

INDEPENDENT RESEARCH

Pharmaceuticals

24th June 2016

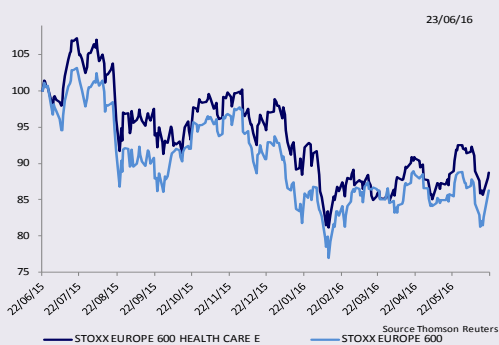
Back from ADA 2016: Update on T2D treatments

Pharmaceuticals

ADOCIA	BUY	FV EUR100 vs. 93
Bloomberg	ADOC FP	Reuters
Price	EUR48.44	High/Low
Market cap.	EUR332m	Enterprise Val
PE (2016e)	37.3x	EV/EBIT (2016e)
		-3.7x
NOVO NORDISK	NEUTRAL	FV DKK400
Bloomberg	NOVOB DC	Reuters
Price	DKK348.2	High/Low
Market cap.	DKK700,775m	Enterprise Val
PE (2016e)	22.9x	EV/EBIT (2016e)
		13.7x
SANOFI	NEUTRAL	FV EUR83
Bloomberg	SAN FP	Reuters
Price	EUR72	High/Low
Market Cap.	EUR92,662m	Enterprise Val
PE (2016e)	13.2x	EV/EBIT (2016e)
		10.4x
ZEALAND	BUY	FV DKK176
Bloomberg	ZEAL DC	Reuters
Price	DKK121	High/Low
Market Cap.	DKK2,969m	Enterprise Val
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 increasingly 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.



Analyst:
Eric Le Berrigaud
 33(0) 1 56 68 75 33
 eleberrigaud@bryangarnier.com

Sector Analyst Team:
 Mickael Chane Du
 Hugo Solvet
 Marion Levi (associate)

Table of contents

1. Background to Diabetes Mellitus	3
1.1. Epidemiology and market.....	3
1.1.1. An epidemic	3
1.1.2. A leading cause of death in the world.....	3
1.1.3. Type 2 diabetes is more common than Type 1.....	3
1.1.4. A growing and dynamic market.....	4
1.2. Pathophysiology	4
1.2.1. How the body processes sugar.....	4
1.2.2. Hallmarks of Type 2 Diabetes	7
1.2.3. Differences between Type 1 and Type 2 Diabetes.....	11
1.3. Basic facts	11
1.3.1. What are the symptoms of Type 2 Diabetes?	11
1.3.2. How to diagnose Type 2 Diabetes	12
1.3.3. Goals for Type 2 Diabetes treatment	13
2. Type-2 Diabetes therapies	14
2.1. Insulin medications	14
2.2. Non-insulin medications	15
2.3. Current Fixed Dose Combination.....	17
2.4. Summary of T2D treatment recommendations.....	17
3. ADA 2016: highlights	19
3.1. Outcome-based studies to the forefront.....	19
3.1.1. LEADER in focus	19
3.1.2. Towards a paradigm shift.....	20
3.2. Novo-Nordisk vs. Sanofi: a few comments	22
3.2.1. Where do Tresiba and Toujeo stand?.....	22
3.2.2. iGlarLixi's presentations well attended but the safety profile with lixisenatide is not yet fully clear.....	23
3.2.3. A not-so-well-anticipated positioning for the two drugs	25
3.3. Adocia is worth a call still	26
Appendix : focus on SGLT.....	29
Adocia (FV EUR100 vs. 93, BUY).....	31
An exciting second-half ahead	31
Novo Nordisk (DKK400, NEUTRAL)	33
Getting stronger	33
Sanofi (FV EUR83, NEUTRAL).....	35
How much diabetes for the new Sanofi?	35
Zealand (DKK176, BUY)	37
Double or quits with lixisenatide in the US.....	37
Price Chart and Rating History	39
References.....	41
Bryan Garnier stock rating system.....	43

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.

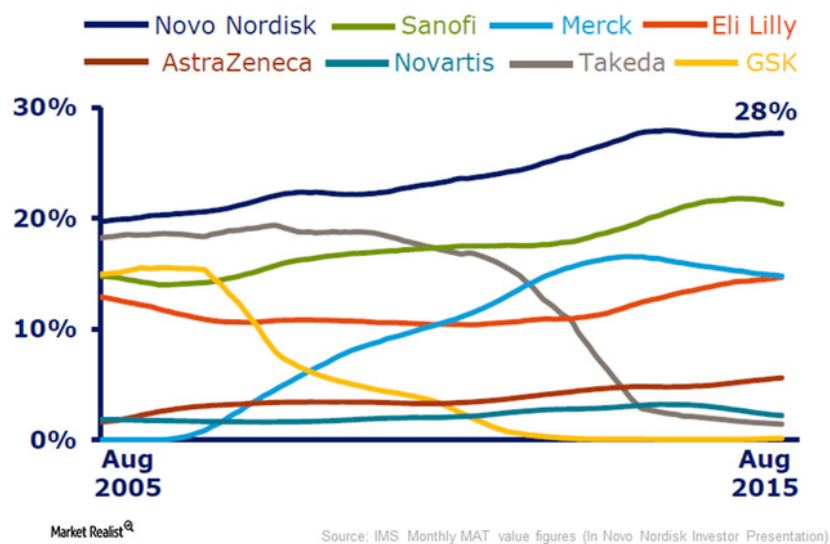
1.1.4. A growing and dynamic market

The global Type 2 Diabetes market is expected to grow at a CAGR of 7.28% over the 2016-2020 period (MedGadget, 2016). Estimates 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

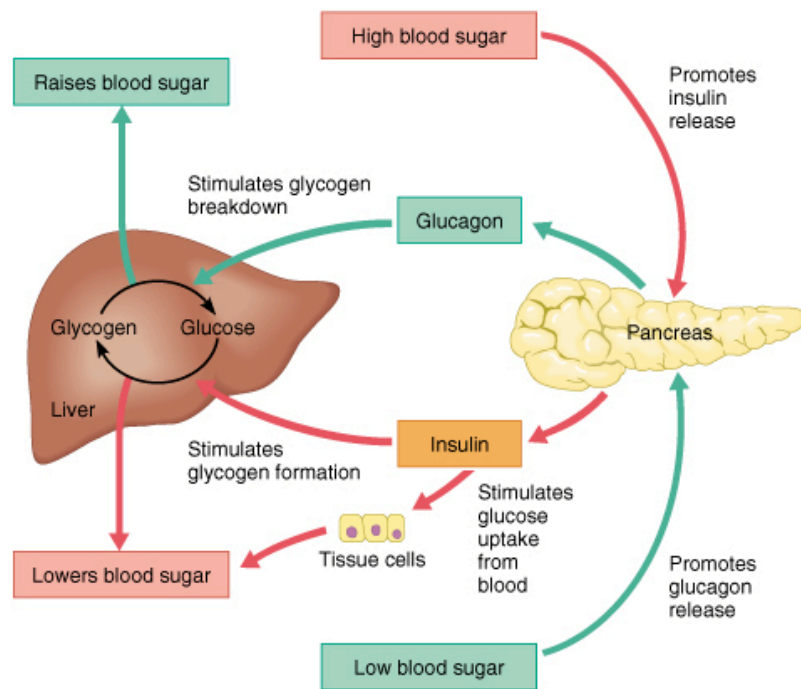
Please see the section headed "Important information" on the back page of this report.

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



Copyright © 2001 Benjamin Cummings, an imprint of Addison Wesley Longman, Inc.

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**

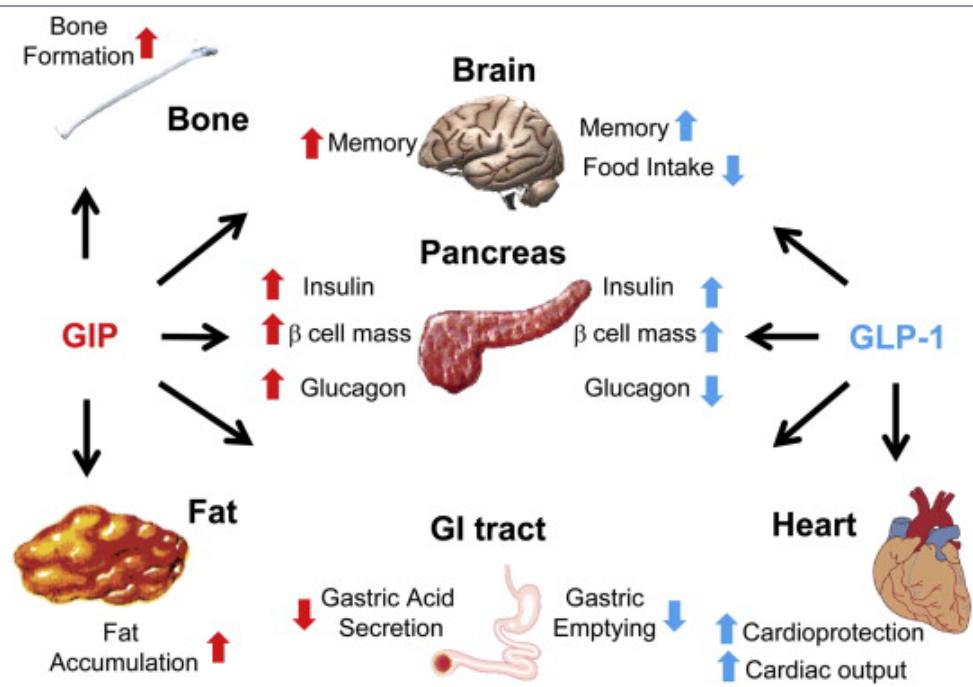
Upon glucose ingestion, Gastric Inhibitory Polypeptide (GIP) and Glucagon-Like Peptide-1 (GLP-1) hormones are produced by intestine cells and have been found to stimulate insulin secretion from pancreatic β -cells. They are called INtestine seCRETion INsulin (incretin) hormones. Both incretin hormones'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

Please see the section headed "Important information" on the back page of this report.

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

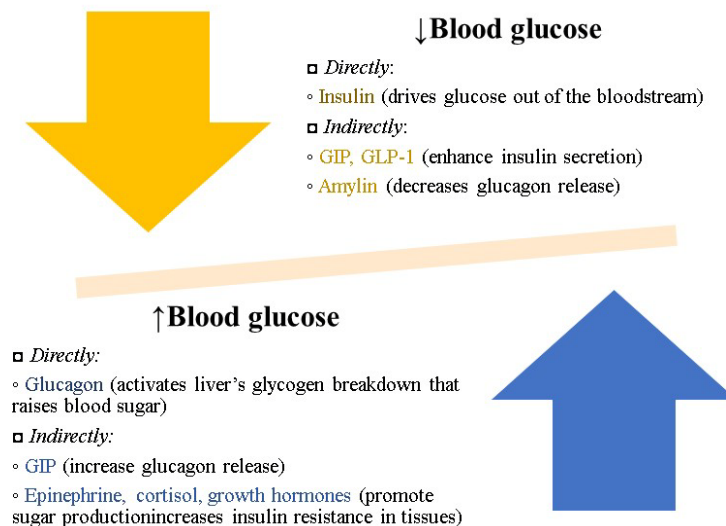
Please see the section headed “Important information” on the back page of this report.

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

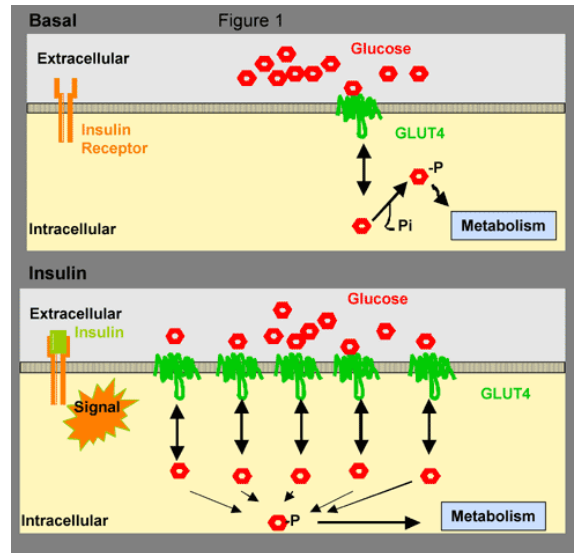
Type 2 diabetes (T2D), which is characterized by hyperglycaemia, is the result of a combination of three dysfunctions:

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).

Please see the section headed "Important information" on the back page of this report.

- ⇒ 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.

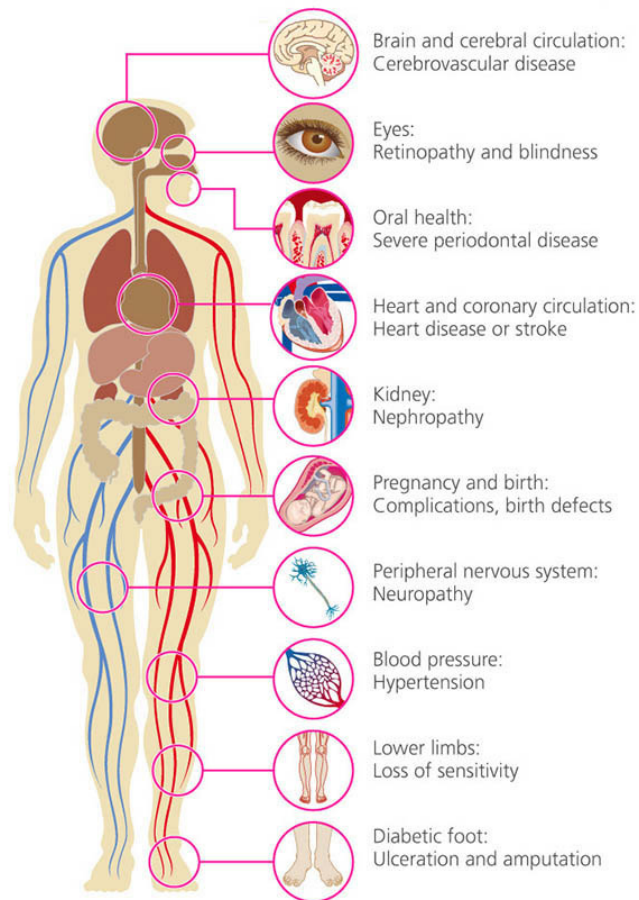
■ Diabetes complications

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)

Please see the section headed "Important information" on the back page of this report.

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

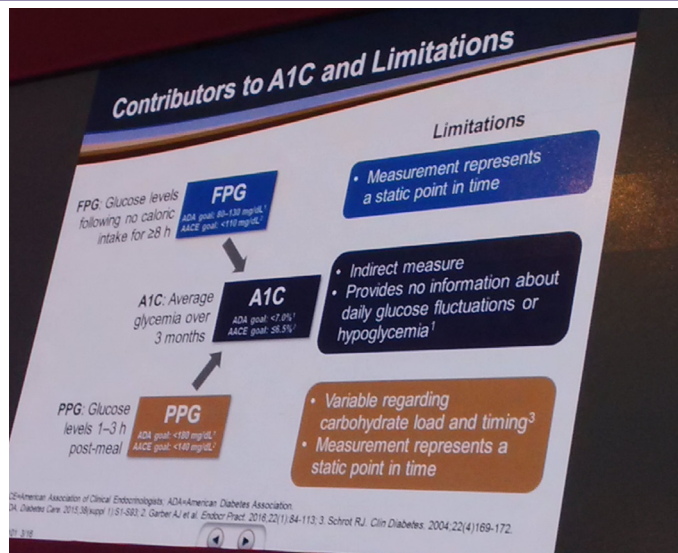
- Asymptomatic	- Polydipsia (excessive thirst)
- Blurred vision	- Polyphagia (excessive hunger)
- Fatigue	- Polyuria (frequent urination)
- Lower-extremity paraesthesia	- Unexplained weight loss
- Nausea/vomiting	

Source: American Diabetes Association (ADA), 2009

1.3.2. How to diagnose Type 2 Diabetes

Fig. 9: Indicators used for diagnosis

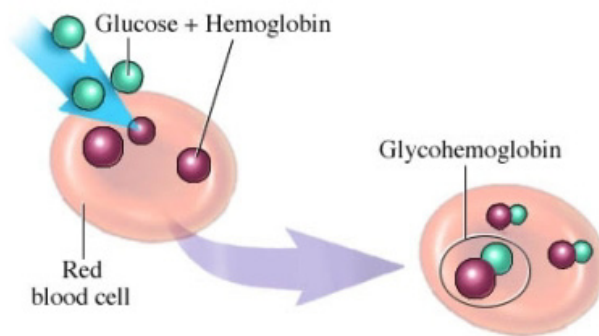
Indicators	Normal	Pre-Diabetes	Diabetes
Fasting Plasma Glucose (FPG)	<100 mg/dl	100-125 mg/dl	>=126 mg/dl
Post glucose-rich beverage (75g glucose): Oral Glucose Tolerance Test (OGTT) - 2h	<140 mg/dl	140-199 mg/dl	>=200 mg/dl
Random plasma glucose and symptoms			>=200 mg/dl
Haemoglobin A1c (HbA1c)	<5,7%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

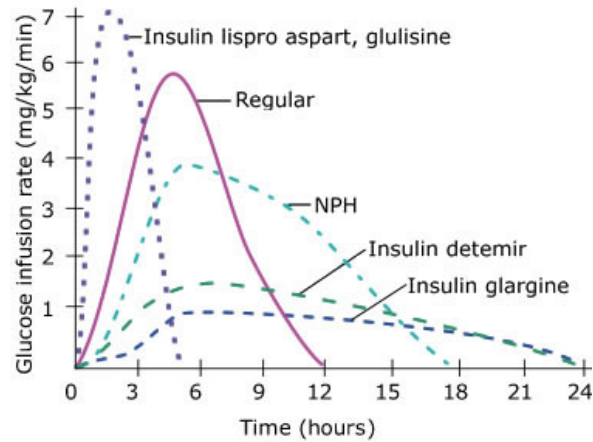
The insulin market leaders are Novo-Nordisk, Sanofi and Eli Lilly. Insulin is prescribed as a monotherapy or in combination with other agents. Historically, the first insulins were extracted from the animal pancreases (pigs, cows) and were purified for human use. However, due to adverse events relating 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 administered 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

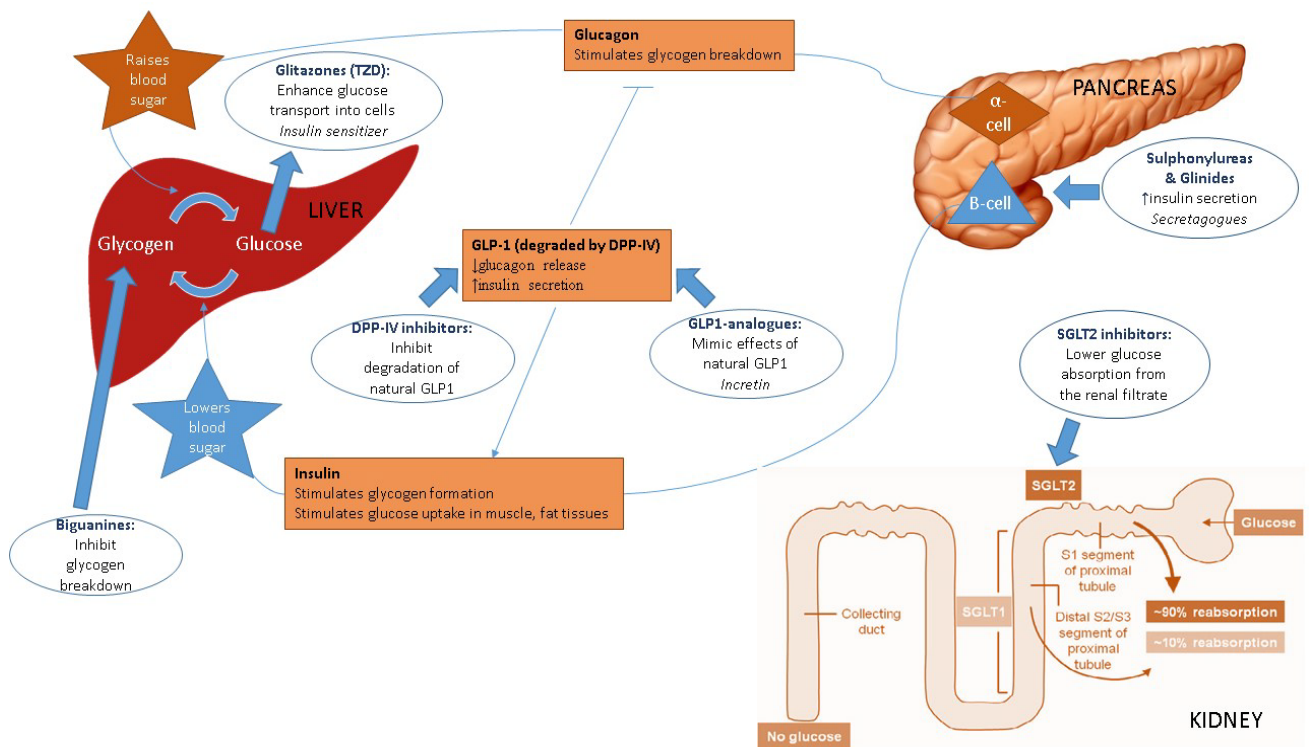
Fig. 13: Different insulins with distinct activity profiles



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					
Meglitinides (Glinides)	Repaglinide	Prandin	Pfizer	1997	Glitazones are PPAR-γ agonists; ↓Decrease insulin resistance in the muscle + fat tissues = "Insulin sensitizers"	Yes	Yes	Moderate	↓postprandial glucose
	Nateglinide	Starlix	Novartis	2000					
Thiazolidinediones (TZD or Glitazones)	Pioglitazone (preferred over Rosiglitazone)	Actos	Abbott/Takeda	1999	Slows intestinal carbohydrate digestion/absorption by inhibiting intestinal α-glucosidase = "Starch blockers"	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	↑insulin secretion; ↓Glucagon secretion from liver after meals by 1/inhibiting DPP-IV activity; 2/ ↑postprandial active incretin (GLP1, GIP)	No	No	Low to moderate	Modest efficacy
	Miglitol	Glyset	Pharmacia & Upjohn	1996					
DPP-IV inhibitors	Sitagliptin	Januvia	Merck	2006	↑insulin secretion; ↓Glucagon secretion ; slows gastric emptying; ↑ satiety	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	Binds bile acids in intestines; may ↑ incretins levels ↓Glucagon secretion ; slows gastric emptying; ↑ satiety	No	No	High	Modest efficacy; may ↓absorption of other drugs
	Liraglutide	Victoza	Novo	2010					
	Albiglutide	Tanzeum	GSK	2014					
Bile acid sequestrant	Dulaglutide	Trulicity	Eli Lilly	2014	Blocks glucose reabsorption 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
	Colesevelam	Welchol	Sanofi	2000					
Amylin mimetics	Pramlintide	Symlin	AZN	2005	Blocks glucose reabsorption by the kidney by inhibiting SGLT2 in the proximal nephron	Yes	No	High	↓postprandial glucose; modest efficacy
	Canagliflozin	Invokana	JNJ	2013					
SGLT-2 inhibitors	Dapagliflozin	Farxiga	AZN	2014		No	No	High	
	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).

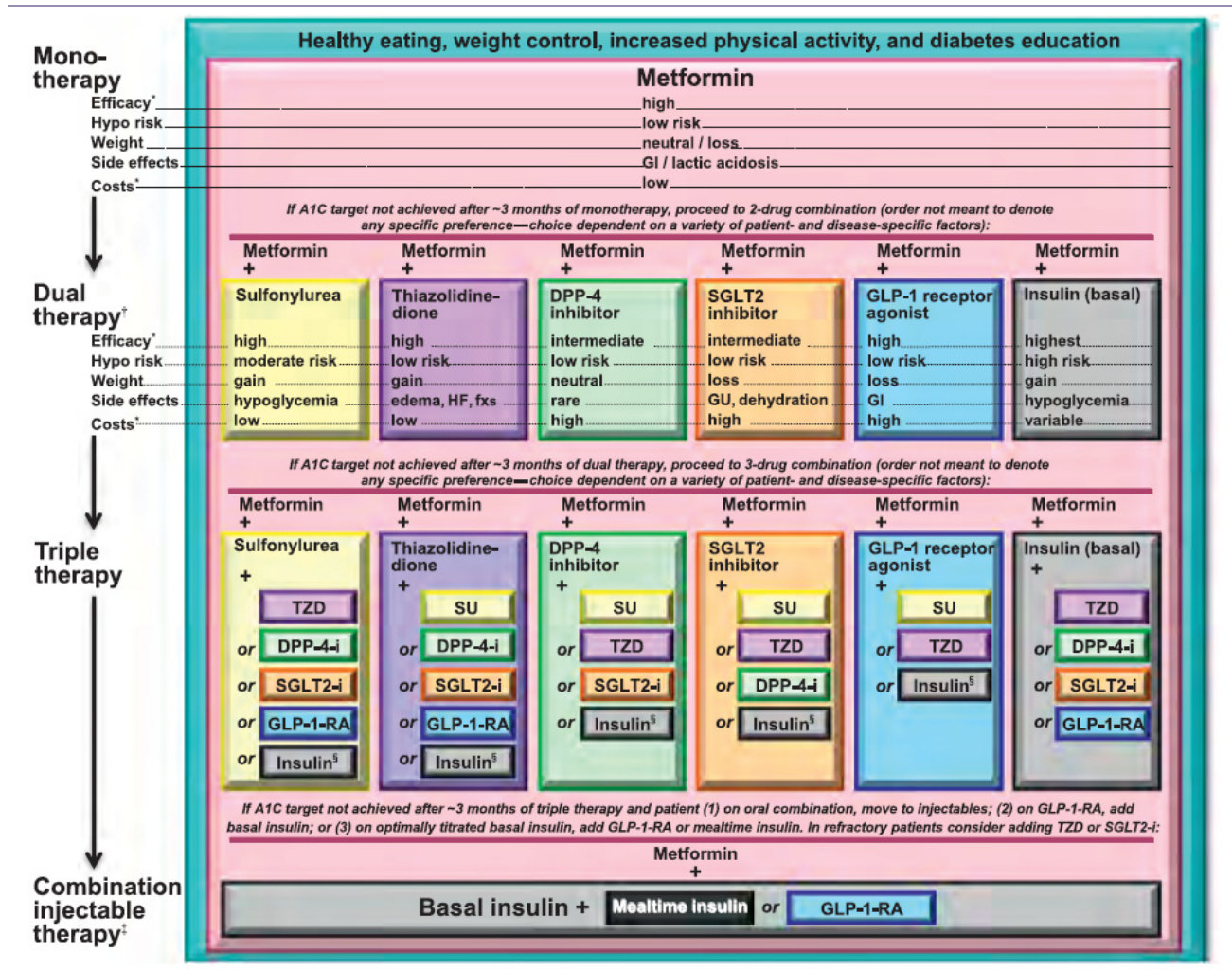
Note that certain drugs, including pramlintide, bromocriptine (dopamine inhibitor), colesvelam and α -glucosidase inhibitors, are not usually favoured as they have limited efficacy, need frequent administration and their efficacy is not sufficient in view of the associated side effects. They are thus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

Please see the section headed "Important information" on the back page of this report.

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

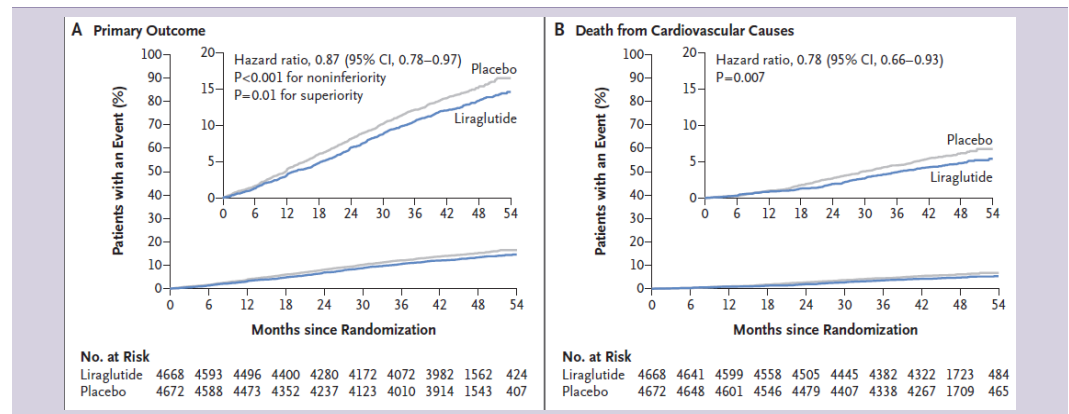
When visiting the ADA 2016 website, a section called “Spotlight on the sessions” quickly stood out, clearly setting the scene for what was going to be key during this annual congress: “this year, in addition to a program of impressive symposia, we will showcase the latest results from two major clinical 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

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).

Primary endpoint reached with HR=0.87

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

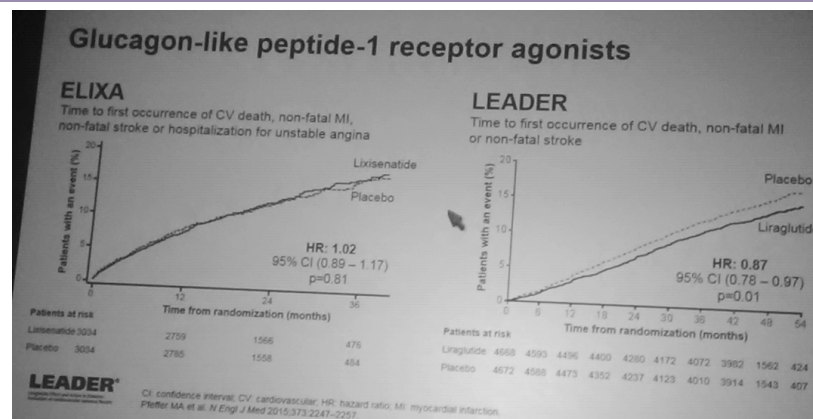
The least impressive number was the reduction in HbA1c which was "only" 0.40% at month 36 compared with a baseline of 8.7%. However the two arms were not comparable in terms of concomitant drug use. At month 36, 1336 patients used insulin in the Lira arm vs 1018 in the placebo arm whereas the percentage was similar at baseline. Liraglutide use was thus associated with an insulin sparing effect.

Please see the section headed "Important information" on the back page of this report.

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 lives 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.

Please see the section headed "Important information" on the back page of this report.

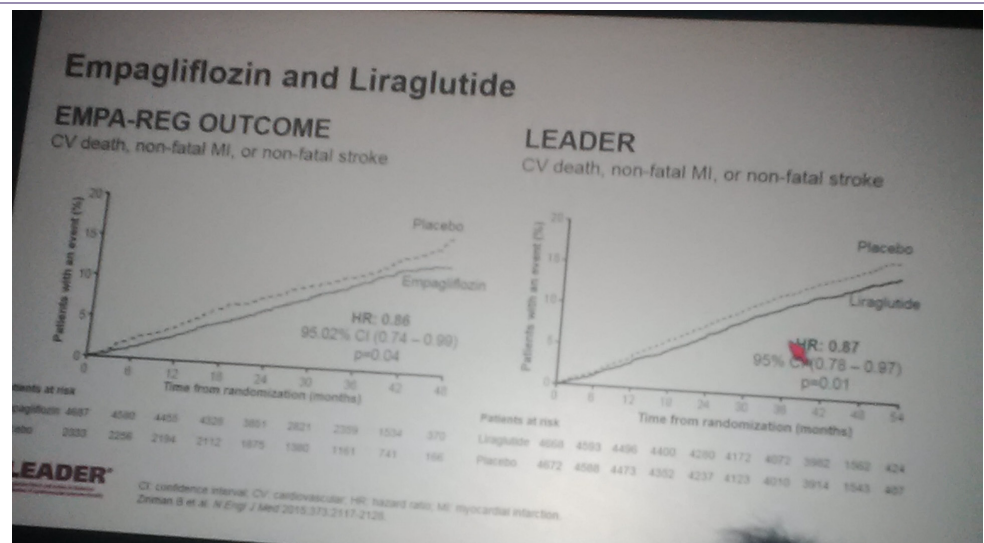
Novo-Nordisk surprised us by saying that they were expecting the EMPA-REG OUTCOME study to go well and afford empagliflozin class-leading status although this actually reflects the desire of the leader in injectable diabetes treatments to see a paradigm shift towards outcomes-based medicines i.e. drugs 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

	SAVOR-TIMI 53	EXAMINE	TECOS	ELIXA
Intervention	Saxagliptin	Alogliptin	Sitagliptin	Lixisenatide
1 st outcome (HR, 95% CI)	1.00 (0.89-1.12)	0.96 (upper 95% CI 1.16)	0.98 (0.88-1.09)	1.02 (0.89-1.17)
Median F/u (yrs)	2.1	1.5	3.0	2.1
HF hospitalization				
Therapy	3.5%	3.1%	3.1%	4.0%
Placebo	2.8%	2.9%	3.1%	4.2%
HF hosp HR (95% CI)	1.27 (1.07-1.51)	1.07 (0.79-1.46)	1.00 (0.83-1.20)	0.96 (0.75-1.23)

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)

Please see the section headed "Important information" on the back page of this report.

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".

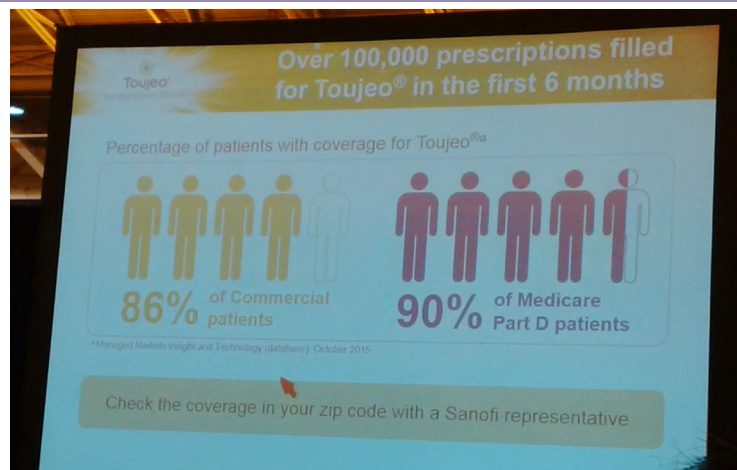
Faced with a strong base of Lantus users, and Sanofi likely to play a price game to maintain volumes, new insulins will have to differentiate on the clinical data.

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)

Please see the section headed "Important information" on the back page of this report.

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.

Please see the section headed "Important information" on the back page of this report.

...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, -0.188

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

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.

A broader target with iGlarLixi vs Xultophy?

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.

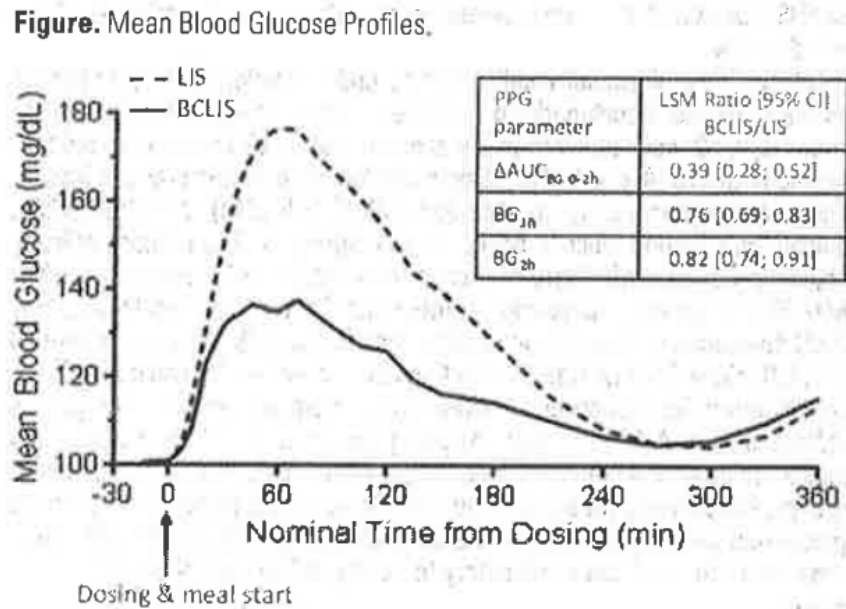
3.3. Adocia is worth a call still

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.

Please see the section headed "Important information" on the back page of this report.

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.

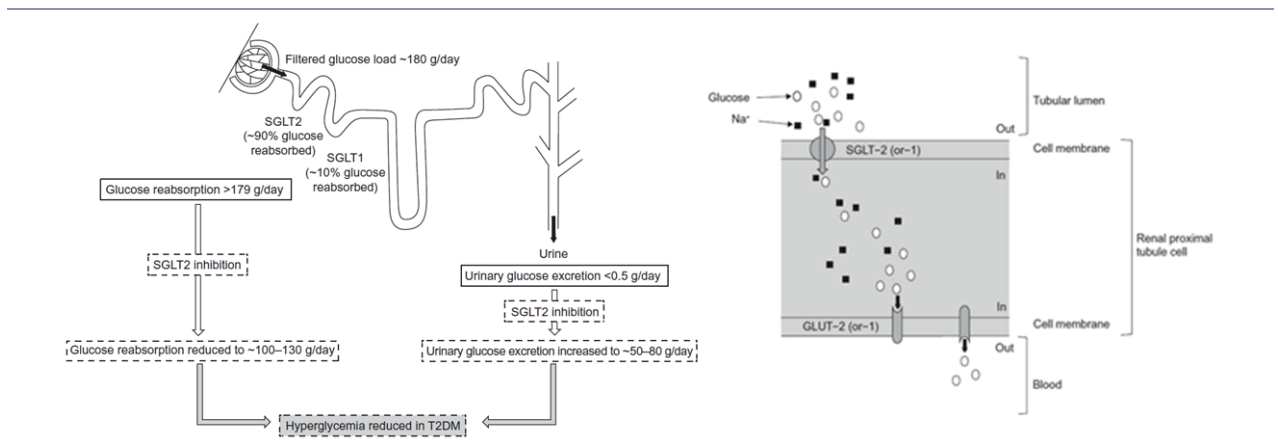
Overall, this presentation and others confirmed the specific interest of the U200 formulation within the BC Lispro global development programme with Lilly. It may also at some point bring HinsBet back at the fore for its U500 component, considering that it should prove superior to the only existing highly 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 SGLT1/SGLT2 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.

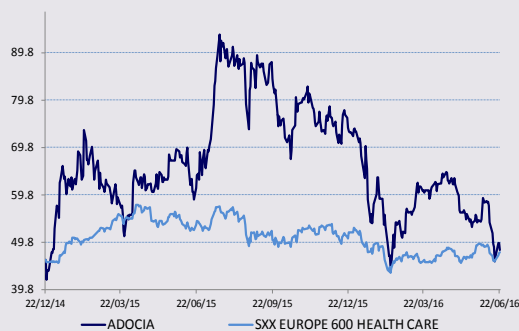
UPDATE
INDEPENDENT RESEARCH

24th June 2016

Healthcare

Bloomberg	ADOC FP
Reuters	ADOC.FR
12-month High / Low (EUR)	93.7 / 44.4
Market capitalisation (EURk)	329,224
Enterprise Value (BG estimates EURk)	276,933
Avg. 6m daily volume ('000 shares)	32.00
Free Float	44.9%
3y EPS CAGR	-1.3%
Gearing (12/15)	-153%
Dividend yields (12/16e)	NM

YE December	12/15	12/16e	12/17e	12/18e
Revenue (EURk)	36,936	42,851	48,931	74,366
EBIT(EURk)	10,103	14,151	23,431	48,866
Basic EPS (EUR)	1.84	1.30	0.18	1.77
Diluted EPS (EUR)	1.84	1.30	0.18	1.77
EV/Sales	7.0x	6.5x	5.9x	2.1x
EV/EBITDA	24.3x	18.9x	12.0x	3.2x
EV/EBIT	25.5x	19.6x	12.2x	3.2x
P/E	26.2x	37.0x	NS	27.2x
ROCE	NM	NM	NM	NM



Adocia


An exciting second-half ahead

Fair Value EUR100 vs. EUR93 (price EUR48.09)

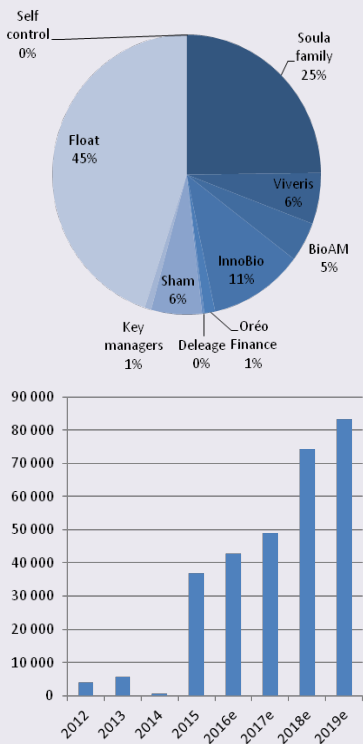
BUY

We expect Adocia to see an exciting 2016 second half with three triggering events: (i) the verdict on the Indian phase III trial with PDGF-BB in foot ulcer; (ii) the entry into phase III for BC Lispro led by Lilly and (iii) a potential licensing agreement for BC Combo. This very strong momentum should again see Adocia in the spotlight.

- The current trends in the diabetes market are beneficial for Adocia since the existing leaders are increasingly driven by innovation while operating under cost constraints. From this perspective, Adocia's BioChaperone is a good fit with the market needs.
- The first application is BC Lispro whose development is on track in trials and should move into phase III under Lilly leadership by the year-end. Together with Novo's Fiasp, it should take the rapid-insulin market to the next level and we expect most of the segment to convert within a relatively short period considering more physiological behaviour and the superior convenience for patients. This is worth EUR59 in our FV.
- However, all eyes are now mainly on BC Combo as it offers the most upside for Adocia. The topic is obviously more debated than BC Lispro since the mixed insulin segment is itself less dynamic and to some extent threatened by others. But it is also less competitive and can be a valuable option for some patients. From a marketing perspective, we are firmly convinced that such a product can leverage a franchise by adding new options when insulin intensification is required. Sanofi looks like a partner of choice since it could create a new glargine-based opportunity in a segment to which it is currently not exposed. To leverage Basaglar, Lilly might be seen as a back-up. Despite applying several layers of caution, we have increased BC Combo's value from EUR23 to EUR31.
- So far, the other two projects are largely free options but it is worth noting that the PDGF-BB Indian phase III data are coming soon. Lastly, HinsBet is less in the news although we were surprised to see Lilly advertising the Humulin U500 KwikPen a lot at ADA, thereby making HinsBet a potential next-generation drug for the company in the category.

	Analyst:	Sector Analyst Team:
	Eric Le Berrigaud	Mickael Chane Du
	33(0) 1 56 68 75 33	Hugo Solvet
	eleberrigaud@bryangarnier.com	Marion Levi (associate)

Adocia



Company description

Adocia was founded in December 2005 by Gerard Soula and his two sons Olivier and Remi. Together they developed BioChaperone®, an innovative delivery system improving therapeutic proteins and modifying some of their properties. Currently, this system is being tested with four different proteins in phase II/III development programmes. A first one known as BC Lispro recently led to an agreement with Eli Lilly, the latter paying an upfront of USD50m. Several milestones and tiered royalties will be paid to Adocia as the drug moves forward. Other projects are open to partnerships over the next two years.

Shareholders	
Soula family	22.1
Financial investors	15.5
Key employees	0.6
Free Float	60.2

Simplified Profit & Loss Account (EURk)	2013	2014	2015	2016e	2017e	2018e	2019e
Revenues	5,589	704	36,936	42,851	48,931	74,366	83,417
Change (%)	39.9%	-87.4%	5 147%	16.0%	14.2%	52.0%	12.2%
Adjusted EBITDA	(3,942)	(16,764)	10,571	14,651	23,931	49,366	58,417
EBIT	(4,302)	(17,161)	10,103	14,151	23,431	48,866	57,917
Change (%)	-29.1%	-299%	-%	-%	65.6%	109%	18.5%
Financial results	9.0	524	2,118	2,118	2,118	2,118	2,118
Pre-Tax profits	(4,293)	(16,637)	12,221	16,269	25,549	50,984	60,035
Exceptionals	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tax	0.0	(4,078)	333	(7,379)	(24,351)	(38,902)	(2,189)
Profits from associates	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Minority interests	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net profit	(4,293)	(20,715)	12,554	8,890	1,198	12,082	57,846
Restated net profit	(4,293)	(20,715)	12,554	8,890	1,198	12,082	57,846
Change (%)	-28.4%	-383%	-%	-29.2%	-86.5%	909%	379%
Cash Flow Statement (EURk)							
Operating cash flows	(3,635)	(18,782)	(14,684)	15,941	10,049	132,242	64,994
Change in working capital	(7,160)	19,229	(11,902)	(1,312)	(1,509)	(1,735)	(1,995)
Capex, net	(428)	(500)	(2,500)	(2,500)	(2,500)	(2,500)	(2,500)
Financial investments, net	400	0.0	0.0	0.0	0.0	0.0	0.0
Dividends	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other	NM	NM	NM	NM	NM	NM	NM
Net debt	(19,414)	(49,800)	(72,062)	(52,291)	(42,567)	(170,573)	(231,072)
Free Cash flow	(10,738)	4,025	(29,086)	12,129	6,040	128,007	60,499
Balance Sheet (EURk)							
Tangible fixed assets	863	975	1,930	3,680	5,430	7,180	8,930
Intangibles assets	3.0	2.0	0.0	250	500	750	1000
Cash & equivalents	19,664	49,800	72,062	52,291	42,567	170,573	231,072
current assets	23,541	50,758	85,982	67,523	59,308	189,050	251,544
Other assets	NM	NM	NM	NM	NM	NM	NM
Total assets	24,885	52,544	88,094	71,635	65,420	197,162	261,656
L & ST Debt	3,036	19,347	20,407	20,407	20,407	20,407	20,407
Others liabilities	2,441	30,692	20,636	27,187	35,538	155,197	161,845
Shareholders' funds	19,406	2,505	47,051	55,941	57,139	69,221	127,068
Total Liabilities	24,884	52,544	88,094	103,535	113,083	244,825	309,319
Capital employed	5,221	2,744	16,032	19,344	22,853	26,588	30,584
Ratios							
Operating margin	(76.97)	(2,438)	27.35	33.02	47.89	65.71	69.43
Tax rate	NM	NM	NM	NM	NM	NM	NM
Net margin	(76.81)	(2,942)	33.99	20.75	2.45	16.25	69.35
ROE (after tax)	(22.12)	(827)	26.68	15.89	2.10	17.45	45.52
ROCE (after tax)	NM	NM	NM	NM	NM	NM	NM
Gearing	(100)	(1,988)	(153)	(93.48)	(74.50)	(246)	(182)
Pay out ratio	NM	NM	NM	NM	NM	NM	NM
Number of shares, diluted	6.21	6.21	6.84	6.84	6.84	6.84	6.84
Data per Share (EUR)							
EPS	(0.69)	(3.33)	1.84	1.30	0.18	1.77	8.46
Restated EPS	(0.69)	(3.33)	1.84	1.30	0.18	1.77	8.46
% change	-28.6%	-383%	-%	-%	-%	-%	-%
EPS bef. GDW	NM	NM	NM	NM	NM	NM	NM
BVPS	3.12	0.40	6.88	8.18	8.35	10.12	18.58
Operating cash flows	(0.59)	(3.02)	(2.15)	2.33	1.47	19.33	9.50
FCF	(1.73)	0.65	(4.25)	1.77	0.88	18.71	8.84
Net dividend	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Source: Company Data; Bryan, Garnier & Co ests.

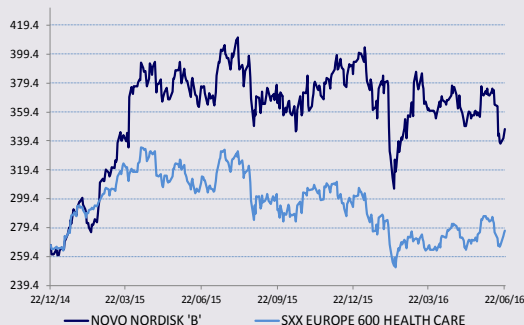
UPDATE
INDEPENDENT RESEARCH

24th June 2016

Healthcare

Bloomberg	NOVOB DC
Reuters	NOVOB.CO
12-month High / Low (DKK)	410.7 / 306.4
Market capitalisation (DKKm)	693,127
Enterprise Value (BG estimates DKKm)	668,315
Avg. 6m daily volume ('000 shares)	2 688
Free Float	71.4%
3y EPS CAGR	9.0%
Gearing (12/15)	-42%
Dividend yields (12/16e)	1.96%

YE December	12/15	12/16e	12/17e	12/18e
Revenue (DKKm)	107,915	114,249	120,921	124,688
EBIT(DKKm)	49,432	48,868	52,924	55,562
Basic EPS (DKK)	13.56	15.00	16.57	17.54
Diluted EPS (DKK)	13.56	15.00	16.57	17.54
EV/Sales	6.2x	5.8x	5.4x	5.0x
EV/EBITDA	12.9x	12.7x	11.4x	10.5x
EV/EBIT	13.6x	13.7x	12.3x	11.3x
P/E	25.4x	23.0x	20.8x	19.6x
ROCE	82.0	76.7	97.8	78.6



Novo Nordisk

Getting stronger

Fair Value DKK400 (price DKK344.40)


NEUTRAL

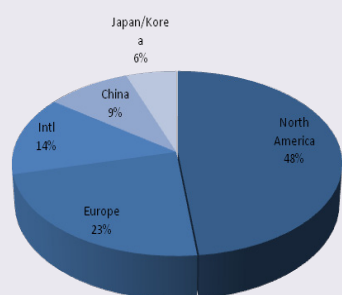
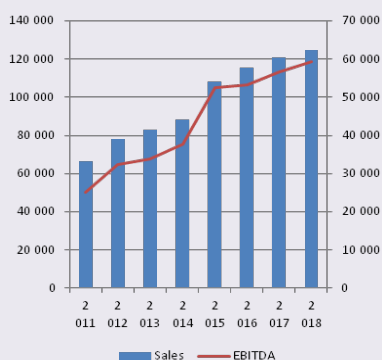
At the 2016 ADA congress in New Orleans, Novo-Nordisk was in the spotlight with the presentation of the LEADER phase III trial results but also with ONSET, DUAL, SUSTAIN and SWITCH. CSO Mads Krogsgaard Thomsen considered this ADA to be the “richest one in his career”. There is little doubt that the group is leading the pack in the field of injectable antidiabetics, the question being how much has yet to be priced in. The coming months will tell.

■ The presentation of the LEADER cv outcome study results was the key event of ADA 2016 in New Orleans earlier this month. While investors sent the stock sharply lower on the following day having been disappointed by the hazard ratio associated with the primary endpoint, the results of the US cohort and comparisons with empagliflozin, this is not our view. The consistency of the results across the various subgroups was remarkable and the safety card was also very clean. Victoza has strengthened its overall profile with LEADER and with SUSTAIN-6 coming, we see Novo-Nordisk running a best-in-class portfolio of GLP-1 analogues. That said, the GLP-1 portion of total revenues is already expected by CS to grow from DKK18bn in 2015 to around DKK30bn in 2020 - without Xultophy which could add another DKK8bn. The real issue? there are too many moving parts in the diabetes field to be able to say for sure that Novo-Nordisk can reach or even exceed these targets. Each opportunity is not fully incremental and some products, like Tresiba with Levemir or Xultophy with monotherapies, will cannibalise the rest of the portfolio. This will therefore have to be closely monitored.

■ Obviously, the coming weeks and months will tell us a lot in terms of the relative competition. FDA decisions on lixisenatide, iGlarLixi and then Xultophy will show if the agency will entertain differences between drugs and how wide the labels are likely to be. We will also learn a lot from pricing strategies. At EASD in September, new data will be presented including from SUSTAIN-6. In Q4 2016, a first approval is expected from the FDA on Fiasp. So far, we expect Tresiba, Xultophy and semaglutide to reach PS of around USD2bn apiece. No change to our numbers, FV and rating..



	Analyst:	Sector Analyst Team:
	Eric Le Berrigaud	Mickael Chane Du
	33(0) 1 56 68 75 33	Hugo Solvet
	eleberrigaud@bryangarnier.com	



Company description

Novo-Nordisk is the worldwide leader in Diabetes where it benefits from strong underlying volume growth due to epidemiology, geographic expansion, mix effects and innovation. Growth has further accelerated in recent quarters as the Danish company successfully added Victoza, a GLP-1 analog, to its wide range of insulins to further strengthen its positioning within the Diabetes field. The drug is quickly gaining market share. Currently, the company is mainly focused on switching its insulins to a new generation of products. In parallel, it is building a franchise in Hemophilia that could significantly leverage margins if NovoSeven is transformed into a diversified product line. In our view, the Novo-Nordisk success story is unlikely to be interrupted in the short term.

Shareholders

Novo A/S Fondation	28.6
Flottant	71.4

Profit & Loss Account (DKK million)	2013	2014	2015	2016e	2017e	2018e
Sales	83,572	88,806	107,915	114,249	120,921	124,688
Change (%)	7.1%	6.3%	21.5%	5.9%	5.8%	3.1%
EBITDA	34,292	37,927	52,391	52,668	56,724	59,362
EBIT	31,493	34,492	49,432	48,868	52,924	55,562
Change (%)	6.8%	9.5%	43.3%	-1.1%	8.3%	5.0%
Financial result	1,046	(396)	(5,961)	(1,300)	(900)	(500)
Pre-Tax profit	32,539	34,096	43,471	47,568	52,024	55,062
Tax	7,355	7,615	8,623	9,989	10,925	11,563
Net profit	25,184	26,481	34,848	37,579	41,099	43,499
Restated net profit	25,184	26,481	34,848	37,579	41,099	43,499
Change (%)	17.5%	5.2%	31.6%	7.8%	9.4%	5.8%

Cash Flow Statement (DKK million)	2013	2014	2015	2016e	2017e	2018e
Operating Cash Flows	26,207	33,840	40,432	41,379	44,899	47,299
Change in working capital	1,218	1,426	(1,188)	574	557	490
Capex, net	2,773	2,064	6,098	7,000	7,000	5,000
Financial investments, net	(13,924)	(14,667)	(17,196)	(14,000)	0.0	0.0
Dividends	9,715	11,866	12,905	16,452	17,354	19,171
Net debt	(15,775)	(15,215)	(19,696)	(24,812)	(44,783)	(67,354)
Free Cash flow	22,704	27,702	33,051	35,567	37,325	41,742

Balance sheet (DKK million)	2013	2014	2015	2016e	2017e	2018e
Shareholders' funds	42,569	40,294	46,969	54,096	77,841	102,169
+Provisions	11,853	17,276	22,398	23,623	23,623	23,623
+Net debt	(15,775)	(15,215)	(19,696)	(24,812)	(44,783)	(67,354)
=Invested Capital	38,647	42,355	49,671	52,908	56,681	58,438
Fixed assets	28,279	30,769	36,665	39,865	43,065	44,265
+ Working Capital	10,368	11,586	13,012	11,824	12,397	12,954
=Capital employed	38,647	42,355	49,677	51,689	55,463	57,221
Total Balance sheet	70,337	77,062	91,805	100,142	123,084	145,573

Financial Ratios	2013	2014	2015	2016e	2017e	2018e
Operating margin	37.68	38.84	45.81	42.77	43.77	44.56
Tax rate	22.60	22.33	19.84	21.00	0.0	21.00
Net margin	30.13	29.82	32.29	32.89	33.99	34.89
ROE (after tax)	59.16	65.72	74.19	69.47	52.80	42.58
ROCE (after tax)	63.98	64.55	81.99	76.69	97.79	78.56
Gearing	(37.06)	(37.76)	(41.93)	(45.87)	(57.53)	(65.92)
Pay out ratio	47.12	48.73	47.21	46.18	46.65	46.65
Number of shares, diluted	2,718	2,630	2,571	2,505	2,480	2,480

Data per Share (DKK)	2013	2014	2015	2016e	2017e	2018e
EPS	9.26	10.07	13.56	15.00	16.57	17.54
Restated EPS	9.26	10.07	13.56	15.00	16.57	17.54
Core EPS	9.26	10.07	13.56	15.00	16.57	17.54
Change (%)	20.9%	8.7%	34.6%	10.7%	10.5%	5.8%
Book Value	15.66	15.32	18.27	21.60	31.39	41.20
Operating Cash flows	9.64	12.87	15.73	16.52	18.11	19.07
FCF	8.35	10.53	12.86	14.20	15.05	16.83
Net dividend	4.17	4.53	6.40	6.75	7.46	7.89

Source: Company Data; Bryan, Garnier & Co ests.

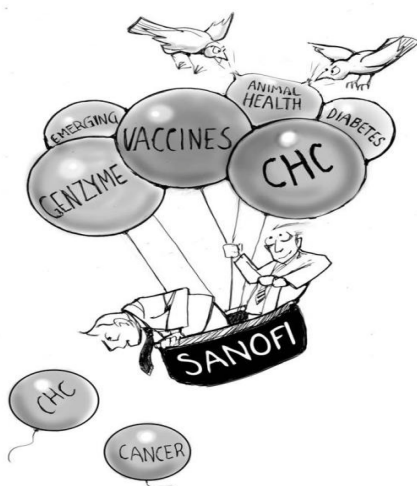
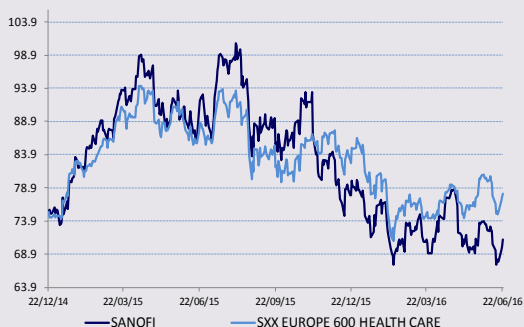
UPDATE
INDEPENDENT RESEARCH

24th June 2016

Healthcare

Bloomberg	SAN FP
Reuters	SASY.PA
12-month High / Low (EUR)	100.7 / 67.3
Market capitalisation (EURm)	91,594
Enterprise Value (BG estimates EURm)	98,993
Avg. 6m daily volume ('000 shares)	2 967
Free Float	91.0%
3y EPS CAGR	2.8%
Gearing (12/15)	13%
Dividend yields (12/16e)	4.22%

YE December	12/15	12/16e	12/17e	12/18e
Revenue (EURm)	36,575	35,963	36,740	38,444
EBIT(EURm)	9,948	9,587	9,591	9,984
Basic EPS (EUR)	5.64	5.40	5.40	5.69
Diluted EPS (EUR)	5.64	5.47	5.52	6.12
EV/Sales	2.7x	2.8x	2.7x	2.5x
EV/EBITDA	8.8x	9.2x	9.3x	8.9x
EV/EBIT	10.0x	10.3x	10.2x	9.6x
P/E	12.6x	13.0x	12.9x	11.6x
ROCE	11.9	11.2	10.9	11.3



Sanofi

How much diabetes for the new Sanofi?

Fair Value EUR83 (price EUR71.17)

NEUTRAL

Sanofi's strategy in diabetes is not that clear but ADA was not the right place to discuss this as nobody was available from the management. It is fair to say that the group is doing its best with what it currently has (i.e. essentially Toujeo) and that iGlarLixi is key for the next few years in terms of keeping the franchise in the guided range or doing better than this. The coming two months will be instructive and potentially exciting.

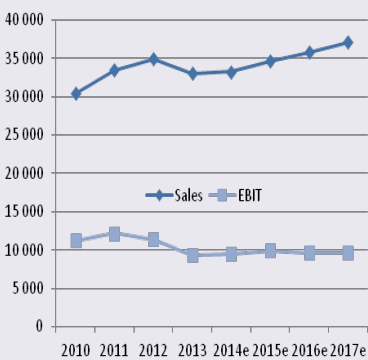
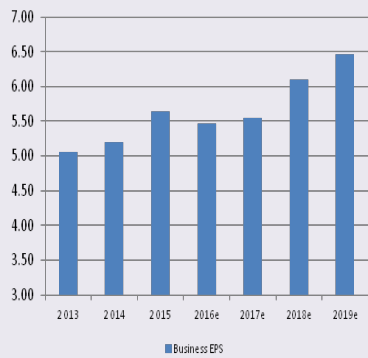
- Everyone agrees that Sanofi is very good at diabetes marketing and that it is doing an excellent job of defending its glargine franchise. In a tough environment, Toujeo is doing fairly well and is highly likely to become a blockbuster - in our view by no later than 2018. However, Sanofi clearly needs a second weapon to compete against Novo-Nordisk and it can't be anything other than iGlarLixi.
- The category is promising in that it is less crowded than others (duopoly) and the clinical data presented at ADA were good in terms of efficacy. Sanofi looks determined and ready to implement an aggressive strategy to make this drug its new flagship product in the diabetes field to intensify treatment after failure with glargine but also as a first injectable after OAD failure. The battle against Novo-Nordisk will be worth following because the positioning of their respective drugs could be slightly different.
- The first goal is currently to get monotherapy and combination both approved by the FDA in July and August respectively. After a 12-2 vote in favour by the Advisory Committee panellists last month, the probability looks fairly high. That said, drug-antibody formation and pen device defaults could make the regulatory process less straightforward than expected with possible label restrictions or even delay in approval
- In our note of 30 May, we highlighted that Sanofi would very probably experience a profound change in product mix in the next few years as CHC, vaccines and Genzyme are expected to enjoy strong growth. Diabetes could go in the opposite direction. However, the rate of decline matters in that this is still a very profitable business; we'll need to wait and see what happens with iGlarLixi at FDA level.



Analyst:
Eric Le Berrigaud
33(0) 1 56 68 75 33
eleberrigaud@bryangarnier.com

Sector Analyst Team:
Mickael Chane Du
Hugo Solvet

Sanofi



Company description

The current Sanofi was formed in 2004 from the merger of two French companies, Sanofi-Synthelabo and Aventis. The new company is a consolidation of various mid-sized companies like Winthrop, Synthelabo, Roussel-Uclaf and, more recently, Genzyme, including diversified companies like Rhône-Poulenc whose businesses in chemicals and agrochemicals were spun off or sold. Today's Sanofi is a diversified healthcare company with strong businesses in animal health, vaccines or consumer health. Under the new leadership of Olivier Brandicourt, it looks determined to reduce the number of businesses while strengthening some of them. This is exemplified by the ongoing asset swap with B.I. where Sanofi sells its animal health division against bigger footprint in CHC. More globally, we see CHC, vaccines and Genzyme becoming more important for the Group.

Shareholders	
L'Oréal	9
Total	5
Free Float	91

Income Statement (EURm)	2013	2014	2015	2016e	2017e	2018e	2019e
Sales	32,951	33,766	36,575	35,963	36,740	38,444	40,310
Change (%)	-5.7%	2.5%	8.3%	-1.7%	2.2%	4.6%	4.9%
EBITDA	10,612	10,655	11,237	10,713	10,441	10,772	10,772
Profits from associates	85.0	147	170	254	370	432	407
Business EBIT	9,324	9,445	9,948	9,587	9,591	9,984	10,983
Change (%)	-17.9%	1.3%	5.3%	-3.6%	0.0%	4.1%	10.0%
Financial result	(503)	(447)	(390)	(386)	(296)	(206)	0.0
Pre-tax result	8,898	8,978	9,514	9,027	9,295	9,778	10,877
Exceptionals	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tax	2,134	2,155	2,187	2,212	2,236	2,341	2,597
Minority interests	162	126	126	20.0	20.0	20.0	20.0
Net result	6,687	6,844	7,371	7,049	7,059	7,437	7,437
Business Net income	6,687	6,843	7,371	6,989	7,059	7,828	8,280
Change (%)	-18.2%	2.3%	7.7%	-5.2%	1.0%	10.9%	5.8%
Cash Flow Statement (EURm)							
Cash flow	7,531	7,483	8,548	8,166	7,959	8,665	9,041
Change in WCR	(124)	988	1,048	54.6	931	919	955
Net Capex	1,398	1,557	3,023	1,850	1,850	1,850	1,500
Net financials investments	(51.0)	2,040	157	0.0	0.0	0.0	0.0
Dividends	3,638	3,676	3,694	3,827	3,919	4,115	4,572
Net debt	6,333	7,473	7,406	7,399	5,970	3,900	1,673
Free Cash flow	6,257	4,938	4,477	5,834	5,347	6,185	6,799
Balance Sheet (EURm)							
Shareholders equity, 100%	57,014	56,268	58,210	58,452	60,812	63,555	66,883
+Provisions	9,619	10,711	10,290	10,290	10,290	10,290	10,290
+Net Debt	6,333	7,473	7,406	7,399	5,970	3,900	1,673
Capital employed	72,990	74,583	77,019	77,255	78,186	78,858	79,959
Intangible assets	67,985	69,801	67,487	67,241	67,411	67,452	67,811
+ WCR	5,712	4,538	2,336	2,818	3,579	4,210	4,952
+ Other / Miscellaneous	(721)	234	1,444	1,444	1,444	1,444	1,444
capital employed	72,990	74,583	77,019	77,255	78,186	78,858	79,959
Total Assets	96,065	97,392	102,321	100,850	103,295	106,181	109,616
Financial Ratios							
Operating margin (%)	28.30	27.97	27.20	26.66	26.10	25.97	27.25
Tax rate (%)	23.98	24.00	22.88	24.50	25.00	25.00	25.00
Net margin	20.29	20.27	20.15	19.44	19.21	20.36	20.54
ROE (after tax) (%)	11.71	12.11	12.91	12.02	11.87	12.63	12.74
ROCE (after tax) (%)	10.29	10.38	11.86	11.15	10.93	11.26	12.19
Gearing	11.11	13.28	12.72	12.66	9.82	6.14	2.50
Payout ratio (%)	54.97	53.97	51.92	55.59	58.29	61.47	66.74
Number of shares, diluted (m)	1,323	1,316	1,306	1,278	1,278	1,278	1,278
Data per Share (EUR)							
Reported EPS	5.00	5.20	5.64	5.40	5.40	5.69	5.69
Adjusted EPS	5.00	5.20	5.64	5.40	5.40	5.69	5.69
Business EPS	5.05	5.20	5.64	5.47	5.52	6.12	6.48
Change (%)	-18.5%	2.9%	8.5%	-3.1%	1.0%	10.9%	5.8%
BV/share	42.99	42.65	44.44	45.59	47.42	49.55	52.14
CF/share	5.69	5.69	6.54	6.39	6.23	6.78	7.07
FCF/share	4.73	3.75	3.43	4.56	4.18	4.84	5.32
Net dividend/share	2.80	2.85	2.93	3.00	3.15	3.50	3.80

Source: Company Data; Bryan, Garnier & Co ests.

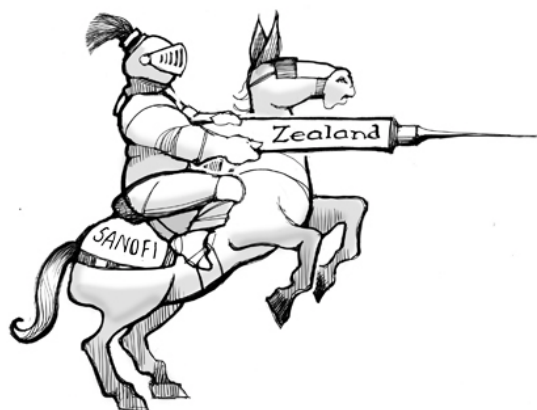
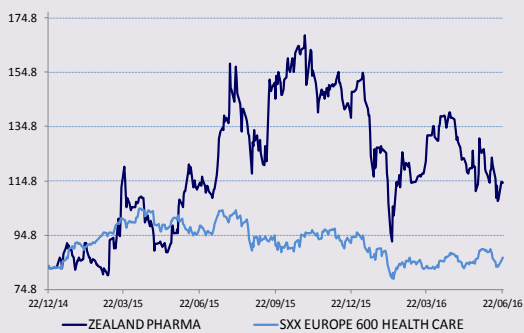
UPDATE
INDEPENDENT RESEARCH

24th June 2016

Healthcare

Bloomberg	ZEAL DC
Reuters	22Z.F
12-month High / Low (DKK)	168.5 / 92.5
Market capitalisation (DKKm)	2,797
Enterprise Value (BG estimates DKKm)	2,859
Avg. 6m daily volume ('000 shares)	121.1
Free Float	81.0%
3y EPS CAGR	
Gearing (12/15)	-50%
Dividend yields (12/16e)	NM

YE December	12/15	12/16e	12/17e	12/18e
Revenue (DKKm)	165.41	474.65	332.60	791.89
EBIT(DKKm)	-81.33	225.69	35.95	451.40
Basic EPS (DKK)	-4.82	6.32	0.53	14.34
Diluted EPS (DKK)	-4.82	6.32	0.53	14.34
EV/Sales	16.1x	6.0x	8.2x	3.3x
EV/EBITDA	NS	12.3x	65.4x	5.7x
EV/EBIT	NS	12.7x	76.3x	5.8x
P/E	NS	18.0x	NS	8.0x
ROCE	NM	NM	NM	NM



Zealand


Double or quits with lixisenatide in the US

Fair Value DKK176 (price DKK114.00)

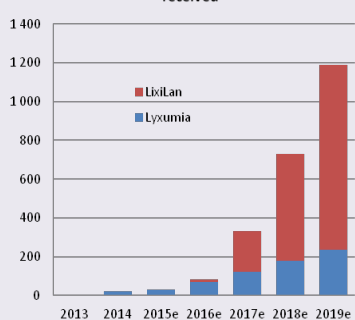
BUY

We anticipate maximum stress for Zealand ahead of the FDA's decision on whether or not to approve lixisenatide in monotherapy and in combination with glargine. Since the AdCom panel voted 12-2 in favour of approval, doubts have not been fully removed and thus we expect the uncertainty to prevail until the last minute. More than two-thirds of our FV derive from lixi-based products and 60% of this comes from the US. Volatility is expected to be high on Zealand.

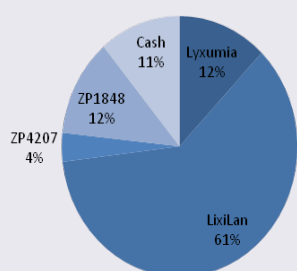
- Zealand is trading at a significant discount to its year high, due not only to market conditions but to remaining doubts on iGlarLixi approval despite a 12-2 vote in favour. The efficacy data, on which a detailed presentation was made at the ADA congress, are very convincing. However, anaphylactic reactions, drug-antibody formation and pen device defaults are dampening the enthusiasm and are likely to do so until the final FDA decision i.e. late July for lixi and August for iGlarLixi.
- If and once it is approved, we are increasingly convinced that Sanofi will deploy the maximum available resources to ensure iGlarLixi's success because this is its best weapon when it comes to winning share in the injectable diabetes market. With a more aggressive pricing strategy than Novo's for Xultophy, we expect Sanofi not only to target the insulin intensification segment (once Lantus has failed) but also that of preferred injectable (after OADs).
- Although price will limit the overall penetration of the class, we witnessed a high level of excitement surrounding the concept of combining basal insulin with a GLP-1 analogue at the ADA congress. Zealand will have a direct interest in the success of iGlarLixi since it receives a 10% royalty on sales.
- A major setback threatening the product could see the FV fall to around DKK50 whereas outright dual approval would propel this towards or even above DKK200. Once this is in the bag, the market will pay increasing attention to the other two major and proprietary assets ZP4207 (glucagon analogue) and ZP4818 (short bowel syndrome). These two should in any case gain more value in the coming months, especially since a deal has been inked with Beta Bionics to develop an artificial pancreas in T1D.

	Analyst:	Sector Analyst Team:
	Eric Le Berrigaud	Mickael Chane Du
	33(0) 1 56 68 75 33	Hugo Solvet
	eleberrigaud@bryangarnier.com	

Cumulative Lyxumia+LixiLan royalties received



What the FV is made of



Company description

Zealand Pharma, created in 1998, describes itself as a biotech company which has leading expertise in peptides. It currently has several partnership agreements with pharma companies and a first product marketed by Sanofi in diabetes. After changes to the Board and Executive Committee, the new strategy focuses on value creation through a mix of partnerships and proprietary developments.

Shareholders

Sunstone BI Funds (Denmark)	19
CDC Innovation (France)	11
LD Pension (Denmark)	10
Free Float	81

Simplified Profit & Loss Account (EURm)	2013	2014	2015	2016e	2017e	2018e
Revenues	6.6	154	165	475	333	792
Change (%)	-96.8%	2 239%	7.6%	187%	-29.9%	138%
Adjusted EBITDA	(180)	NM	(75.3)	232	42.0	458
EBIT	(186)	(73.5)	(81.3)	226	36.0	451
Change (%)	-673%	-60.4%	-10.6%	-%	-84.1%	1 155%
Financial results	1.9	1.0	(38.5)	(26.4)	(19.3)	0.51
Pre-Tax profits	(184)	(72.5)	(120)	79.2	(49.3)	348
Exceptionals	0.0	0.0	0.0	0.0	0.0	0.0
Tax	0.0	7.5	5.9	0.0	0.0	0.0
Profits from associates	0.0	0.0	0.0	0.0	0.0	1.0
Minority interests	0.0	0.0	0.0	0.0	0.0	1.0
Net profit	(184)	(65.0)	(114)	79.2	(49.3)	348
Restated net profit	(184)	(65.0)	(114)	79.2	(49.3)	348
Change (%)	-605%	-64.6%	-75.3%	-%	-162%	-%

Cash Flow Statement (EURm)

Operating cash flows	(166)	(42.2)	(254)	(129)	50.0	2.8
Change in working capital	(3.6)	16.8	(140)	(208)	99.3	(345)
Capex, net	(4.6)	(4.5)	(4.5)	(5.0)	(6.0)	(8.0)
Financial investments, net	0.0	0.0	0.0	0.0	0.0	0.0
Dividends	0.0	0.0	0.0	0.0	0.0	0.0
Other	0.0	300	0.0	0.0	0.0	0.0
Net debt	(311)	(271)	(127)	60.9	(56.8)	(184)
Free Cash flow	(174)	(22.4)	(259)	(134)	44.0	(5.2)

Balance Sheet (EURm)

Tangible fixed assets	18.6	17.6	15.8	20.8	26.8	34.8
Intangibles assets	NM	NM	NM	NM	NM	NM
Cash & equivalents	286	538	440	145	189	184
current assets	20.1	30.1	40.1	50.1	60.1	71.1
Other assets	13.7	12.1	34.3	34.3	34.3	34.3
Total assets	NM	NM	NM	NM	NM	NM
L & ST Debt	0.0	267	313	206	133	0.0
Others liabilities	NM	NM	NM	NM	NM	NM
Shareholders' funds	316	253	252	438	463	943
Total Liabilities	30.8	76.8	69.5	69.5	69.5	69.5
Capital employed	5.6	(285)	(188)	(211)	(224)	(215)

Ratios

Operating margin	NM	NM	NM	NM	NM	NM
Tax rate	NM	NM	NM	NM	NM	NM
Net margin	NM	NM	NM	NM	NM	NM
ROE (after tax)	NM	NM	NM	NM	NM	NM
ROCE (after tax)	NM	NM	NM	NM	NM	NM
Gearing	(98.24)	(107)	(50.45)	13.89	(12.27)	(19.52)
Pay out ratio	0.0	0.0	0.0	0.0	0.0	0.0
Number of shares, diluted	22,680	22,680	23,639	23,639	23,639	23,639

Data per Share (EUR)

EPS	(8.10)	(2.87)	(4.82)	6.32	0.53	14.34
Restated EPS	(8.10)	(2.87)	(4.82)	6.32	0.53	14.34
% change	-606%	-64.6%	-68.3%	-%	-91.7%	-%
EPS bef. GDW	(8.10)	(2.87)	(4.82)	6.32	0.53	14.34
BVPS	(1.36)	(3.38)	(2.94)	(2.94)	(2.94)	(2.94)
Operating cash flows	(7.32)	(1.86)	(10.76)	(5.46)	2.12	0.12
FCF	(7.68)	(0.99)	(10.95)	(5.67)	1.86	(0.22)
Net dividend	0.0	0.0	0.0	0.0	0.0	0.0

Source: Company Data; Bryan, Garnier & Co ests.

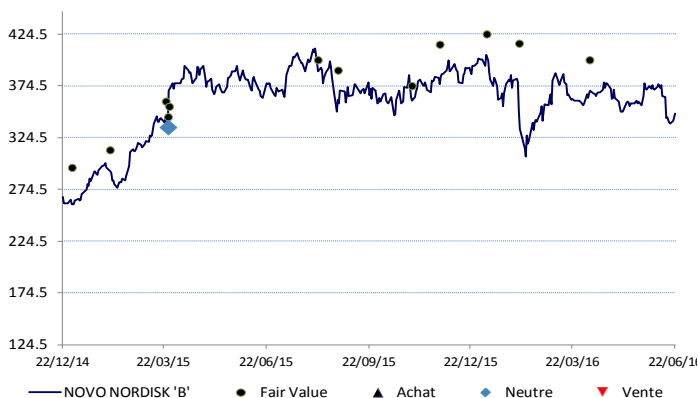
Price Chart and Rating History Adocia



Ratings		
Date	Ratings	Price
22/01/15	BUY	EUR61.6

Target Price	
Date	Target price
06/04/16	EUR93
22/03/16	EUR100
21/07/15	EUR113
15/04/15	EUR98
06/02/15	EUR95
22/01/15	EUR93
08/08/13	EUR14.4
08/03/13	EUR19.5

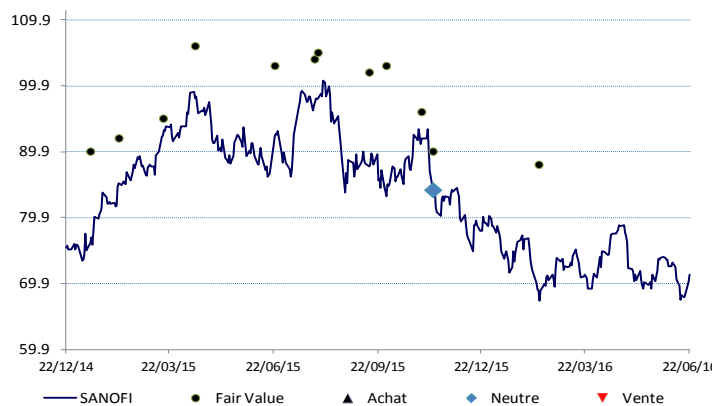
Novo Nordisk



Ratings		
Date	Ratings	Price
26/03/15	NEUTRAL	DKK340.7
19/12/13	BUY	DKK190.5

Target Price	
Date	Target price
06/04/16	DKK400
03/02/16	DKK416
05/01/16	DKK425
24/11/15	DKK415
30/10/15	DKK375
25/08/15	DKK390
07/08/15	DKK400
06/08/15	Under review
27/03/15	DKK355
26/03/15	DKK345
24/03/15	DKK360
02/02/15	DKK313
30/12/14	DKK296

Sanofi



Ratings

Date	Ratings	Price
09/11/15	NEUTRAL	EUR86.9
18/07/11	BUY	EUR54.7

Target Price

Date	Target price
30/05/16	EUR83
02/05/16	EUR86
01/04/16	EUR87
10/02/16	EUR88
09/11/15	EUR90
30/10/15	EUR96
29/09/15	EUR103
14/09/15	EUR102
31/07/15	EUR105
28/07/15	EUR104
23/06/15	EUR103
14/04/15	EUR106
17/03/15	EUR95
06/02/15	EUR92
12/01/15	EUR90
29/10/14	EUR87

Zealand



Ratings

Date	Ratings	Price
14/09/15	BUY	DKK122
04/09/15	NEUTRAL	DKK130
17/09/13	BUY	DKK65.5
12/09/13	Under review	DKK78
16/05/13	BUY	DKK76
08/02/13	SELL	DKK99.5
04/04/11	BUY	DKK70.5

Target Price

Date	Target price
18/05/16	DKK176
06/04/16	DKK180
23/11/15	DKK200
30/10/15	DKK160
14/09/15	DKK168
04/09/15	DKK150
16/07/15	DKK154
26/06/15	DKK128
27/04/15	DKK125
21/03/14	DKK83.5
07/02/14	DKK87
17/09/13	DKK90

References

- American Diabetes Association (ADA). (2009). Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*, 32, 62-67.
- American Diabetes Association (ADA). (2015, 03). *DKA (Ketoacidosis) & Ketones*. Retrieved 06 13, 2016, from diabetes.org: <http://www.diabetes.org/living-with-diabetes/complications/ketoacidosis-dka.html?referrer=https://www.google.fr/>
- American Diabetes Association (ADA). (n.d.). *Statistics About Diabetes*. Retrieved 06 13, 2016, from diabetes.org: <http://www.diabetes.org/diabetes-basics/statistics/?referrer=https://www.google.fr/>
- American Diabetes Association. (2016). Standards of medical care in Diabetes - 2016. *The journal of clinical and applied research and education*, 39(1), 1-119.
- Boyle, Honeycutt, Narayan, Hoerger, Geiss, Chen, & Thompson. (2001). Projection of Diabetes Burden Through 2050. *Diabetes Care*, 24(11), 1936-1940.
- Chisholm, F. (2015, 07 31). *Type 2 Diabetes Mellitus Treatment Market Value Will Reach \$39B by 2021*. Retrieved 06 21, 2016, from Drug Discovery & Development: <http://www.dddmag.com/article/2015/07/type-2-diabetes-mellitus-treatment-market-value-will-reach-39b-2021>
- Fonseca, V. A. (2009). Defining and characterizing the progression of type 2 diabetes. *Diabetes Care*, 32(2), 151-156.
- Fowler, M. J. (2008). Microvascular and Macrovascular Complications of Diabetes. *Clinical Diabetes*, 26(2), 77-82.
- Fresh Holistics. (2014, 09 04). *Blood sugar basics*. Retrieved 06 13, 2016, from freshholistics.com: <http://freshholistics.com/articles/2014/8/27/blood-sugar-basics>
- Healncure.com. (n.d.). *USPSTF research and findings for screening and managing Diabetes in adults*. Retrieved 06 15, 2016, from Healncure.com: <https://www.healncure.com/new-patients/resources/uspstf/uspstf-research/>
- International Diabetes Federation (IDF). (n.d.). *France*. Retrieved 06 13, 2016, from idf.org: <http://www.idf.org/membership/eur/france>
- Leto, & Saltiel. (2012). Regulation of glucose transport by insulin: traffic control of GLUT4. *Nature Reviews Molecular Cell Biology*, 13, 383-396.
- Market Realist. (n.d.). *What to Expect from Novo Nordisk's 4Q15 Earnings*. Retrieved 06 21, 2016, from Market Realist: <http://marketrealist.com/2016/01/expect-novo-nordisks-4q15-earnings/>
- McGraw Lab. (n.d.). *Insulin-regulated movement of GLUT4*. Retrieved 06 21, 2016, from Weill Cornell University: <http://weill.cornell.edu/biochem/mcgraw/insulin-regulated>

- MedGadget. (2016, 04 01). *Global Type 2 Diabetes Market Reviews To Grow At CAGR of 7.28% Between 2016-2020: MarketResearchReports*. Retrieved 06 21, 2016, from MedGadget: <http://www.medgadget.com/2016/04/global-type-2-diabetes-market-reviews-to-grow-at-cagr-of-7-28-between-2016-2020-marketresearchreports-biz.html>
- Nauck, M. A. (2014). Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. *Drug design, development and Therapy*, 1335-1357.
- Olokoba, & Obateru. (2012). Type 2 Diabetes Mellitus: A review of current trends. *Oman Medical Journal*, 27(4), 269-273.
- Pillay, & Govender. (2013). Amylin Uncovered: A Review on the Polypeptide Responsible for Type II Diabetes. *BioMed Research International*, 2013, 1-17.
- R.Owens, D. (2002). New horizons-Alternative routes for insulin therapy. *Nature Reviews-Drug discovery*, 1, 529-540.
- Schmitz, Brock, & Rungby. (2004). Amylin Agonists: a novel approach in the treatment of diabetes. *Diabetes*, 53, 233-238.
- Song, Onishi, Koepsell, & Vallon. (2016). Sodium glucose cotransporter SGLT1 as a therapeutic target in diabetes mellitus. *Expert opinion on therapeutic targets*, 1-17.
- Sprague, & Arbeláez. (2011). Glucose Counterregulatory Responses to Hypoglycemia. *Pediatr Endocrinol Rev*, 9(1), 463-475.
- Tran, Zielinski, & Roach. (2015). Pharmacologic treatment of type 2 diabetes: oral medications. *Annual of pharmacotherapy*, 49(5), 540-556.
- University of California (UCSF). (n.d.). *Treatment Goals*. Retrieved 06 16, 2016, from USCF.edu: <http://dtc.ucsf.edu/types-of-diabetes/type1/understanding-type-1-diabetes/basic-facts/treatment-goals/>
- World Health Organization (WHO). (n.d.). *Diabetes*. Retrieved 06 13, 2016, from who.int: <http://www.who.int/mediacentre/factsheets/fs312/en/>
- Yabe, & Seino. (2011). Two incretin hormones GLP-1 and GIP: Comparison of their actions in insulin secretion and β cell preservation. *Progress in Biophysics and Molecular Biology*, 107(2), 248-256.

Bryan Garnier stock rating system

For the purposes of this Report, the Bryan Garnier stock rating system is defined as follows:

Stock rating

BUY	Positive opinion for a stock where we expect a favourable performance in absolute terms over a period of 6 months from the publication of a recommendation. This opinion is based not only on the FV (the potential upside based on valuation), but also takes into account a number of elements that could include a SWOT analysis, momentum, technical aspects or the sector backdrop. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.
NEUTRAL	Opinion recommending not to trade in a stock short-term, neither as a BUYER or a SELLER, due to a specific set of factors. This view is intended to be temporary. It may reflect different situations, but in particular those where a fair value shows no significant potential or where an upcoming binary event constitutes a high-risk that is difficult to quantify. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.
SELL	Negative opinion for a stock where we expect an unfavourable performance in absolute terms over a period of 6 months from the publication of a recommendation. This opinion is based not only on the FV (the potential downside based on valuation), but also takes into account a number of elements that could include a SWOT analysis, momentum, technical aspects or the sector backdrop. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.

Distribution of stock ratings

BUY ratings 56.5%

NEUTRAL ratings 34%

SELL ratings 9.5%

Research Disclosure Legend

1	Bryan Garnier shareholding in Issuer	Bryan Garnier & Co Limited or another company in its group (together, the "Bryan Garnier Group") has a shareholding that, individually or combined, exceeds 5% of the paid up and issued share capital of a company that is the subject of this Report (the "Issuer").	No
2	Issuer shareholding in Bryan Garnier	The Issuer has a shareholding that exceeds 5% of the paid up and issued share capital of one or more members of the Bryan Garnier Group.	No
3	Financial interest	A member of the Bryan Garnier Group holds one or more financial interests in relation to the Issuer which are significant in relation to this report	No
4	Market maker or liquidity provider	A member of the Bryan Garnier Group is a market maker or liquidity provider in the securities of the Issuer or in any related derivatives.	No
5	Lead/co-lead manager	In the past twelve months, a member of the Bryan Garnier Group has been lead manager or co-lead manager of one or more publicly disclosed offers of securities of the Issuer or in any related derivatives.	No
6	Investment banking agreement	A member of the Bryan Garnier Group is or has in the past twelve months been party to an agreement with the Issuer relating to the provision of investment banking services, or has in that period received payment or been promised payment in respect of such services.	No
7	Research agreement	A member of the Bryan Garnier Group is party to an agreement with the Issuer relating to the production of this Report.	No
8	Analyst receipt or purchase of shares in Issuer	The investment analyst or another person involved in the preparation of this Report has received or purchased shares of the Issuer prior to a public offering of those shares.	No
9	Remuneration of analyst	The remuneration of the investment analyst or other persons involved in the preparation of this Report is tied to investment banking transactions performed by the Bryan Garnier Group.	No
10	Corporate finance client	In the past twelve months a member of the Bryan Garnier Group has been remunerated for providing corporate finance services to the issuer or may expect to receive or intend to seek remuneration for corporate finance services from the Issuer in the next six months.	No
11	Analyst has short position	The investment analyst or another person involved in the preparation of this Report has a short position in the securities or derivatives of the Issuer.	No
12	Analyst has long position	The investment analyst or another person involved in the preparation of this Report has a long position in the securities or derivatives of the Issuer.	No
13	Bryan Garnier executive is an officer	A partner, director, officer, employee or agent of the Bryan Garnier Group, or a member of such person's household, is a partner, director, officer or an employee of, or adviser to, the Issuer or one of its parents or subsidiaries. The name of such person or persons is disclosed above.	No
14	Analyst disclosure	The analyst hereby certifies that neither the views expressed in the research, nor the timing of the publication of the research has been influenced by any knowledge of clients positions and that the views expressed in the report accurately reflect his/her personal views about the investment and issuer to which the report relates and that no part of his/her remuneration was, is or will be, directly or indirectly, related to the specific recommendations or views expressed in the report.	Yes
15	Other disclosures	Other specific disclosures: Report sent to Issuer to verify factual accuracy (with the recommendation/rating, price target/spread and summary of conclusions removed).	No

A copy of the Bryan Garnier & Co Limited conflicts policy in relation to the production of research is available at www.bryangarnier.com



BRYAN, GARNIER & CO

London	Paris	New York	Munich	New Delhi
Beaufort House 15 St. Botolph Street London EC3A 7BB Tel: +44 (0) 207 332 2500 Fax: +44 (0) 207 332 2559 Authorised and regulated by the Financial Conduct Authority (FCA) and the Financial Conduct Authority (FCA) Autorité de Contrôle prudentiel et de resolution (ACPR)	26 Avenue des Champs Elysées 75008 Paris Tel: +33 (0) 1 56 68 75 00 Fax: +33 (0) 1 56 68 75 01 Regulated by the Financial Conduct Authority (FCA) and the Autorité de Contrôle prudentiel et de resolution (ACPR)	750 Lexington Avenue New York, NY 10022 Tel: +1 (0) 212 337 7000 Fax: +1 (0) 212 337 7002 FINRA and SIPC member	Widenmayerstrasse 29 80538 Munich Germany +49 89 2422 62 11	The Imperial Hotel Janpath New Delhi 110 001 Tel +91 11 4132 6062 +91 98 1111 5119 Fax +91 11 2621 9062 Geneva rue de Grenus 7 CP 2113 Genève 1, CH 1211 Tel +4122 731 3263 Fax +4122731 3243 Regulated by the FINMA

Important information

This document is classified under the FCA Handbook as being investment research (independent research). Bryan Garnier & Co Limited has in place the measures and arrangements required for investment research as set out in the FCA's Conduct of Business Sourcebook.

This report is prepared by Bryan Garnier & Co Limited, registered in England Number 03034095 and its MIFID branch registered in France Number 452 605 512. Bryan Garnier & Co Limited is authorised and regulated by the Financial Conduct Authority (Firm Reference Number 178733) and is a member of the London Stock Exchange. Registered address: Beaufort House 15 St. Botolph Street, London EC3A 7BB, United Kingdom

This Report is provided for information purposes only and does not constitute an offer, or a solicitation of an offer, to buy or sell relevant securities, including securities mentioned in this Report and options, warrants or rights to or interests in any such securities. This Report is for general circulation to clients of the Firm and as such is not, and should not be construed as, investment advice or a personal recommendation. No account is taken of the investment objectives, financial situation or particular needs of any person.

The information and opinions contained in this Report have been compiled from and are based upon generally available information which the Firm believes to be reliable but the accuracy of which cannot be guaranteed. All components and estimates given are statements of the Firm, or an associated company's, opinion only and no express representation or warranty is given or should be implied from such statements. All opinions expressed in this Report are subject to change without notice. To the fullest extent permitted by law neither the Firm nor any associated company accept any liability whatsoever for any direct or consequential loss arising from the use of this Report. Information may be available to the Firm and/or associated companies which are not reflected in this Report. The Firm or an associated company may have a consulting relationship with a company which is the subject of this Report.

This Report may not be reproduced, distributed or published by you for any purpose except with the Firm's prior written permission. The Firm reserves all rights in relation to this Report.

Past performance information contained in this Report is not an indication of future performance. The information in this report has not been audited or verified by an independent party and should not be seen as an indication of returns which might be received by investors. Similarly, where projections, forecasts, targeted or illustrative returns or related statements or expressions of opinion are given ("Forward Looking Information") they should not be regarded as a guarantee, prediction or definitive statement of fact or probability. Actual events and circumstances are difficult or impossible to predict and will differ from assumptions. A number of factors, in addition to the risk factors stated in this Report, could cause actual results to differ materially from those in any Forward Looking Information.

Disclosures specific to clients in the United Kingdom

This Report has not been approved by Bryan Garnier & Co Limited for the purposes of section 21 of the Financial Services and Markets Act 2000 because it is being distributed in the United Kingdom only to persons who have been classified by Bryan Garnier & Co Limited as professional clients or eligible counterparties. Any recipient who is not such a person should return the Report to Bryan Garnier & Co Limited immediately and should not rely on it for any purposes whatsoever.

Notice to US investors

This research report (the "Report") was prepared by Bryan Garnier & Co Limited for information purposes only. The Report is intended for distribution in the United States to "Major US Institutional Investors" as defined in SEC Rule 15a-6 and may not be furnished to any other person in the United States. Each Major US Institutional Investor which receives a copy of this Report by its acceptance hereof represents and agrees that it shall not distribute or provide this Report to any other person. Any US person that desires to effect transactions in any security discussed in this Report should call or write to our US affiliated broker, Bryan Garnier Securities, LLC, 750 Lexington Avenue, New York NY 10022. Telephone: 1-212-337-7000.

This Report is based on information obtained from sources that Bryan Garnier & Co Limited believes to be reliable and, to the best of its knowledge, contains no misleading, untrue or false statements but which it has not independently verified. Neither Bryan Garnier & Co Limited and/or Bryan Garnier Securities LLC make no guarantee, representation or warranty as to its accuracy or completeness. Expressions of opinion herein are subject to change without notice. This Report is not an offer to buy or sell any security.

Bryan Garnier Securities, LLC and/or its affiliate, Bryan Garnier & Co Limited may own more than 1% of the securities of the company(ies) which is (are) the subject matter of this Report, may act as a market maker in the securities of the company(ies) discussed herein, may manage or co-manage a public offering of securities for the subject company(ies), may sell such securities to or buy them from customers on a principal basis and may also perform or seek to perform investment banking services for the company(ies).

Bryan Garnier Securities, LLC and/or Bryan Garnier & Co Limited are unaware of any actual, material conflict of interest of the research analyst who prepared this Report and are also not aware that the research analyst knew or had reason to know of any actual, material conflict of interest at the time this Report is distributed or made available..