However, one of the T2D hallmarks is β-cell dysfunction that can start as early as 12 years before T2D diagnosis and continues as the disease progresses. The β-cell decline is well advanced by the time T2D is diagnosed in a given individual. T2D patients' pancreases will show volume deficits due to a decreased number of β-cells, with glucose and lipid deposits.

Four mechanisms can explain inadequate insulin production: 1/Glucotoxicity (depletes insulin secretory granules from β-cells, thus decreasing the available insulin response to glucose stimuli); 2/Lipotoxicity (affects the conversion of pro-insulin into insulin, thus reducing insulin secretion); 3/An accumulation of toxic amyloid fibers; 4/Inflammation (pro-inflammatory mediators, ROS, complement contributing to pancreas tissue destruction). Lastly, genetic predisposition favours β-cell function failure (Fonseca, 2009).

- ⇨ Since β-cell function declines progressively, non-insulin monotherapies (metformin, rosiglitazone, glyburide etc.) inevitably fail to treat T2D over time due to a lack of insulin secretion.

- ⇨ Strategies to decrease/delay T2D progression consist of eliminating glucose toxicity (early treatment, early insulin); eliminating lipotoxicity (thiazolidinediones, decrease in free fatty acids); decreasing apoptosis/increase regeneration of pancreatic cells (incretin hormones).

- ⇨ Beta cell function decline along with s worsening in insulin resistance contribute to diabetes progression.

This β-cell deterioration leads T2D patients to be insulin-dependent. Hence, the classification "Insulin-dependent" for T1D as opposed to "Non-insulin dependent" for T2D is incorrect. By contrast, in T1D, pancreatic β-cells undergo autoimmune destruction resulting in insulin deficiency (American Diabetes Association (ADA), 2009).

3/Excessive or inappropriate glucagon secretion

To offset the lack of glucose storage necessary to our functional metabolism, the body tends to produce more glucose, hence the observed elevated glucagon level after meals.

Also, it has been observed that T2D patients have subnormal amounts of GIP and their β-cells do not respond properly to GLP-1, preventing glucagon levels from being suppressed as in normal conditions after a meal.

- ⇨ GLP-1 and amylin hormones can be used to control post-meal glucagon and blood sugar.

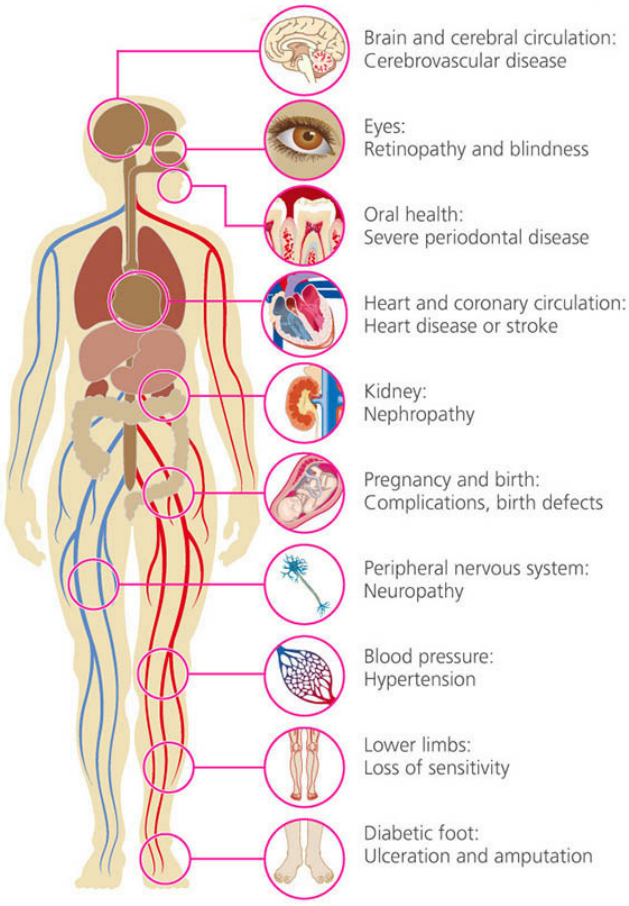
- **Diabetes complications**

If left untreated, hyperglycaemia can lead to microvascular and macrovascular complications, affecting the patient's quality of life and life expectancy. Although T1D and T2D differ in terms of their pathophysiology, they share similar diabetes complications.

Microvascular complications refer to diseases affecting the small blood vessels and include: the kidney (kidney failure: nephropathy), eyes (blindness: retinopathy), and nerves (death and pain: neuropathy). Also, microvascular complications include sores and ulcers on patients' legs/feet that can lead to amputation. Microvascular complications result from the formation of reactive oxygen species (ROS), engendering narrowing/occlusion of the small blood vessels over time.

Macrovascular complications refer to diseases affecting the larger blood vessels and leading to cardiovascular diseases (CVD). T2D patients accumulate risk factors such as abdominal obesity, hypertension, hyperlipidaemia and increased coagulability, all of which promote CVD. The main cause of macrovascular complications is atherosclerosis which narrows arterial walls throughout the body (heart, brain, lower limbs). Atherosclerosis occurs as a result of chronic inflammation producing ROS, which in turn triggers a cascade of events that form plaques and narrow blood vessels (Fowler, 2008).

Fig. 6: Microvascular and Macrovascular complications in diabetes



Source: Healncure.com, s.d.

- **Risk factors**

  - Age

  - Lifestyle (physical inactivity, alcohol, smoking, obesity, glucose-rich diet, hypertension, dyslipidaemia)

  - Genetics (family history of diabetes, ethnicities)

1.2.3. Differences between Type 1 and Type 2 Diabetes

Fig. 7: Type 1 Diabetes vs. Type 2 Diabetes

	Type 1 Diabetes (T1D)	Type 2 Diabetes (T2D)
Age of onset	Juvenile	Adult
Progression	Abrupt	Gradual
Cause	No insulin	Insulin resistance; declining insulin production
	Autoimmune disease destroying pancreatic β-cells	Pancreatic β-cell failure ("burn-out")
Prevalence	5%	95%
Body	Thin/Normal	Obese
Symptoms	Severe	Less severe, severe
Ketoacidosis	Common	Rare
Auto-antibodies	Usually present	Absent
Consequences	Kidney, eyes, cardio, legs	Kidney, eyes, cardio, legs
Treatment	Insulin	Non-insulin, insulin, diet, change in lifestyle

Source: American Diabetes Association, 2016

1.3. Basic facts

1.3.1. What are the symptoms of Type 2 Diabetes?

Fig. 8: Clinical manifestations

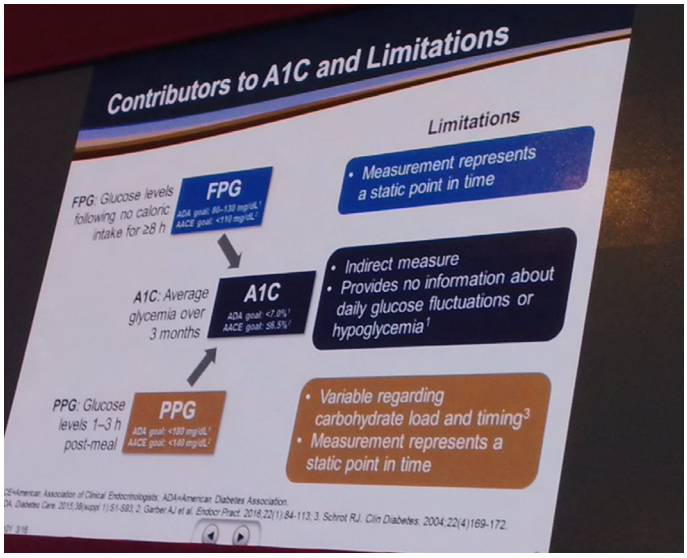
- Asymptomatic
- Blurred vision
- Fatigue
- Lower-extremity paraesthesia
- Nausea/vomiting
- Polydipsia (excessive thirst)
- Polyphagia (excessive hunger)
- Polyuria (frequent urination)
- Unexplained weight loss

Source: American Diabetes Association (ADA), 2009

1.3.2. How to diagnose Type 2 Diabetes

Fig. 9: Indicators used for diagnosis

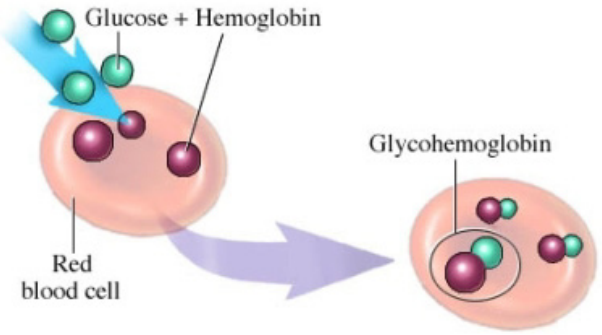
Indicators	Normal	Pre-Diabetes	Diabetes
Fasting Plasma Glucose (FPG)	<100 mg/dl	100-125 mg/dl	>=126 mg/dl
Post glucose-rich beverage (75g glucose): Oral Glucose Tolerance Test (OGTT) - 2h	<140 mg/dl	140-199 mg/dl	>=200 mg/dl
Random plasma glucose and symptoms			>=200 mg/dl
Haemoglobin A1c (HbA1c)	<5,7%	5,7-6,4%	>=6,5%



Source: American Diabetes Association, 2016

Haemoglobin A1c (a protein transporting oxygen in red blood cells) is glycosylated when blood glucose levels are too high. Since red blood cells have a lifespan of 120 days, the percentage of glycosylated haemoglobin is used as a surrogate marker for monitoring abnormal spikes in blood glucose over the previous 3-4 months. This represents a long-term blood glucose measure. The ADA recommends A1c as a test to diagnose pre-diabetes and diabetes (American Diabetes Association, 2009).

Fig. 10: Glycosylated Hemoglobin measures blood glucose variability



Source: (Antipuesto, 2010)

1.3.3. Goals for Type 2 Diabetes treatment

Diabetes is not yet curable and therapies only aim to: 1/reach and maintain normal ranges for blood sugar; 2/reduce the risk of diabetes-related co-morbidities (macro/microvascular complications).

To achieve these goals, the current medications aim to:

1/ reduce insulin resistance;

2/ reduce glucose production by the liver;

3/ increase insulin secretion.

Fig. 11: Blood glucose goals for Type 2 Diabetes patients under treatment

Blood glucose targets for adults with diabetes	
A1C	<6,5-7%
Pre-prandial capillary PG	80-130 mg/dl
Peak post-prandial capillary PG	<180 mg/dl
Depending on hypoglycaemia or adverse event risks, more or less stringent targets are defined according to the patient's health history	

Source: (American Diabetes Association, 2016)

2. Type-2 Diabetes therapies

2.1. Insulin medications

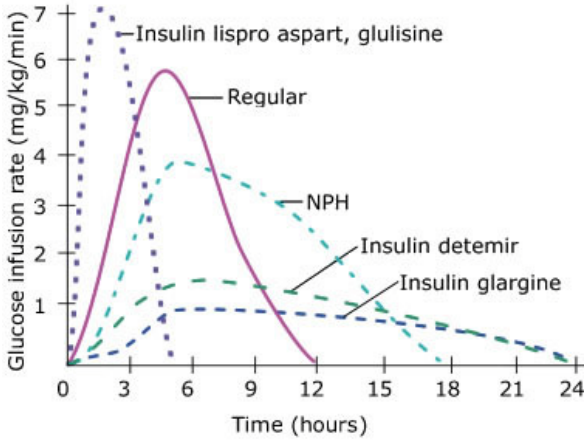
The insulin market leaders are Novo-Nordisk, Sanofi and Eli Lilly. Insulin is prescribed as a monotherapy or in combination with other agents. Historically, the first insulins were extracted from the animal pancreases (pigs, cows) and were purified for human use. However, due to adverse events relating to their origin (allergic reactions), recombinant human insulins (human insulin produced by bacteria) have since replaced animal-derived insulins. In addition, as human insulin has a four to six hour half-life, different formulations have enabled variations in the pharmacokinetic insulin profile. Consequently, insulins are classified according to their onset, peak and duration of action. Currently, insulin is administered either by injection (syringe, pen), a continuous subcutaneous insulin infusion device (CSII, also known as an insulin pump), infusion (injection directly into the vein, in hospital) or through the pulmonary route (the only approved inhaler is Afrezza) (R.Owens, 2002).

Fig. 12: Five classes of insulin

Type	DCI	Drug name	Company	Onset	Peak	Duration	Comment
Rapid-acting (insulin analog)	Insulin Aspart	NovoLog	Novo Nordisk	5-15min	30-90min	3-5hr	short duration of action; use before meals; less hypos than regular insulin
	Insulin Glulisine	Apidra	Sanofi				
	Insulin Lispro	Humalog	Eli Lilly				
	Insulin inhaled	Afrezza	Mannkind				
Short-acting (regular insulin)	Human Regular insulin	Humulin R	Eli Lilly	30min	1-3hr	4-8hr	used when a slower onset of action or a longer duration is desired; usually injected 15-30min before a meal
Intermediate /long-acting (isophane or zinc insulin)	Human NPH (Neutral Protamine Hagedom)	HumuLIN N	Eli Lilly	1-3hr (NPH, Lente, Ultralente)	4-8hr	8-12hr (NPH); 8-24hr (ultralente)	slow onset, longer duration of action; used to control glucose levels between meals; combined to faster-acting insulins to maximize the benefits of a single injection
		NovoLIN N	Novo Nordisk				
Long-acting insulin	Insulin detemir	Levemir	Novo Nordisk	30-60min	no peak	16-24hr	longer duration of action; usually combined to short-acting insulin; once daily administration
	Insulin glargine	Lantus	Sanofi				
	Insulin degludec	Tresiba	Novo Nordisk				
Premixes (intermediate/short-acting)	NPH/Regular	Humulin 70/30	Eli Lilly	10-30min	2-4hr	14-24h	Usually admistrated 2-3 times a day; provide benefits of short/basal insulin in a single injection
	NPH/Regular	Novolin 70/30	Novo Nordisk		2-12hr	>24hr	
	NPH/Aspart	Novolog 70/30	Novo Nordisk		1-4hr	>24hr	
	NPH/Lispro	Humalog75/25	Eli Lilly		30min-3hr	16-20hr	
	NPH/aspart	NovoMix 70/30	Novo Nordisk		1-4hr	>24hr	
	degludec/aspart	Ryzodeg 70/30	Novo Nordisk		1-4hr	>24hr	
	NPH/lispro	Humalog 50/50	Eli Lilly		1-4hr	12-22hr	

Source: American Diabetes Association, 2016, Street Account

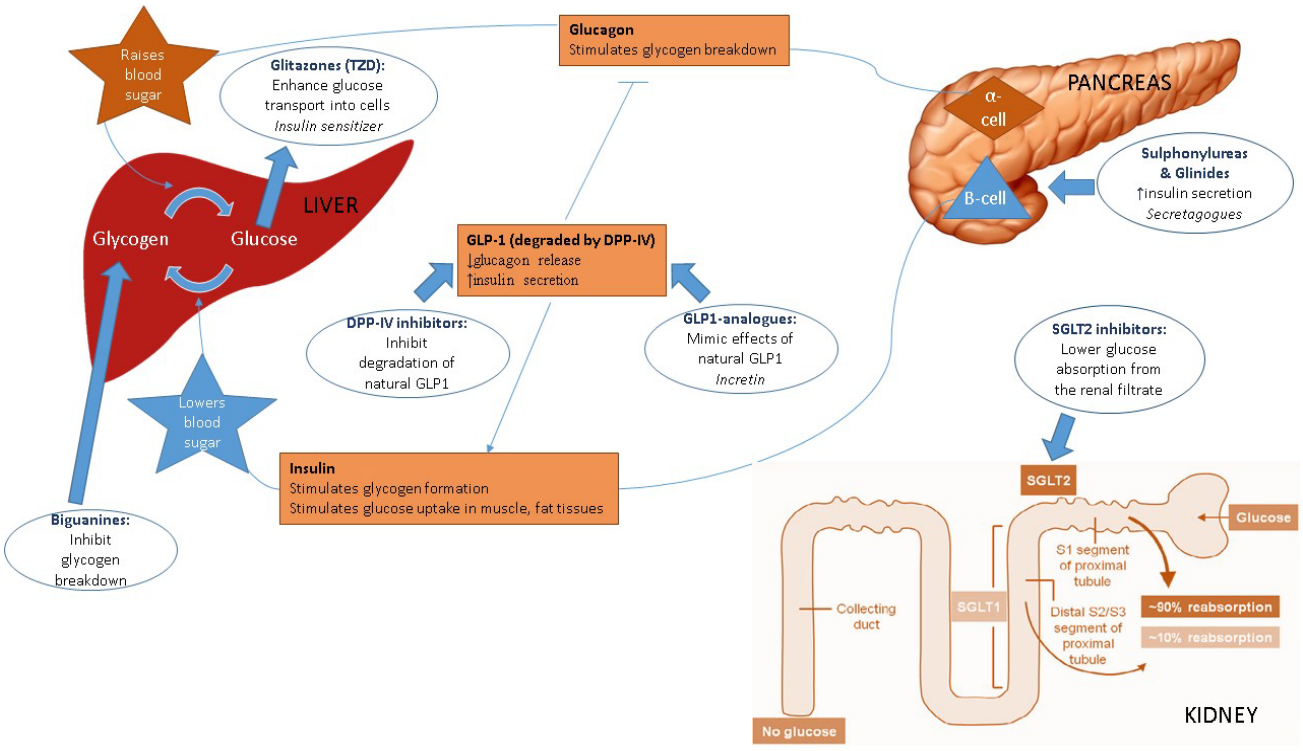
Fig. 13: Different insulins with distinct activity profiles



Source: University of California (UCSF), s.d.

2.2. Non-insulin medications

Fig. 14: Overview of the main non-insulin classes of drugs



Source: Bryan, Garnier & Co

Fig. 15: Non-insulin therapies fall into numerous therapeutic classes

Class	Compounds	Drug name	Company	FDA approval	MoA	Hypos	Weight gain	Cost	Advantages/Comments
Biguanines	Metformin	Glucophage	BMS	1994	↓Glucose production from the liver; increase glucose uptake (intestines) and utilization (better insulin sensitivity)	No	No	Low	↓CVD events (UKPDS)
Sulfonylureas (SFU)	Glyburide	Diabeta	Sanofi	1984	↑insulin secretion from the pancreas = "Secretagogues", "inulin releasing pills"	Yes	Yes	Low	↓Microvascular risk (UKPDS); preferred SFU for old patients
	Glimepiride	Amaryl	Sanofi	1995					
	Glipizide	Glucotrol	Pfizer	1984					
Meglitinides (Glinides)	Repaglinide	Prandin	Novo Nordisk	1997		Yes	Yes	Moderate	↓postprandial glucose
	Nateglinide	Starlix	Novartis	2000					
Thiazolidinediones (TZD or Glitazones)	Pioglitazone (preferred over Rosiglitazone)	Actos	Abbott/Takeda	1999	Glitazones are PPAR-y agonists;↓Decrease insulin resistance in the muscle + fat tissues = "Insulin sensitizers"	No	Yes	Low	Avandia may cause or worsen heart failure, requires liver monitoring; Avandia has been suspended by the EMA in 2010, Actos was found to lead to bladder cancer after 1v of use
	Rosiglitazone	Avandia	GSK	1999					
α-glucosidase inhibitors	Acarbose	Precose	Bayer	1995	Slows intestinal carbohydrate digestion/absoption by inhibiting intestinal α-glucosidase =" Starch blockers"	No	No	Low to moderate	Modest efficacy
	Miglitol	Glyset	Pharmacia & Upjohn	1996					
DPP-IV inihibitors	Sitagliptin	Januvia	Merck	2006	↑insulin secretion; ↓Glucagon secretion from liver after meals by 1/inhibiting DPP-IV activty; 2/↑postprandial active incretin (GLP1, GIP)	No	No	High	Incretin-based therapies; Well tolerated;↓postprandial glucose; ↓ some CVD risk factors; ↑heart rate
	Saxagliptin	Onglyza	AZN	2009					
	Linagliptin	Tradjenta	BI	2011					
	Alogliptin	Nesina	Takeda	2013					
GLP-1 agonists	Exenatide	Byetta	AZN	2005	↑insulin secretion; ↓Glucagon secretion ; slows gastric emptying; ↑ satiety	No	No	High	
		Bydureon	AZN	2012					
	Liraglutide	Victoza	Novo Nordisk	2010					
	Albiglutide	Tanzeum	GSK	2014					
	Dulaglutide	Trulicity	Eli Lilly	2014					
Bile acid sequestrant	Colesevelam	Welchol	Sanofi	2000	Binds bile acids in intestines; may ↑ incretins levels	No	No	High	Modest efficacy; may ↓absorption of other drugs
Amylin mimetics	Pramlintide	Symlin	AZN	2005	↓Glucagon secretion ; slows gastric emptying; ↑ satiety	Yes	No	High	↓postprandial glucose; modest efficacy
SGLT-2 inhibitors	Canagliflozin	Invokana	JNJ	2013	Blocks glucose reabsoption by the kidney by inhibiting SGLT2 in the proximal nephron	No	No	High	Effective at all stages of T2D; associated with lower CVD event rate and mortality; ↓blood pressure
	Dapagliflozin	Farxiga	AZN	2014					
	Empagliflozin	Jardiance	Eli Lilly	2014					

Source: American Diabetes Association (ADA), 2009 (Tran, Zielinski, & Roach, 2015) (University of California (UCSF), s.d.), Street Account, (Olokoba & Obateru, 2012)

2.3. Current Fixed Dose Combination

Fig. 16: Existing dual fixed dose combination

Class	Class	Drug Name	Company	FDA Approval
Glyburide (SFU)	Metformin	Glucovance	BMS	2000
Glipizide (SFU)	Metformin	Metaglip (discontinued), but various generics	BMS	2002
Rosiglitazone (TZD)	Metformin	Avandamet	GSK	2002
Pioglitazone (TZD)	Metformin	ActoPlus Met	Takeda	2005
Rosiglitazone (TZD)	Glimepiride (SFU)	Avandaryl (discontinued) but various generics	GSK	2005
Pioglitazone (TZD)	Glimepiride (SFU)	Duetact	Takeda	2006
Sitagliptin (DPP-IV)	Metformin	Janumet	Merck Sharp	2007
Pioglitazone (TZD)	Metformin	ActoPlus Met XR	Takeda	2009
Saxagliptin (DPP-IV)	Metformin XR	Kombiglyze XR	AZN	2010
Linagliptin (DPP-IV)	Metformin	Jentadueto	BI	2012
Sitagliptin (DPP-IV)	Metformin	Janumet XR	Merck	2012
Alogliptin (DPP-IV)	Metformin	Kazano	Takeda	2013
Alogliptin (DPP-IV)	Pioglitazone (TZD)	Oseni	Takeda	2013
Canagliflozin (SGLT2)	Metformin	Invokamet	JNJ	2014
Dapagliflozin (SGLT2)	Metformin	Xigduo XR	AZN	2014
Empagliflozin (SGLT2)	Linagliptin (DPP-IV)	Glyxambi	BI	2015
Empagliflozin (SGLT2)	Metformin	Synjardy	BI	2015
Degludec (insulin)	Liraglutide (GLP1)	Xultophy	Novo Nordisk	(PDUFA sept-2016)

Source: Street Account

2.4. Summary of T2D treatment recommendations

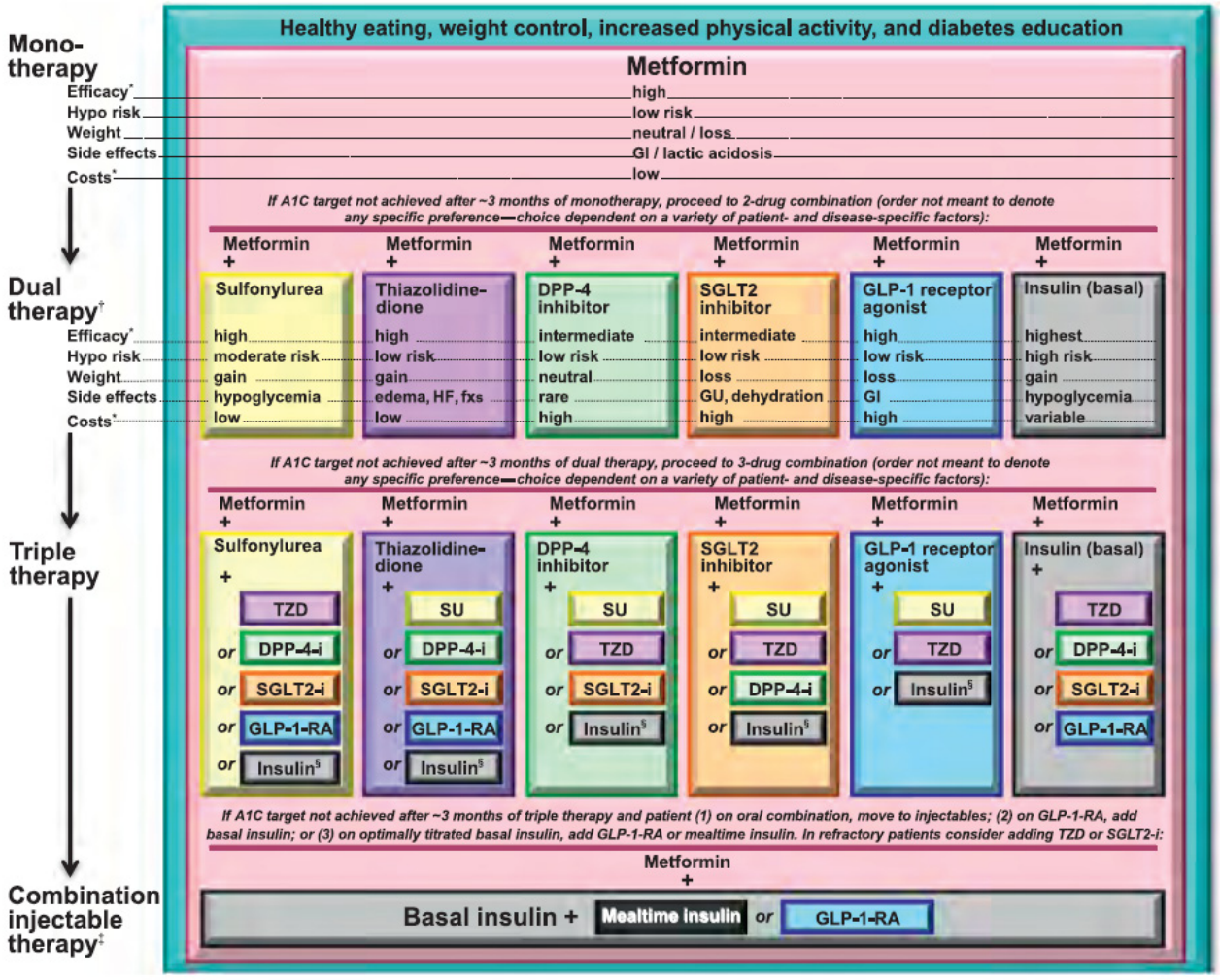
In terms of pharmacologic therapy strategy, the American Diabetes Association (ADA) recommends: 1/starting with lifestyle changes such as losing weight and practising a sport. If these changes alone do not allow glycaemic goal achievement, then 2/Metformin should be added as a preferred initial therapy if tolerated and not contraindicated. 3/For newly diagnosed patients who show symptoms and/or have elevated glucose levels or A1c, insulin therapy should be considered with/without other agents. 4/If non-insulin monotherapy (OAD) does not allow goal achievement despite maximal doses, then a second oral agent, a GLP1 agonist or basal insulin should be added. 5/Eventually, if still not sufficient, insulin therapy should not be delayed as the Type 2 Diabetes worsens (American Diabetes Association, 2016).

Note that certain drugs, including pramlintide, bromocriptine (dopamine inhibitor), colesevelam and α-glucosidase inhibitors, are not usually favoured as they have limited efficacy, need frequent administration and their efficacy is not sufficient in view of the associated side effects. They are thus only prescribed in specific situations.

Risks factors for hypoglycaemia are: 1/insulin secretagogue or insulin dosing is too high 2/ingested glucose is decreased (missed meals, overnight); 3/glucose utilization is increased (sport); 4/endogenous glucose production is decreased (after alcohol); 5/sensitivity to insulin is increased (overnight, or in the event of weight loss/improved fitness/improved glycaemic control); 6/insulin clearance is decreased (in event of renal failure).

⇨ With this in mind, dosing management is crucial for T2D patients.

Fig. 17: Detailed therapy strategy for T2D



Source: American Diabetes Association, 2016

3. ADA 2016: highlights

3.1. Outcome-based studies to the forefront

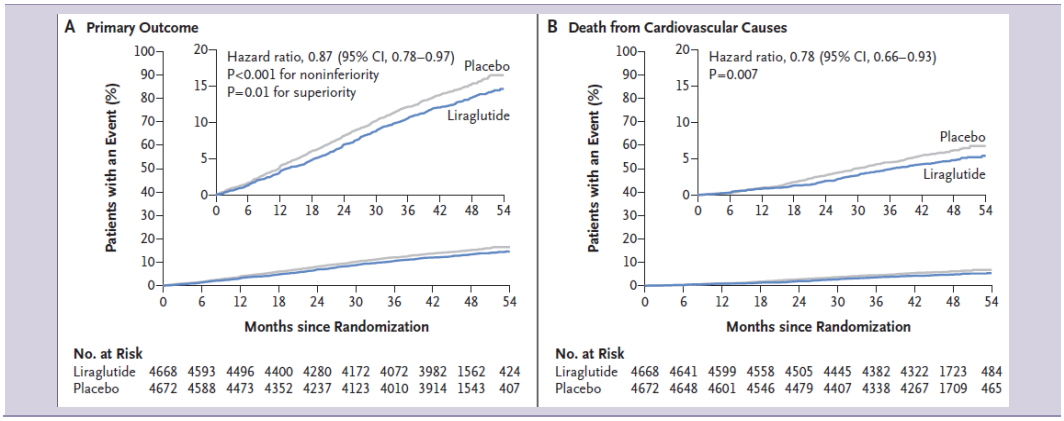
When visiting the ADA 2016 website, a section called "Spotlight on the sessions" quickly stood out, clearly setting the scene for what was going to be key during this annual congress: "this year, in addition to a program of impressive symposia, we will showcase the latest results from two major clinical trials – The Liraglutide Effect and Action in Diabetes – Evaluation of Cardiovascular Outcome Results (LEADER) Trial and Update from the EMPA-REG Outcome Trial".

3.1.1. LEADER in focus

Primary endpoint reached with HR=0.87

Several investigators from the LEADER cv outcomes study presented the results at the ADA congress in New Orleans on 13 June 2016. The overall impression was very good although it is fair to say that risk reduction in 3-point MACE (primary endpoint) only hit the low-end of the expected range with HR of 0.87. However, the result is very consistent across each of the three points i.e. non-fatal stroke (HR: 0.89), non-fatal MI (HR: 0.88) and, more importantly, cv death where the risk was reduced by a remarkable 22%. This contrasts with the EMPA-REG OUTCOME results where empagliflozin did not show a benefit on stroke. When a 6-component endpoint is considered, the statement is the same and the results are actually very consistent over all the sub-groups, while liraglutide also beat placebo on renal microvascular events (not on eye-related events however).

Fig. 18: Key endpoints from the LEADER phase III trial



Source: New England Journal of Medicine, S.P. Marso and Others – 16 June 2016

A very good safety profile

The safety results were just as impressive since liraglutide beat placebo on serious and severe adverse events and also presented fewer hypos. This has to do with the protocol that allowed for use of other antidiabetics to achieve glycemic control. In the placebo arm, people used more insulins and SU, hence the hypos. Nausea and vomiting were reported in under 2% of the patients which is probably due to the duration of the trial. This is all the more surprising in that the average dose of Lira was 1.78 mg. In any case, there were very few discontinuations, making the trial very robust.

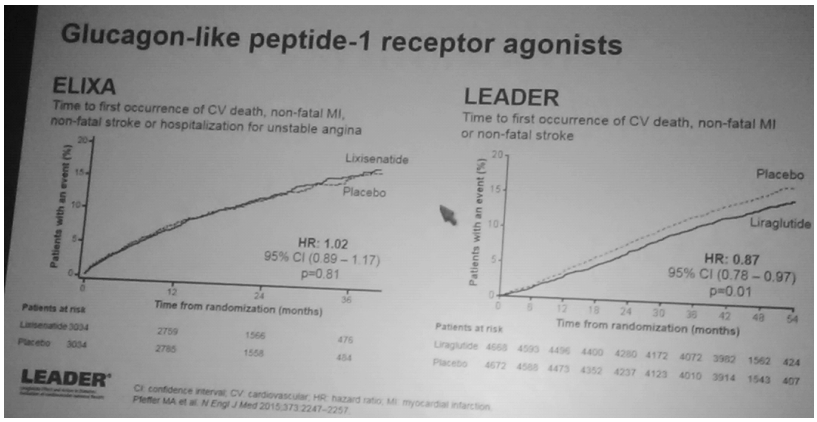
An insulin-sparing effect

The least impressive number was the reduction in HbA1c which was "only" 0.40% at month 36 compared with a baseline of 8.7%. However the two arms were not comparable in terms of concomitant drug use. At month 36, 1336 patients used insulin in the Lira arm vs 2018 in the placebo arm whereas the percentage was similar at baseline. Liraglutide use was thus associated with an insulin sparing effect.

On neoplasms, there is nothing significant to report (no difference by tissue), the same holding true for pancreatitis (including acute cases).

Lastly, the conclusion by the principal investigator compared the results with those of ELIXA and EMPA-REG OUTCOME after calling for caution when comparing non head to head trials. Despite some protocol differences, putting ELIXA and LEADER on the same slide (see Fig. 19) didn't do Sanofi and Zealand any favours and obviously helps Victoza. When trying to explain the difference, he suggested that half lifes and overall profiles, as well as molecular specificities, could be responsible. When comparing the results to those of empagliflozin, he mainly noted that the effects were various in nature, a benefit coming more rapidly with empa (diuretic?) vs a longer but more-consistent effect with lira (anti thrombotic?). The difference was also reflected in the influence on strokes.

Fig. 19: Comparison made by principal investigator in his conclusion



Source: Bryan, Garnier & Co (picture from ADA 2016 congress in New Orleans)

We deem the overall results to be good; not outstanding, but solid. They should help Novo Nordisk consolidate its leadership in the GLP-1 market. That said, we are not sure how much it can impact and expand the market vs CS expectations. There has been disappointment from the investment community in general, probably because a 13% risk reduction for the primary endpoint was the minimum expected and also because EMPA-REG Outcome looks competitive with an oral formulation that may delay the use of injectable drugs.

Note that Novo Nordisk's GLP-1 franchise amounted to 17% of total turnover in 2015 (DKK18.6bn) and we expect its contribution to reach 36% towards 2021e (BGe) or DKK47bn.

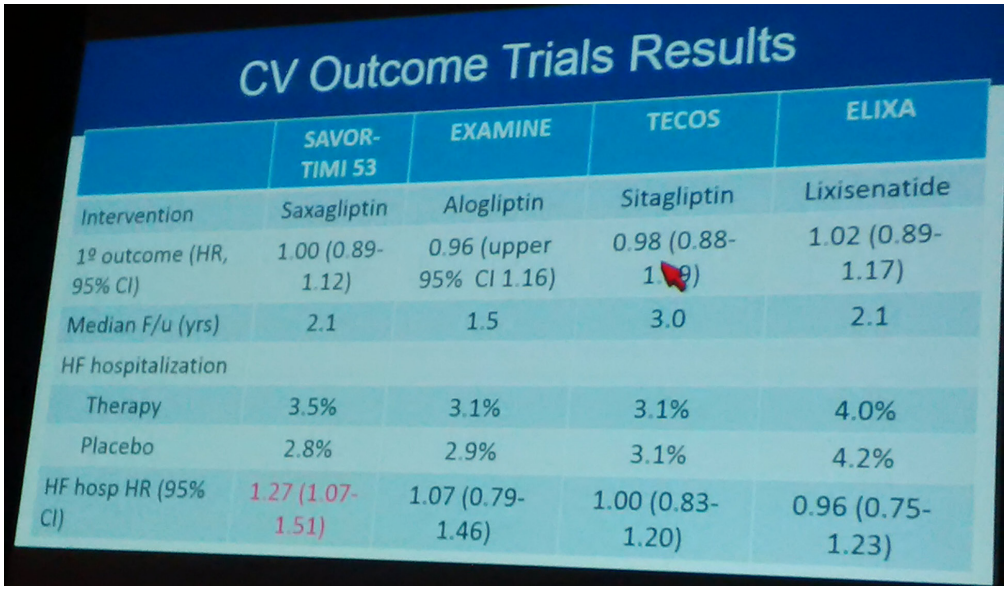
3.1.2. Towards a paradigm shift

CV outcome studies: from no harm to a benefit

CV outcome studies have been put in place by the FDA for antidiabetic drugs after the scandal with TZDs suggesting that members of this class may be detrimental to the heart (rosiglitazone, Avandia, in particular), emerging long after their launch and after having become blockbusters. Sponsors were thus asked to conduct CV outcome studies as a post-marketing commitment for drugs already on the market and as part of the filing for future drugs. Although this was first seen as excessive by many pharmaceutical companies, it could well turn out to be a major advantage for drugs meeting the endpoint and proving to be not only non-inferior to placebo but possibly superior. With EMPA-REG OUTCOMES and now LEADER, this has happened a couple of times, giving the relevant drugs a significant advantage over the competition. At the ADA congress it was very clear that diabetes and cardiovascular diseases are closely linked. For instance, the risk of myocardial infarction is more than five times higher in patients with diabetes.

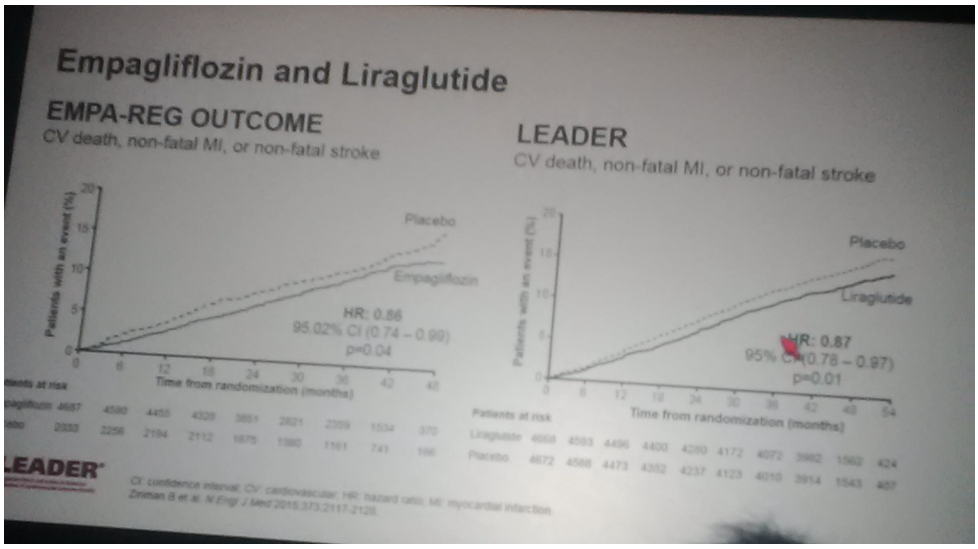
Novo-Nordisk surprised us by saying that they were expecting the EMPA-REG OUTCOME study to go well and afford empagliflozin class-leading status although this actually reflects the desire of the leader in injectable diabetes treatments to see a paradigm shift towards outcomes-based medicines i.e. drugs that have successfully carried out CV outcome studies and have demonstrated a clear benefit. Novo-Nordisk believes that antidiabetic drugs can no longer be approved and be commercially successful based only on biological criteria. They must also show micro and macro-vascular benefits. As illustrated in Fig. 20 from a presentation made at the ADA congress this year, CV morbi-mortality trial results are increasingly used by speakers in sessions and, while the aim was initially to establish that the drug candidate was not detrimental to the heart (for historical reasons, in reference to what happened with rosiglitazone), it is moving in the direction of a benefit now that two studies have proven positive (EMPA-REG OUTCOME and LEADER), with a third study expected at EASD (SUSTAIN-6).

Fig. 20: CV outcome trial results increasingly advertised at diabetes conferences



Source: Bryan, Garnier & Co (picture from ADA 2016 congress in New Orleans)

Fig. 21: LEADER and EMPA-REG OUTCOMES compared at ADA 2016



Source: Bryan, Garnier & Co (picture from ADA 2016 congress in New Orleans)

3.2. Novo-Nordisk vs. Sanofi: a few comments

From the various presentations we attended as well as our conversations with company representatives, please find below some comments and remarks on a limited number of important topics for the two companies.

3.2.1. Where do Tresiba and Toujeo stand?

It is difficult to see exactly how big the last generation of basal insulins can be. Obviously, they occupied the largest part of Sanofi and Novo's respective booths at ADA but it is unclear how they are perceived by physicians and whether the step forward is seen as major or mainly as marketing driven.

Basaglar: not a lot to say beyond price

The question may rather be: where do we go from glargine in the basal insulin market? When attending presentations about basaglar (launch announced for 15 December 2016), the only question that really mattered was not answered, i.e. "what will the price be?," because nothing really impressed about the drug and the Lilly representatives reiterated that they were expecting it to be "non-substitutable to Lantus". It is going to be "another glargine".

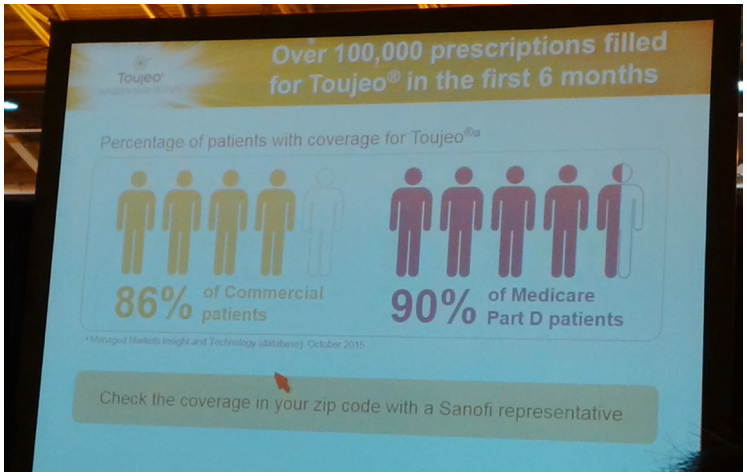
Faced with a strong base of Lantus users, and Sanofi likely to play a price game to maintain volumes, new insulins will have to differentiate on the clinical data.

Improved pens

At Tresiba and Toujeo's two large booths in the Exhibit Hall, the people in charge first highlighted the superiority of the new pens used with the drugs i.e. FlexTouch and a new SoloStar that are obviously more convenient. Then, when going into more detail, the easiest way to keep it simple while making the demo very visual was to empty the insulin contained in a pen of Lantus and in a pen of Toujeo side by side on a piece of tissue paper to see the difference in volume terms and to illustrate what more a concentrated insulin entails.

When moving to the Product Theater for sponsored presentations on Toujeo, physicians of course tried to emphasize the benefit of requiring fewer injections on average to reach a similar HbA1c level and to reduce the rate of hypoglycemic events while benefiting from good insurance coverage (see Fig.22).

Fig. 22: Toujeo enjoys good insurance coverage



Source: Bryan, Garnier & Co (picture from ADA 2016 congress in New Orleans)

Toujeo's pen has clear limitations

In other non-sponsored presentations, however, the pen's limitations were also stressed, including when contrasted with the Novo-Nordisk technology. SoloStar contains only 450 units and delivers a maximum of 80 units per injection whereas FlexTouch with Tresiba can go as high as 600 and 160 respectively. With single copay, an individual can get three pens representing 1,800 units of Tresiba in total but only 1,350 units of Toujeo i.e. a 25% difference. Everything counts. From presentations made at the AACE congress in 2012 and at the ADA congress in 2016, we understand that about 35% of Type 2 diabetics require a maintenance dose of 60 U or more and 17% a dose of 100 U or more.

Sanofi's SoloStar pen used on Toujeo is thus slightly more sensitive than the previous version and so can be seen as slightly superior whereas the rate of nocturnal hypos is a tad lower. Is this enough to justify the price differential that will inevitably grow between Lantus and Toujeo?

Data to come on Tresiba vs. Toujeo

Simultaneously, Novo-Nordisk is seeking best-in-class status with Tresiba and should soon disclose comparative PK/PD data comparing the drug to Toujeo. The group also plans a major SWITCH study results advertising campaign in the leading journals but also in the media to make them available to general practitioners (GPs) and not only to specialists. Novo-Nordisk estimates that about 55% of prescriptions for Tresiba in the US are filled by GPs (only 23% by PCPs). The group said it was happy with an NBRx share that is now close to 10% in the US although will take time for this to translate into robust sales figures (c.USD30m in Q1 2016).

So the jury is out and it is really tough to forecast peak sales for the new-generation basal insulins.

3.2.2. iGlarLixi's presentations well attended but the safety profile with lixisenatide is not yet fully clear

Sanofi had two leading products to advertise during this ADA 2016: Toujeo, mainly from a marketing perspective as a superior product to Lantus and iGlarLixi, with two oral presentations for the two phase III studies Lixilan-O and Lixilan-L being well attended by ADA visitors.

Good efficacy results for iGlarLixi

Efficacy-wise, the two studies reported fairly good results and clearly demonstrated the value of adding lixisenatide to Lantus to further improve glycaemic control. Although a short period of time is required to adjust doses and find the right balance, the difference is significant with the comparative arms. In LixiLan-L for instance, at the end of the 24-week treatment period, HbA1c was reduced by 1.13% to 6.9% vs 0.62% (to 7.5%) on average and 55% of patients had HbA1c below 7% vs. 30%. Lastly, the change in body weight was 1.4 kg on average in favour of iGlarLixi vs Lantus (-0.7 vs +0.7 kg). And neither the presentations by investigators nor the questions from the public (no more than two or three per session) came back to the discussions held during the advisory committee panels in May about safety points. The overall impression was thus very good and the appetite for such combinations to more effectively treat patients to target looks high with the caveat that attendance at ADA is not necessarily representative of the standard prescribing physician base.

The AdCom vote was unequivocal…

That said, as of today, i.e. before we know if the drugs will be approved in the US, which label they will carry and the pricing strategies that will be implemented, our conviction is that GLP-1/basal insulin combinations should be very successful since the results are impressive with a single injection. To some extent this was also reflected in the AdCom recommendation for each of the two drugs last May when Xultophy and iGlarLixi received a respective 16-0 and 12-2 votes in favour of their approval by the FDA.

…but safety issues remain

Coming back to the discussions during the Advisory Committee meetings, we would like to highlight a few elements it is worth bearing in mind when approaching PDUFA dates for lixisenatide: (i) anaphylactic reactions; (ii) antibody drug formation; (iii) perfectible pen device.

We don't plan to dwell long here on the issues surrounding allergic reactions although some argue that this must be crystal clear for the approval of a drug in a chronic condition. In our view, however, the 11 events adjudicated as anaphylactic reactions were usually low in severity and the incidence of 0.1% is not different from other GLP-1 receptor agonists like dulaglutide for instance (0.3%). The same incidence is reported in the Sanofi Pharmacovigilance database arising from the real-life experience in Europe. Referring to the only case of anaphylactic shock, the Allergic Reaction Assessment Committee (ARAC) concluded that no specific antibody was found and that the case was exceptional. We don't expect a warning as a consequence but rather a simple mention and observation of other potential cases. Moreover, it should be stressed that panellists during AdCom agreed that Sanofi used a very sensitive detection system for picking up allergic reactions that may not have been used by others previously.

More worrying, in our view, is the immunogenicity section of the briefing documents prepared for the AdCom meeting. By week 24, approximately 70% of lixisenatide-treated subjects were ADA positive compared to less than 8% in the placebo group and single-digit numbers for other GLP1 agonists with the exception of exenatide-based products that are in the 20%-49% range. One can argue that Bydureon, with 49% ADA, does not carry a mention on its label and has no restrictions beyond the simple reporting of numbers in the immunogenicity section of the P.I. However, the difference is that a higher proportion of patients have ADA formation with lixisenatide and the influence on HbA1c reduction is increasing with time. Anecdotally (?), they also report more side effects. How comfortable will the FDA be with this observation? We are not sure but we assume it could be ratcheted up from straightforward post-marketing surveillance to a more restrictive label or even a request for further investigation before granting approval (CRL?).

Fig. 23: Impact of drug antibodies on HbA1c at week 24 and week 76

Table 21: Mean change from baseline for HbA1c at 24 weeks for lixisenatide treated subjects in a pool of 8 placebo-controlled studies by antibody status and titer

	n/N	LS mean change	SE	95% CI
Ab negative	621/1954	-0.83	0.044	-0.92, -0.746
Ab positive	1333/1954	-0.82	0.036	-0.895, -0.755
– < LLOQ	854/1890	-0.88	0.043	-0.963, -0.796
– ≥ LLOQ to ≤ 100 nmol/L	370/1890	-0.63	0.05	-0.732, -0.534
– > 100 nmol/L	45/1890	-0.16	0.131	-0.418, 0.096

Source: Adapted from Table 23 of the Summary of Clinical Efficacy for NDA 208471

Table 22: Mean change from baseline for HbA1c at 76 weeks for lixisenatide treated subjects in a pool of 5 placebo-controlled studies by antibody status and titer

	n/N	LS mean change	SE	95% CI
Ab negative	304/960	-0.96	0.059	-1.071, -0.842
Ab positive	656/960	-0.69	0.046	-0.781, -0.602
– < LLOQ	374/957	-0.92	0.055	-1.031, -0.818
– ≥ LLOQ to ≤ 100 nmol/L	249/957	-0.58	0.064	-0.701, -0.449
– > 100 nmol/L	30/957	-0.52	0.17	-0.853, -.0188

Source: Adapted from Table 24 of the Summary of Clinical Efficacy for NDA 208471

Source: FDA Advisory Committee – briefing documents (May 2016)

Last but not least, iGlarLixi's pen device system was discussed at length during the Adcom meeting and its complexity was behind one of the two negative votes while others voting in favour of the drug nevertheless mentioned that the pen needed improvements. The fact that two very similar pens are used, one with 10-40 units of glargine and 5-20µg of lixisenatide and the other with 30-60 units and 10-20µg respectively, is confusing.

Beyond confusion, the reviewers were also uncomfortable with the way in which the two drugs would be titrated especially for patients switching from a basal insulin who require a significant reduction in the dose of insulin with a significant risk of hypoglycaemia. Use of a suboptimal dose of lixisenatide (5µg) whose efficacy is not proven as a single agent was also questioned.

In the end, we are left with the impression that the jury is still out for lixisenatide and iGlarLixi in terms of US approval. The PDUFA dates are set for the end of July and the end of August respectively and we believe that there is still some unpredictability and uncertainty regarding a straightforward approval considering the factors underlined above. Around lixisenatide monotherapy, the focus will be on drug antibody formation whereas iGlarLixi will have more to do with the pen device.

3.2.3. A not-so-well-anticipated positioning for the two drugs

A broader target with IglarLixi vs Xultophy?

Over the last six months, we have seen a shift in Novo-Nordisk and Sanofi strategies with their combinations of GLP-1 and basal insulins. We are not only talking about price. Our understanding remains that, although priced slightly more reasonably than at first, Novo-Nordisk will price Xultophy at a meaningful premium to Tresiba (i.e. above USD20 per day) whereas Sanofi is likely to position iGlarLixi between Lantus and Victoza (i.e. daily cost in the USD10-15 range).

At the Capital Markets Day in November 2015, our understanding was that Xultophy would be Novo's lead franchise product based on the outstanding clinical data obtained and the convenience for the patient (two very effective drugs in a single daily injection). Since then, positive data from SWITCH and LEADER have further strengthened its overall efficacy profile by stressing the uniqueness of each component and its superiority versus the direct competition. We did, however, find the CSO more balanced in his judgement this time, calling Xultophy an option "for late-stage diabetes", irrespective of the label. A narrowed label would in any case keep the drug for patients who failed under basal insulin AND GLP-1 analogue. A broader one would most likely open up the market to failers under one of the two components or to sub-segments like patients with very high HbA1c levels. Excluding this type of exception, Xultophy is not for T2D patients naïve of therapy and this could allow Novo-Nordisk to implement a relatively high price strategy as stated above and to keep other references for earlier stages of the disease, including the Tresiba and Victoza stand-alone products.

Based on LixiLan-O results and using a more aggressive pricing strategy, Sanofi could conceive of iGlarLixi as a new backbone when a first injectable drug needs to be considered. This is also because Sanofi has little choice within its Diabetes business to try offset upcoming competition on Lantus [note that the 2016-2018 guidance is to maintain the annual sales decline in the 4%-8% range].

Unlike our initial understanding, it now looks like Novo-Nordisk sees Xultophy mainly in cases when insulin intensification is required whereas iGlarLixi is targeting both uncontrolled glargine users and patients looking for a first injectable therapy.

To answer physicians' question about what comes next if Xultophy fails, Novo-Nordisk considers that, once a maximum dose of Xultophy has been used, there are three remaining possibilities: (i) a return to individual components and the use of semaglutide together with Tresiba; (ii) dual insulin therapy; (iii) the addition of another insulin.

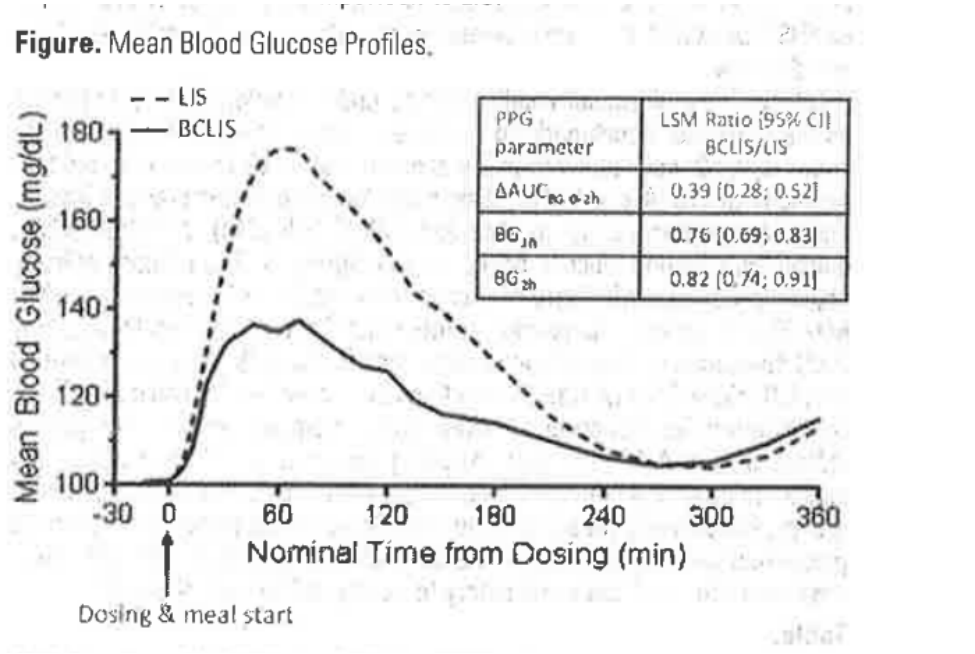
3.3. Adocia is worth a call still

This year's ADA congress provided some interesting insights regarding Adocia as we deem the company offering to be compelling in the light of the market's current needs, i.e. innovation at a reasonable cost. While Novo-Nordisk often positions itself at the high end of the market with truly innovative solutions now increasingly backed by morbi-mortality benefits, there is also a need for balanced propositions that can also address the problem from a volume perspective.

BC Lispro well on track

With BioChaperone Lispro, Adocia is targeting the ultra-fast-acting insulin segment of the market that should ramp up with the successive launches of Novo-Nordisk's Fiasp and then Lilly's drug over the next few years. At the ADA Congress, although this drug class was not the focus of discussions unlike new basal and combination therapies, these drugs were presented as a next wave and a clear step forward in the fast-acting-insulin category. What was once again shown during an oral presentation at the ADA, and reflected in Fig.24 in Type 1 diabetics below, is the more physiological prandial action of BC Lispro compared to lispro after meal ingestion, resulting in much improved blood glucose control.

Fig. 24: Ultra-rapid BC Lispro in T1D patients (abstract 294-OR)



Source: Bryan, Garnier & Co (picture from ADA 2016 congress in New Orleans)

We remain very optimistic about this BC Lispro therapeutic candidate which should soon be more visible as Lilly is expected to start phase III trials in late 2016, triggering a milestone payment to Adocia that we expect to amount to USD50m.

BC Combo now key

Of course, from a share price standpoint, this is enough to cover the full valuation of Adocia as we value BC Lispro at EUR59 per share. However, reaching a FV of approaching or exceeding EUR100 will require other valuable assets, starting with a BC combo which remains Adocia's number one priority for the coming 12 to 18 months. It is fair to say that premixed insulins or combinations of short and long-acting insulins were hardly at the forefront of the ADA congress in New Orleans but it can be argued that this is because the field is currently very quiet. It looks as though Novo-Nordisk has not (yet) decided to do much with Ryzodeg at least in major markets where it is not a priority. In some targeted markets where Tresiba and Xultophy can only make progressive in-roads and where Lilly is a strong leader in the premixed insulin segment (hence where it can grab market share from Humalog Mix), like Mexico, Novo-Nordisk is promoting Ryzodeg more aggressively but there are only limited examples so far.

We see Novo-Nordisk as being in a very promising position given the huge amount of innovative drugs coming to market over the next few years. As a consequence, the company is compelled to make choices which are in some ways fairly easy to make. The dynamics effectively clearly favour the basal insulin segment where, with Tresiba, for the first time it has a competitive product that can make Novo-Nordisk the class leader. Beyond this, Xultophy is also a very attractive and profitable opportunity for the group. Lastly, Fiasp and semaglutide are two more great products that are an excellent fit with the current market trends, whereas the premixed segment appears less dynamic.

Again, a good new proposition in this field could easily find a way to re-boost this market segment and companies other than Novo-Nordisk, with a narrower range of new products to promote, could be interested in doing so with a volume rather than value-based strategy. BC Combo could be such a valuable proposition which is simple to use, effective (combining two current leading agents) and very affordable for the majority of patients. Because the two components will soon be available with biosimilars, it is easy to see that, for one player involved in this race, BC Combo could be an attractive opportunity to leverage a franchise with a reasonable pay-back.

Sanofi as the partner of choice

For Adocia, Sanofi still looks like the partner of choice because it could (i) diversify the partnership base; (ii) offer a solution that was to date unachievable, i.e. mix glargine with a short-acting insulin and deliver what could be the best-in-class combination; (iii) combine Lantus with biosimilar lispro currently in late-stage development and offer Sanofi an alternative to iGlarLixi for patients requiring insulin intensification.

To date, Adocia has found Sanofi reluctant to engage in advanced discussions about BC Combo because the segment appears unattractive; this is, however, largely due to a misunderstanding about market trends and the increased complexity of the diabetes treatment algorithm. With Peter Guenter now assuming responsibility for the Diabetes and CV GBU, a clock reset is possible because Sanofi does not look all that well equipped to compete in a changing environment. His experience in emerging markets might also be an advantage when revisiting the advantages of BC Combo.

Alternatively, Lilly could find a way to leverage Basaglar while benefiting from a competitive offer to Ryzodeg in a segment the company knows very well as it continues to generate over USD2bn in annual sales with the Humalog Mix product range.

Although a deal on BC Combo might not be as lucrative as on BC lispro despite a more advanced stage of development, simply due to the fact that the segment is less attractive and dynamic, we believe that there is still a reasonable chance of Adocia striking a deal with one of the two above-mentioned insulin big players. If this proves unsuccessful, it may then be time to open discussions with a challenger in the field with, for example, a company with another biosimilar glargine like Merck. Our understanding is also that Adocia would be ready to assume more responsibility for BC Combo development compared to BC Lispro which could mean investing more and sharing costs but, in the end, retaining more of the value.

Lastly, on a more general note for Adocia, we noted a continued significant level of interest in the artificial pancreas and a meaningful presence of insulin pump manufacturers at the ADA Congress. This is why their recent announcement to discontinue research and development in oncology to reallocate resources towards a new project with BC glucagon makes sense. In the short-term, however, this is also sensitive for the concentrated forms of insulin on which Adocia and partner Lilly are working like BC Lispro U200 and Hinsbet. For instance, we attended a presentation by Dr. W. Lane from the Mountain Diabetes and Endocrine Center in Asheville (North Carolina) who emphasized the increasing need for concentrated insulins, mainly for obese Type 2 Diabetes patients with severe insulin resistance who are either on CSII (continuous subcutaneous insulin infusion) or require several daily injections.

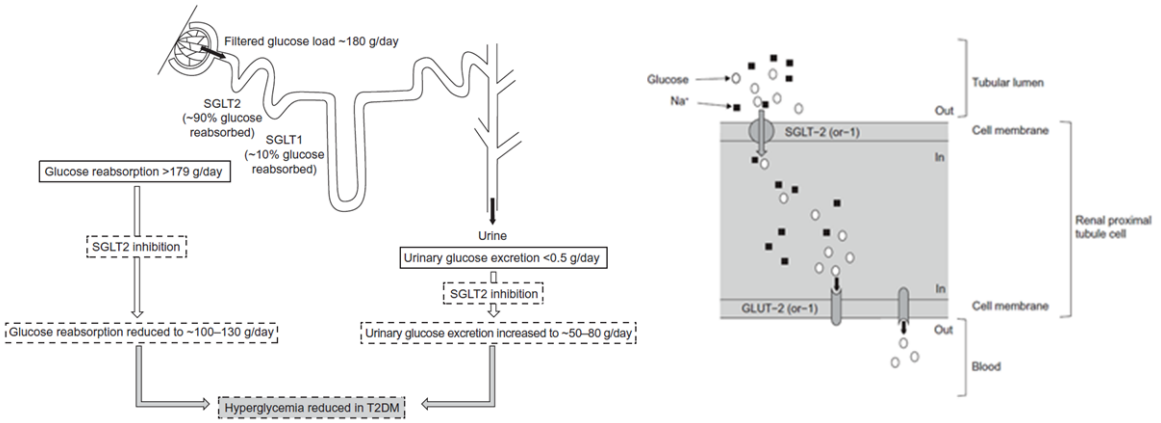
Overall, this presentation and others confirmed the specific interest of the U200 formulation within the BC Lispro global development programme with Lilly. It may also at some point bring HinsBet back at the fore for its U500 component, considering that it should prove superior to the only existing highly concentrated form of insulin i.e. Humulin U500, which is now available in a pen formulation called Humulin R U-500 KwikPen that Lilly advertised a lot at ADA. Either an improved product at Lilly or another player with a competing product to Lilly's remain potential partnership candidates for HinsBet.

Appendix : focus on SGLT

- Transport of glucose (kidney, intestines) back to the bloodstream

The Sodium Glucose co-Transporter SGLT family comprises six members, with SGLT2 and SGLT1 being the most studied. SGLTs employ glucose transporters that use the electrochemical gradient of sodium to transport sugar molecules against a chemical gradient into cells. SGLT1 and SGLT2 contribute to glucose homeostasis by absorbing glucose in the small intestine (SGLT1 only) and in the tubular system of the kidney (essentially SGLT2; SGLT1 to a lesser extent). As a result, the reabsorbed glucose returns to the bloodstream and prevents urinary glucose loss.

Fig. 25: Blockade of the renal tubular reabsorption of glucose decreases hyperglycaemia in T2D glucose



Source: Nauck, 2014

- SGLT1 expression and regulation

While the SGLT1 is strongly expressed in the apical brush border of the small intestine and the late proximal tubule of the kidney, SGLT2 is only expressed in the proximal tubule system of the kidney. It is worth mentioning that luminal nutrients (in the intestines) upregulate SGLT1 expression. Eventually, SGLT1 expression has also been observed in several tissues including the small intestine, kidney, skeletal muscle, lung and heart amongst others. Importantly, it has been demonstrated that diabetes mellitus upregulates intestinal SGLT1 expression and increases renal SGLT1-mediated glucose reabsorption to avoid hypoglycaemia.

- SGLT1 roles

SGLT1 has two main roles in glucose management: 1/it mediates intestinal glucose absorption; and 2/it modulates the secretion of incretins (GLP1, GIP). In a normal kidney, SGLT1 has a modest glucosuric effect but this effect is increased when more glucose is delivered (when SGLT2 is overwhelmed), as shown in studies in mice where SGLT2 were inhibited.

SGLT1 may also have a role in cardiac damage. Indeed, upregulated SGLT1 in diabetic heart might have a role in Reactive Oxygen Species (ROS) production and the accumulation of glycogen in cardiomyocytes. Despite SGLT1 expression in the heart, SGLT1 physiological role remains unclear and further studies are needed to determine whether SGLT1 or SGLT2/1 inhibitors have a good safety profile and permit higher cardiovascular benefits compared with SGLT2 inhibitors or more traditional agents. SGLT1 inhibition does not seem to lead to serious GI adverse events based on the LX411 phase II data published so far (it had been expected to be a concern, more specifically about severe diarrhea).

SGLT1 or combined SGTL1/SGLT1-2 inhibition represents an interesting new antidiabetic concept:

1/ It reduces hyperglycaemia by enhancing glucosuria (excretion of the glucose in the urine), in particular when SGLT2 is either inhibited or overwhelmed by hyperglycaemia (diabetes). Inhibition of SGLT1 delays and attenuates postprandial glucose spikes.

2/ It induces a sustained release of the gastrointestinal incretin (GLP-1) that in turn increases insulin secretion from the pancreas and may increase weight loss;

3/ It could potentially protect T2D patients from CVD events.

The two most advanced projects in development are Lexicon's sotagliflozin (LX4211), in partnership with Sanofi, which has started phase III trials and Novartis' LIK066 for which proof-of-concept data are expected in the second half of 2016. The balance between SGLT-1 and SGLT-2 inhibition by a single agent will be determined in clinical trials fairly soon and positioning between T1D and T2D or between diabetes and obesity will be better characterised, as well as the exact benefit-risk profile.

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