

Pharmaceuticals Sector  
Core activities: Drug development  
Core area of activity: Obesity and diabetes  
Listing: Unlisted

## **Bridge BioResearch plc**



*Bridge BioResearch's two lead candidates are innovative drug concepts in the related fields of diabetes and obesity. With some glimmer of efficacy, and safety already in evidence, clinical validation could yield substantial rewards.*

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I certify that this report represents my own opinions.

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## Key Points

24 November 2008

Price: 80p

*Bridge BioResearch plc is focused on innovative emerging drugs for the treatment of metabolic/lifestyle diseases. Its two lead candidates, currently advancing into clinical trials, are innovative drug concepts in the related fields of diabetes and obesity. With some glimmer of efficacy, and safety already in evidence, upcoming clinical validation could put the company on the road to lucrative upfront, milestone and royalty payments.*

- **The focus on metabolic/lifestyle diseases is potentially a lucrative one** – Get the safety/efficacy profile and the cost/benefit ratio of a drug right in this field and the rewards can be substantial.
- **Lifestyle diseases are both a serious public health threat and an economic calamity** – The threat obesity poses to modern society is well known but the same can also be said for diabetes. While adequate treatment is available for the latter, much remains to be achieved. In obesity, there is still all to play for.
- **The lifestyle drug market is very large and potentially explosive for good drugs** – We have estimated market sizes of around US\$100 billion for obesity and US\$27 billion for Type 2 Diabetes in the key markets. The dynamics in these markets are such that a drug with an incremental benefit and reasonable cost/benefit ratio can achieve deep market penetration rapidly and benefit from the buoyant longer term growth prospects of these markets.
- **Bridge's lead candidates have the 'right stuff' to make significant inroads here** – Both 2-OHOA and isosteviol/STX03 are unusual in that their putative mechanism of action affects multiple targets which seem to translate into multiple benefits. The ability to link obesity and diabetes with hypertension, in both cases, offers the potential, if human clinical validation holds up, of a very disruptive market entrant.
- **Over the next 12 months, the focus is on human clinical validation** – As ever, Proof of Concept clinical trials (Phase I for 2-OHOA and Phase II for STX03) will be the clinchers. The translation of currently available data to full human safety and efficacy data seem circumstantially obvious in this case but, in the end, the trial results will always be the clincher.
- **Bridge's simple, low cost business model lowers investor risk and improves survivability** – In tough times, the ability to survive is a quintessential ingredient for an emerging pharma company. Assuming the success of the current round of financing, the company should be able to deliver the PoC data required to achieve early partnerships with big pharma triggering significant upfronts and later milestones and royalties.
- **Bridge's management have been engaged in some astute dealmaking!** – The IP collected from Spain and Denmark stacks up scientifically, offers good market protection with a confirmed freedom to operate and at a very reasonable cost. The vendors have retained upside linked to success and Bridge are the designated execution team to make market success a reality.
- **Our valuation analysis indicates that the current offering price level is conservative and fair** – In a market where public prices have plummeted, it may seem a tall order to look for a pre money valuation of around £35 million. Our valuation analysis indicates a fair value in the £1.02 to £1.51 range which, when matched to a price of 80p in the last round, seems like a reasonable level to go for with significant upside left on the table for investors.
- **Diamond in the rough?** – Bridge is an unconventional company from an unconventional source financed in an unconventional way. However, the experienced management team, supported by a highly qualified group of scientific/clinical advisors, seems to be on track for what could be a very lucrative participation in what we view as an explosively dynamic segment of the market.

### Current fair value of equity

Expected value	£44.5m
<b>Value per share</b>	<b>£1.02</b>
Optimistic scenario	£65.9m
<b>Value per share</b>	<b>£1.51</b>

### Company details

Shares issued (m)	43.8
Fully diluted (m)	44.8
Market Cap'n (£m)	35
Website:	<a href="http://www.bridgebiosearch.com">www.bridgebiosearch.com</a>

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## Overview

Bridge BioResearch was set up with the aim of building an international drug discovery and development company by providing the development 'bridge' between the richness of academic research and large pharma. In its short life, the company has made a series of acquisitions and product licensing deals. These have focused on drugs aimed at providing novel, more effective therapeutic modalities, to lifestyle-driven metabolic diseases.

### **From a standing start in late 2004, Bridge has built a very promising metabolic disease pipeline**

With a small amount of funds, a 'virtual' operation with low overheads and an experienced team to source and evaluate projects, Bridge has built a pipeline of drugs focused on obesity, Type 2 diabetes (T2D) and hypertension. If the putative profile of these drugs is confirmed in development, the potential for market penetration is significant. As these diseases appear to be either causalities of each other (obesity leads to T2D and hypertension...etc) or co-morbidities, the ability to affect them simultaneously with one drug would represent a significant therapeutic breakthrough.

### **Olive oil derivative might just be what the doctor called for after all**

We have all been told repeatedly how the Mediterranean diet (which is high in olive oil) provides cardiovascular benefits. 2-hydroxyoleic acid (2-OHOA), a derivative of olive oil, a fully patented compound with weight reducing and anti-hypertensive (lowering of blood pressure) activity in animals could have an ideal profile for treating people with metabolic complications such as obesity, diabetes and dyslipidaemia<sup>1</sup>.

### **Medicinal plant extract could prove to be a boon for late onset Type 2 diabetes**

South American native Indian populations have known for ages the metabolic benefits of ingesting (usually as a tea) preparations of the plant *Stevia Rebaudiana Bertoni*. This plant has also provided a source of commercial sweetener for the food industry for decades making it, and its components, an extensively safety tested mixture. The extraction of the components stevioside and isosteviol (STX03) from this plant has led to the discovery of significant anti-diabetic properties which, given the voluminous safety data, could lead to a new class of OAD's<sup>2</sup>.

### **Inflammatory pathways have been implicated in T2D of late and CD14 is a central character in that story**

Bridge has three targets that act at a key trigger point to the inflammatory pathway that is thought to be a key underlying molecular mechanism in the persistent degradation of pancreatic function that drives the pathological development

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<sup>1</sup> dyslipidemia is a disease characterised by high levels of serum cholesterol

<sup>2</sup> OAD's are oral anti-diabetic drugs

of T2D. CD14 is considered to be the lead candidate here which, whether in recombinant form or as a small molecular mimic, could be a significant player in this segment of the diabetes market.

**Given the projected capital needs to push the current pipeline forward, Bridge has a full plate**

We are projecting capital needs in the £5 million range through to 2010 but the timing of one or the other upfront payment from a partnership could come earlier than expected. Should this happen our projected cashflow needs would drop to the £2.5 million range. We believe that Bridge will remain constrained on how many additional pipeline candidates that it can take on. The current pipeline looks to us to have some very promising candidates. Failure rates in this type of endeavour are quite high but both STX03 and 2-OHOA seem to us to be significantly de-risked from a safety standpoint although more data will be required to confirm this. The animal models used to test the efficacy of these drugs are well-established and have translated well into human clinical trials. Steviol, the cousin of isosteviol/STX03 has been subjected to human clinical trials where both safety and efficacy were displayed. However, because this compound is transformed in the gut into STX03 (which displays higher absorption rates in the blood), the latter became the preferred lead for development. All in all, we are reasonably confident that success is a strong possibility here which could lead to upfront payments as early as 2009 but more likely by 2010 and milestones and royalties beyond.

**With a shareholder base of over 650 investors and an unusual brand of capital-raising, Bridge may be able to get the needed capital to make this happen**

With the capital markets in turmoil and institutional investor risk appetite at a very low level, conventional wisdom would lead one to believe that raising capital for such a venture might be somewhat of a tall order. Bridge's brand of capital-raising from mostly high net worth individuals might enable them to squeak through despite this turbulent environment. Until this is done though, this will remain one of the weak spots of the story. Certainly, the company had been able, to date, to raise sufficient capital to meet its needs and we can only consider it likely that this will continue.

**Assuming adequate capital, the opportunity is substantial and potentially highly lucrative**

We are estimating that at this early stage of development, the company is worth somewhere in the £1.02 - £1.51 range under both the core and more aggressive scenarios that we have laid out. As always, our valuation at this stage of development is indicative of value rather than absolute. Should the promising profiles of these drugs translate into clinical safety and efficacy in humans, the value of the company would be significantly higher. On balance, subject to financing, this company seems to be a good value opportunity for investors to participate in potential drugs that target the few remaining blockbuster areas which are either poorly met (as in Type 2 diabetes) or unmet (as in obesity).

## Valuation

As with most earlier stage pharma development companies, the ability to construct a realistic, valuation model must necessarily involve the elaboration of a set of assumptions as to future developments and as to the ability of each component of the company's pipeline to achieve its target therapeutic profile.

In Bridge's case, two out of the three lead drugs in its pipeline appear to have been de-risked to some degree. 2-OHOA, as a hydroxylated derivative of the naturally occurring oleic acid (essentially olive oil) has, by its very nature, a likely clean profile. Isosteviol, as a naturally occurring component of a plant, whose extract has been abundantly tested and used as a food additive has, at the very least, an aura of safety which will need to be further tested at therapeutically-relevant doses. These lead compounds probably have probabilities of success (PoS) that are higher than their stage of development would let on in terms of safety. However, from an efficacy standpoint, these drugs are roughly at their stage of development but as these are essentially natural compounds whose metabolism is well established there are few toxicity/tolerance surprises to be expected. Furthermore, the animal disease models used have historically translated well into humans and isosteviol's cousin and parent (stevioside and steviol) from which it is derived, have both been tested in humans and display no significant toxicity and some of the desired efficacy that is targeted for this compound. Hence, we have assigned a slight premium on the PoS for both of these compounds and have given a low PoS to CD14.

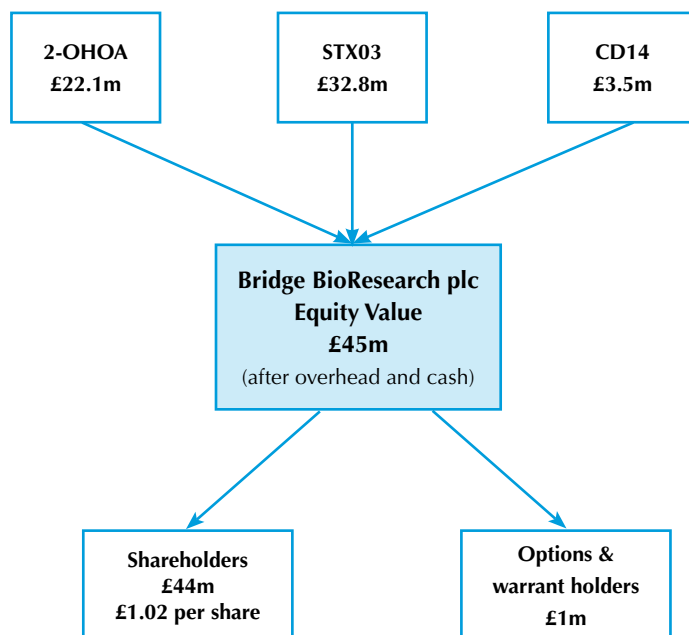
We have assumed that both 2-OHOA and isosteviol (STX03) will be tested through their Proof of Concept stage (PoC) which can be either at Phase I such as in the case of 2-OHOA, or a Phase II trial as in the case of isosteviol. CD14 is likely to be licensed out early although efforts may be expended to find a small molecule mimic preferably in a 'repositioned' format.

We are making the assumption that these proprietary compounds, should they demonstrate the desired safety and efficacy profile, can find a significant place in their respective marketplaces. The obesity market is screaming out for a more effective and relatively side-effect free drug to enable significant weight loss. The additional blood pressure lowering properties of 2-OHOA are an extraordinary bonus as obesity is often co-morbid with hypertension. The hypotensive properties of stevioside and stevia in animals and humans should translate into humans as stevia is transformed into isosteviol by gut bacteria; giving the latter directly resolves problems of variable absorption and bioavailability as the transformation is acidity dependant. Although the company will not make the anti-hypertensive effect of this drug a primary indication, it could well be a secondary indication at the very best, and at worst, a potent marketing tool. Our projection of a 9-10 percent penetration of this huge market is partly based on the use of this secondary property of the drug.

## Fair value summary (£m)

Scenario	Core	Optimistic
Development drugs		
- 2-OHOA	22.1	29.0
- STX03	32.8	48.6
- CD14	3.5	3.5
Less: overhead	13.5	14.3
<b>Expected value of pipeline</b>	<b>44.9</b>	<b>66.8</b>
Add: other assets	0.0	0.0
Add: starting cash + new funds	0.4	0.4
Total current value for firm	45.3	67.2
Less: Bank & other debt	0.0	0.0
Total value to equity claims	45.3	67.2
Less: warrants & options	0.8	1.3
Ordinary equity holders	44.5	65.9
Value per share (£)	<b>1.02</b>	<b>1.51</b>

## Components of Bridge BioResearch's entity value



## Drug portfolio

### Summary of core valuations for each drug (£m)

Drug	2-OHOA	STX03***	CD14
<i>Royalty revenue*</i>			
<b>EV of royalties</b>	<b>129.9</b>	<b>219.1</b>	<b>96.0</b>
Likelihood of success (PoS)	23%	41%	5%
<b>EMV of royalties</b>	<b>30.4</b>	<b>90.8</b>	<b>4.8</b>
Add: EMV of upfront payments**	0.4	0.7	0.2
Add: EMV of milestone payments	1.9	3.0	0.4
less: EMV of dev costs	1.0	1.1	0.3
<b>EMV</b>	<b>31.6</b>	<b>93.5</b>	<b>5.0</b>
per share (£ ps)	0.72	2.14	0.11
<b>After tax EMV</b>	<b>22.1</b>	<b>65.4</b>	<b>3.5</b>
<i>Detailed valuation on page</i>	31	49	51

### Summary of optimistic valuations for each drug (£m)

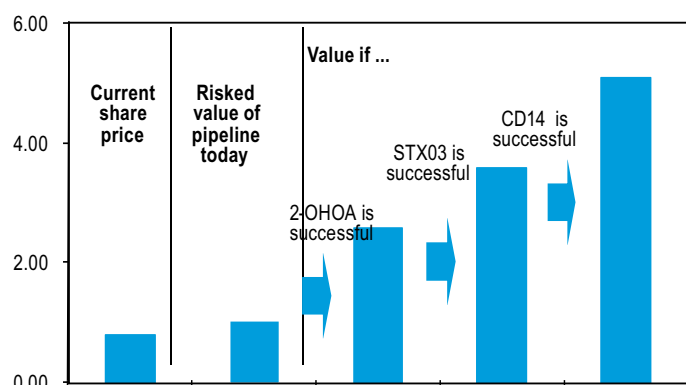
Drug	2-OHOA	STX03***	CD14
<i>Royalty revenue*</i>			
<b>EV of royalties</b>	<b>172.1</b>	<b>328.1</b>	<b>97.1</b>
Likelihood of success (PoS)	23%	41%	5%
<b>EMV of royalties</b>	<b>40.3</b>	<b>135.9</b>	<b>4.9</b>
Add: EMV of upfront payments**	0.4	0.7	0.2
Add: EMV of milestone payments	1.9	3.0	0.4
less: EMV of dev costs	1.0	1.1	0.3
<b>EMV</b>	<b>41.5</b>	<b>138.5</b>	<b>5.1</b>
per share (£ ps)	0.95	3.17	0.12
<b>After tax EMV</b>	<b>29.0</b>	<b>97.0</b>	<b>3.5</b>
<i>Detailed valuation on page</i>	31	49	51

\* EV = expected value; EMV = expected monetary value (i.e., risked expected value)

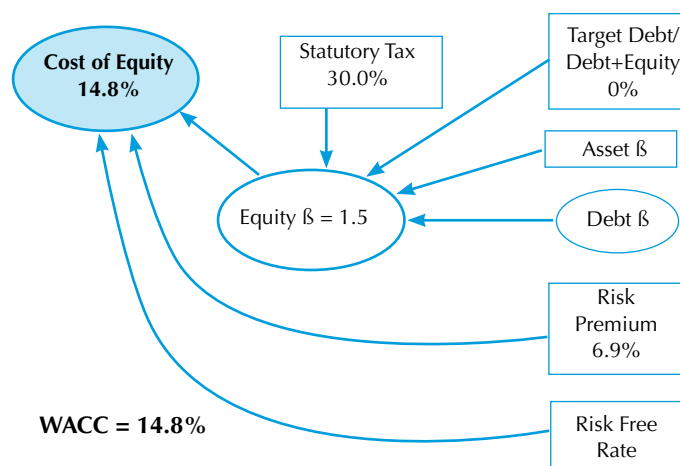
\*\* upfront, milestone and development costs have been risked based on probability of being incurred

\*\*\* valuation shown before Bridge's share

## Current EMV and value if pipeline is successful (£ps)



## Weighted cost of capital



The Type 2 diabetes (or T2D) market has been, and continues to be, a very attractive pharmaceutical market. None of the drugs on the market have attained the sustained therapeutic effect that would be desirable in this disease. STX03 or isosteviol appears to have some rather unique biological characteristics which, if verified in the clinic, would enable it to carve out a significant chunk of that market. Despite this, we have assigned a percent penetration of this highly competitive market that is only at a slight premium to the sort of 5-ish percent such drugs might normally garner. Our projection of a 5.6-7% penetration translates, nevertheless into a very large number.

Of course, we are also assuming that the company will be able to raise the finances to support the clinical development programmes already in hand. In the current environment this is not an easy task to accomplish but the company's track record at raising money seems to indicate that it might be able to do so even in these tough times.

As per usual, we have applied modified industry standard (diMasi in this case) PoS levels as well as relatively standard financial parameters that are listed in the accompanying table. The PoS's for these drugs are, necessarily, on the low side consistent with their relatively early stage of development. The result is that our core valuation comes in at around £1.02 and our more optimistic model at just over £1.51. It is easy to imagine scenarios where these may prove to be conservative. The company's stated price objective for its upcoming private placement of stock is in the 80p range which according to this analysis provides investors with built-in upside.

### **While the R has been taken out of this, the D remains very much a risk**

The stated strategy of Bridge is to license in compounds that are significantly de-risked by research and early development and then to develop them through PoC. The pipeline as it stands has some very interesting drugs with preclinical data that is highly indicative of safety and efficacy. The models used for both diabetes and obesity are very well characterised and do translate well into humans; ergo the perceived de-risking. Nevertheless, the risk that these fail to produce significant effects in the clinic remains and investors must be cogniscent of the fact that failure remains an option despite the de-risked profile of these candidates.

### **The pipeline remains rather narrow**

While the process of de-risking that the company uses as a filter for choosing its licensing candidates increases the chances of successful development, the pipeline displayed at this time remains narrow. Drug development is a risky business and while Bridge is not taking the later stage pivotal trial risk of its pipeline, failure rates even at this stage remain high. With such a narrow pipeline, investors are assuming a degree of 'concentration' risk that is beyond that of a company with a broader pipeline of products.

### **Clinical data remains sparse and somewhat circumstantial**

Absent clinical data on 2-OHOA it is difficult to say what will happen. However, as a simple oleic acid derivative, the emergence of significant toxicity would be very surprising indeed. Nevertheless, until 2-OHOA is tested in humans, any views on efficacy remain in the realm of conjecture. Similarly with STX03, the evidence that it might be safe and effective is derived from preclinical work in animals and data from steviol (STX02) human clinical trials. While there is good evidence that steviol is converted to isosteviol in vitro (and ostensibly in vivo) and that giving isosteviol directly circumvents variable absorption/bioavailability, the translation of any human data based on the use of stevia (STX02) is not a given and requires formal clinical testing. While the data points in the right direction but only clinical validation will clinch our optimal enthusiasm for the product.

### **Management is untested in this venture setting**

The management team has significant experience in the execution of pharmaceutical transactions, product development and the analysis of market opportunities. The strategy of the company stems from this experience and is supported by what appears to be an expert advisory board comprised of well-known individuals in the field of metabolic diseases. Despite this, none of the management team has a track record in bringing such a venture to fruition which does pose an additional risk.

### **The competition is fierce in these markets**

With potential market sizes in the multiple billion dollars, the competition to generate drugs in the metabolic disease/lifestyle space is brutal. Both small and large companies are very busy trying to develop drugs that have an optimal safety/efficacy profile and can provide a sustainable solution to these diseases. It is difficult for investors (expert or not) to uncover which approach is going to be successful in the final analysis and therefore equally difficult to know what Bridge's drugs, if successfully developed, will be up against. This translates into uncertainty as to how attractive any resulting drugs might be to potential development partners and hence the potential for upfront payments and milestones they would be prepared to assign.

### **Limited resources at hand**

Bridge has constructed a business model that is very fleet-footed, flexible and low-cost. By farming out most development work to CRO's (clinical research organisations), it can maintain a low fixed cost base. This 'virtual' model is being employed by many companies and is a very legitimate path forward. Nevertheless, even PoC trials and any preclinical work triggers significant costs and the company will need to raise sufficient cash to finance the programmes already in its pipeline. There can be no assurances that it will be able to do so in what is currently a very tough environment.

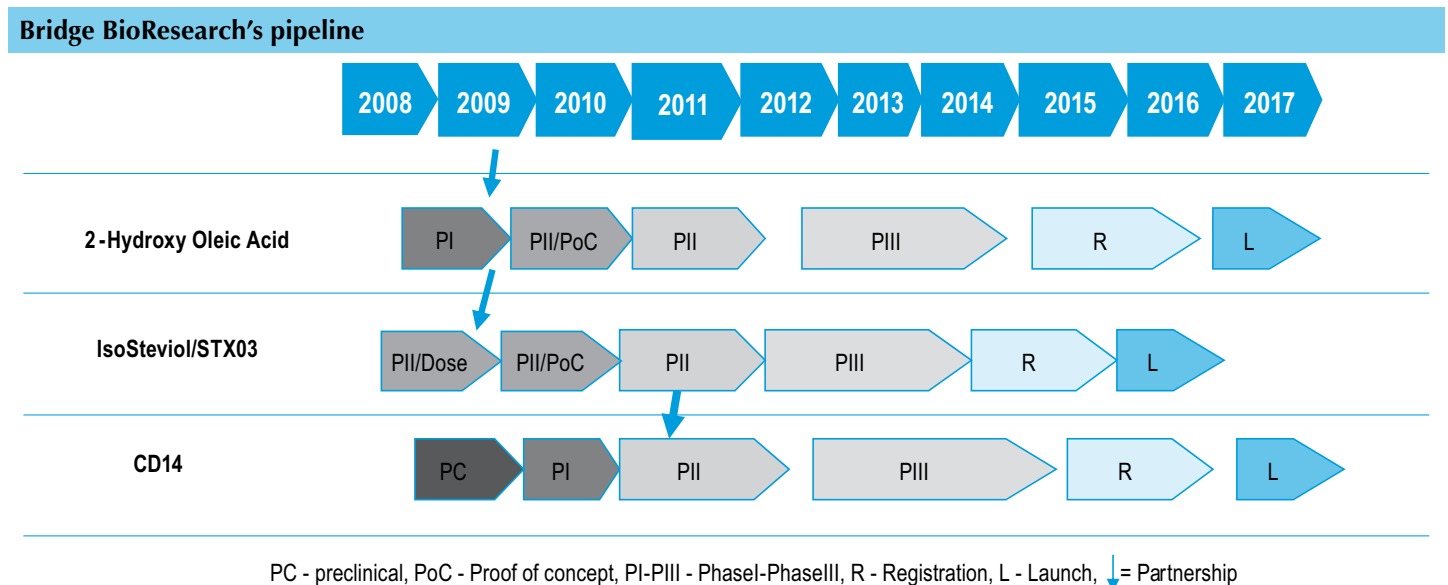
Bridge BioResearch is a drug development company aiming to act as a bridge between academic/early preclinical work and the Proof of Concept (PoC) clinical trials required for licensing to large pharmaceutical companies. In its short life, the company has made a series of product licensing deals and acquisitions, focused on drugs aimed at providing novel, more effective therapeutic modalities in the lifestyle-driven metabolic disease arena.

## A successful pipeline building exercise has been executed with very little capital

In four separate transactions, Bridge has built a pipeline of drug candidates in this field focused primarily on Type 2 diabetes (T2D) and obesity, with spin-off applications in hypertension. These transactions included:

- three early stage patents acquired in 2005;
- a patent license agreement in January 2006 with the 'Universitat de les Illes Balears' in Palma de Mallorca in Spain for 2-hydroxyoleic acid for the treatment of obesity, hypertension and other metabolic disorders;
- the acquisition of 50.6 percent of Mellitus, a Barcelona-based drug discovery spinoff from the University of Girona focused on 3 drug targets in the area of T2D (CD14, MBL and BPI<sup>3</sup>) in July of 2006. Subsequently, 100 percent of these patents was acquired through the issue of 170k shares;
- the acquisition of 50.066 percent of Stevia Aps from Gentofte in Denmark, the developer of a novel plant-derived compound called isosteviol (STX03) for the treatment of T2D with an option to acquire a further 10 percent of the company under pre-defined conditions.

The resulting pipeline is depicted in the accompanying figure and shows a series of candidates with approvals slated for the 2015-2017 period with partnerships targeted for the 2009-2011 window.



NOTE: 2-hydroxy Phase 1 will be in healthy obese – thus secondary endpoint will be weight loss = PoC

Source: Bridge BioResearch

<sup>3</sup> MBL and BPI were superseded by STX03 which offers a more rapid and less costly route to the same market

To execute these transactions, Bridge has raised a total of £2.1 million in cash (at prices ranging from 30p to 80p) from a series of private placements, mainly to private individuals and issued 470k shares to the principals and companies involved in these various project.

### **A business strategy well adapted to the times that we live in**

Bridge's primary business strategy is to seek promising drug candidate concepts that are emanating from academic laboratories or their commercial spinoffs at a relatively early stage of their development. It then aims to 'bridge the gap' between the benchtop and the early preclinical, or even clinical work towards full-blown preclinical and clinical studies, required to establish the proof of each concept for full licensing to large pharma. This strategy enables a 'virtual-like' structure with relatively low capital needs, where the bulk of development activities can be 'farmed-out' to independent companies specialised in contractual R&D activities. Hence, the ability to run a lean organisation with little in the way of overhead is its principal advantage.

### **Opportunistic, well thought through and commercially driven project analysis process**

Our analysis of the company indicates that the basis for choosing the projects that now make up its pipeline, while opportunistic, is based on what appears to be solid scientific grounds. Assisted by what appears to be very skilled Board of scientific advisors, Bridge has been able to identify a series of drug candidates that withstood our scrutiny.

### **Lifestyle-driven metabolic diseases are a problem of epidemic magnitude requiring better solutions**

Metabolic diseases that are driven by lifestyle choices (albeit with some genetic components involved as well) have taken on epidemic proportions, underlie diseases with substantial morbidity and mortality and are responsible for a very significant share of healthcare costs and loss of economic productivity on a global basis.

### **The staggering market potential for obesity drugs remains largely untapped**

The potential markets for drugs in these areas are of gargantuan proportions. We estimate, on the basis of current drug pricing, that the total overweight/obesity market worldwide is of the order of US\$780 billion in 2008 based on publicly available estimated prevalence data. Of this, key markets (US, EU, and Japan) represent a current value of around US\$140 billion. If limited to obesity alone, these markets are estimated to represent a current value of US\$235 billion and US\$96 billion respectively. We are estimating that these markets will

experience substantial growth as increasingly efficacious and safer products come to market. However, despite the staggering potential size of these markets, the current market for drugs is very low with current products totaling sales of around US\$0.5-1 billion. Lack of significant efficacy and medical rationale, along with unacceptable side-effects, have hampered the ability to trigger reimbursement for these drugs and therefore limited their market development.

**In Type 2 diabetes (T2D), the current crop of drugs do a job but it is not enough**

The advent of oral anti-diabetics (OAD) over the past thirty years has blossomed into a US\$10+ billion market in the key markets<sup>4</sup> worldwide. However, here too, despite a high penetration into patient populations (estimated at around 70 percent), the efficacy of the drugs currently on the market does not fundamentally alter the course of the disease; it merely delays it – albeit significantly. Coming up with a disease-altering OAD is considered to be a blockbuster area for development. T2D market growth rates are significantly above average and hence continue to represent a major pharma market opportunity.

Hence, in both cases (T2D and obesity) the need for a safer and more effective drug continues to offer significant blockbuster potential and the candidates and concepts that comprise Bridge’s pipeline look quite promising in this regards.

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<sup>4</sup> Key markets include US, Western Europe, Japan and 10% of the Rest of World (ROW)

## Pipeline Overview

### **Background: the emergence of lifestyle diseases as major killers**

In the early 20th century, the vast majority of deaths were linked to communicable diseases. In 1900, the three main causes of disease were Tuberculosis, Enteritis/Diarrhea and Pneumonia/Influenza. With the discovery of Penicillin by Alexander Fleming in 1928, treatment of these diseases became possible and the lifespan of individuals lengthened considerably. Concomitantly, the end of the Second World War heralded a period of significant economic growth linked to a substantial rise in disposable income and a dramatic alteration in diet, particularly in developed countries. To underline the multifactorial nature of this disease, amongst the highest prevalence rates you will find Spain and Greece, who despite diets rich in olive oil, are plagued with obesity mostly due to an increasingly sedentary lifestyle.

The shift in post WWII diets and increasingly sedentary lifestyle has in turn increased the prevalence of what is called 'lifestyle-driven metabolic diseases'. Today these are a major source of both morbidity and mortality. Diet, alcohol and smoking along with this lifestyle have conspired to trigger a substantial increase in the incidence of a wide variety of metabolic disorders including vascular, hepatic, respiratory, dermatological, nephritic, behavioural, bone and CNS related diseases. While genetic predisposition certainly plays a role in the genesis of these conditions, lifestyle factors are the primary trigger leading to the conditions that eventually culminate in significant morbidity and mortality in the populations of developed countries and, as incomes rise and lifestyles evolve, increasingly in developing countries as well. In fact, the WHO has recognised many of these diseases as epidemic in and of themselves.

Most diseases of metabolic origin tend to be linked to diet and the progressive degradation of the vascular system through atherosclerosis<sup>5</sup>. In fact the exact aetiology of most of these diseases is only partially known and much remains to be learned. But the accumulation of scientific data driven by the development of biochemistry, immunology, cellular and molecular biology and the drugs that have been derived from this knowledge, has significantly expanded our knowledge of these mechanisms. Together with the development of better animal models, the tools available for further study have enabled significant advances towards therapies aimed at providing more effective resolution of these diseased states.

### **Overview of obesity**

**Obesity** is a fundamental, lifestyle-driven cause of metabolic disorders. An extensive literature have emerged over the past 40 years that demonstrates a definitive, causal link between lifestyle (sedentary versus active), weight (overweight or obese) and diseases such as kidney disease, diabetes, stroke and cardiovascular diseases in general. It has, for the most part, been established that vascular disorders play a significant role in pancreatic, kidney, peripheral artery disease, cerebrovascular and cardiovascular disorders and that this is primarily driven by the evolution of lifestyle choices and diet. Even many cancers appear to have, as part of their overall risk factors, lifestyle and dietary considerations at

<sup>5</sup> Atherosclerosis is characterised by a progressive hardening of the arterial cell wall and the accumulation of arterial wall plaques that result in a narrowing of the arterial passages. This can trigger a variety of diseases including cardiovascular, kidney and the like.

their root. The recent WCRF/AICR report on Food, Nutrition, Physical Activity and the Prevention of Cancer, concluded that excess body fat (through the consumption of too much red meat and other processed foods) is a leading factor in the aetiology of cancer<sup>6</sup>.

The focus of Bridge is to tackle diseases that are central to what is a mortality trend of epidemic proportions. Obesity, or simply being clinically overweight, is central to much of the disease burden of metabolic and other vascular disorders. The approach that the company has taken is related to the well known low incidence of metabolic disorders in Mediterranean regions driven by a diet rich in mono or poly-unsaturated fats and low in saturated fats. Central to this diet is olive oil which is 80 percent composed of a mono unsaturated fat called Oleic Acid.

Also central to the current metabolic disease burden is **diabetes** in general but particularly **Type-2 diabetes** or **Non Insulin Dependent Diabetes Mellitus (NIDDM)**. This is responsible, through its progression, for a significant degree of morbidity which eventually leads to high rates of mortality over time.

### **Weight and obesity: the hub of metabolic/lifestyle diseases**

It is probably safe to say that most metabolic diseases are linked in one way or another to being overweight or obese. While genetic and other factors (such as smoking and alcohol intake) certainly play a role, the combination of excessive dietary intake along with a relatively sedentary life, will inevitably conspire to set in motion, the molecular events that will lead to a plethora of lifestyle/metabolic conditions such as cardiovascular (hypertension, myocardial infarction, peripheral artery disease, etc) and cerebrovascular disease (stroke), diabetes, CKD (chronic kidney disease), liver cirrhosis and the like. Hence the importance of finding a therapeutic modality that can be used as an adjunctive therapy, along with lifestyle adjustments (diet, exercise, etc) to bring an individual's BMI<sup>7</sup> into a normal range. The implications for morbidity and mortality in the general population are so vast as to defy reasonable market and financial analysis.

The disease profile of obesity is very complex indeed. Many mechanisms are thought to be involved and it is not surprising as the list of causalities underlying this condition includes many pathways of metabolism. Most of these mechanisms revolve around sugar and fat metabolism as well as signaling between the brain (centres of appetite, satiety and satiation) and the gut. Clearly the latter are so fundamental to life that they have evolved very complex networks of pathways to function with many redundant systems waiting to be activated when the core system fails. Hence finding a highly effective approach to this is not a simple task. To better understand this question, we will go through a bit of the biology behind this condition, keeping a mindful eye on the objective at hand: highlighting the potential importance of 2-OHOA, Bridge's novel entry into the fray of potential obesity market participants.

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<sup>6</sup> see report on [www.dietandcancer.org](http://www.dietandcancer.org)

<sup>7</sup> BMI or Body Mass Index is a statistical measure of weight versus height that is commonly used as indication of being overweight or obese. It has limitations but is generally a pretty good indicator of the weight profile of a patient.

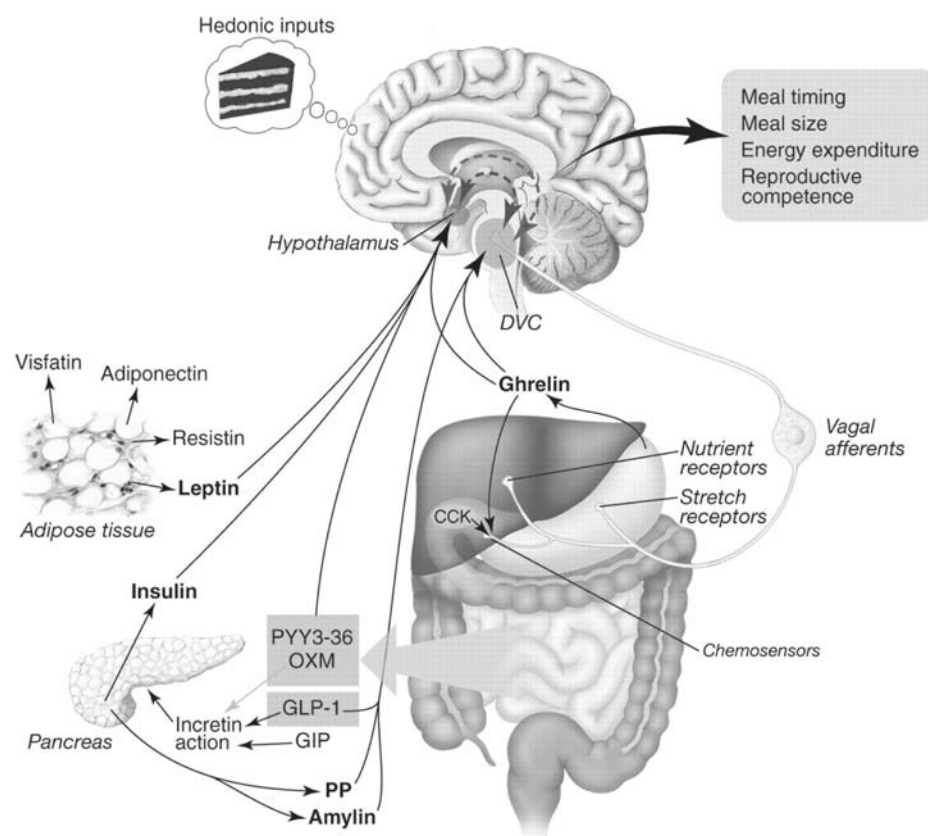
## Weight and obesity: some basic biological principles

To cover this complex subject in a paragraph is a task that even this author will not attempt. A basic summary though might be useful for the reader to understand what is at stake here. Clearly the propensity for an individual to put on excessive weight is related to many factors including genetic predisposition, sugar and animal fat intake, and geographically-related evolutionary adaptation.

The basic mechanism of food intake versus weight are embodied in a signaling relationship between the hypothalamus in the brain, the gut and adipose tissue where our fat is stored which acts to maintain the energy balance that the body needs to function properly. This involves a complex set of sensors and signals that have the ability to modulate the amount of food we take in.

As depicted in the accompanying graphic, the hypothalamic region of the brain is connected via a nerve pathway (the vagal afferents) that acts as a sensor to signal to the brain that something is going on in the peripheral organ (in this case the gastrointestinal tract). So when you eat, your stomach gets distended which signals the brain. Peripheral signals, in the form of signaling hormones such as leptin and adiponectin in adipose tissue and insulin in the pancreas, are used to signal the brain their energy status (surplus or deficit) whereas ghrelin, will signal extreme hunger from the stomach and various gut hormones such as PYY<sub>3-36</sub>, pancreatic polypeptide, amylin and oxyntomodulin will signal a state of satiety<sup>8</sup> to the brain.

### Gut regulatory mechanisms



Source: Badman et al., Science (2005);307:1909 - 1914

<sup>8</sup> Satiety is defined as the point at which the system feels that it has had too much nutrient intake.

This is only part of the story but our purpose is served by pointing out that this complex system (and more) is clearly open to malfunction, overstimulation, decrease in sensitivity and the like; in other words, ripe for dysfunction leading to an overweight condition which can lead to clinical obesity.

Underlying all of this are additional mechanisms involved in how the body metabolises nutrients such as proteins, fats and sugars. In normal metabolism, energy inputs are required and nutrition provides the feedstock for these inputs. However, the body has the ability to determine how much of the nutrients ingested it needs through the complex system just described. What does it do with the excess? It will digest some of the remainder and process it for disposal through excretion but the rest (sugars or fat) might be either deposited or transformed to be deposited in the form of fat in what is called adipose tissue. The principles behind the function of adipose tissue are not only to store energy for future use but also to regulate the amount of circulating fat to avoid some of the toxic effects that excess lipid have on other tissues. In fact, it is believed that this 'lipotoxicity' is one of the reasons that tissues become de-sensitised to insulin which is the molecular pathology underlying the genesis of type-2 diabetes.

The body knows that it needs energy stores for when ready nutrients are not available. It uses these 'adipose' stores to do just that; squirreling away some energy for a rainy day. It is the efficiency (or lack thereof) of this system that underlies the propensity of an individual to be overweight or obese. While some of this may be modulated genetically, there is a considerable amount of environmental input into this. Consistent, excessive usage or challenge of these regulatory mechanisms could also impact on how efficiently they work. Nevertheless, for our purposes, the knowledge that adipose tissue deposition is a key mechanistic technology is core to the proposition underlying 2-OHOA as a therapeutic agent.

We will not pretend to have covered this subject exhaustively as we would be rapidly 'found out' if we did. We have tried, as best as we could, to cut to the chase so that the mechanism through which a putative anti-obesity drug such as 2-OHOA might become better understood.

### **Current and future therapeutic strategies for the treatment of obesity**

It is obvious that the size of this market has attracted considerable attention and generated a number of therapeutic approaches to the problem. Despite the efforts expended, the value of current drugs aimed at this market amount to less than US\$0.5-1 billion (estimates of the size of this market vary and are difficult to ascertain) and does not reflect the enormous potential of this market.<sup>9</sup>

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<sup>9</sup> In this section we have been significantly inspired by an excellent recent review from Cooke D. and Bloom S, *Nature Rev. Drug Discov*; (2006);5: 919-931

Current strategies employed by drugs approved as anti-obesity drugs fall into the following categories:

- centrally active appetite suppressants (amphetamines);
- centrally active energy balance modulators (sibutramine/Meridia);
- metabolic blockers/lipase inhibitors (orlistat/**Xenical**);
- surgical approaches through gastrointestinal bypass.

Overall there are a number of strategies being pursued that find their origins in the overall mechanisms of appetite, hunger and satiety described above. These fall into three main categories which include:

- drugs affective on central nervous system mechanisms (neurotransmitters and receptors);
- those effecting signaling pathways (gut hormone agonists/antagonists);
- peripherally acting drugs (principally lipid metabolism modulators).

To cover all of these is beyond the scope of this report but there are a few examples of drugs which will serve to illustrate the point.

### ***Centrally acting drugs***

The brain/gut connection discussed above implies that finding drugs that interfere with appetite mechanisms (i.e., lowering the amount one eats) should be a valid anti-obesity strategy. Amphetamines are well known appetite suppressants which are prone to abuse but are effective short term treatments for the management of non-genetic obesity which is approved by the FDA. The use of these drugs is severely restricted as their effect on pulmonary hypertension, cardiac valvulopathy constitute serious side-effects<sup>10</sup> and the risk of abuse and dependency a very undesirable potential behavioural outcome in a group already plagued with low self-esteem and depression. This did serve the purpose of highlighting the validity of targeting serotonin-related nerve pathways as a means of achieving appetite suppression. In fact, sibutramine, the Active Pharmaceutical Ingredient (API) of Abbott Labs' **Meridia (Subitramine)**, is such a compound, inhibiting the re-uptake of both serotonin and noradrenaline and is approved for the management of obesity, weight maintenance and management in the US and elsewhere. This drug has achieved limited market penetration and is controversial in that it can produce hypertension and tachycardia, a risk/benefit ratio not particularly well suited in this population of patients.

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<sup>10</sup>These side effects sunk the fen-fen combination involving fenfluramine and phentermine therapy marketed by American Home Products and was the subject of a major court case and massive settlement in the US.

The second generation of drugs in this category involve further selective serotonin receptor inhibitors some of which have now entered Phase III clinical trials (e.g., drugs such as **Locaserin** or Arena Pharmaceutical's APD 356). The newest central acting drug categories involve what is called the endogenous cannabinoid or CB<sub>1</sub> receptor which is defined by the fact that it binds cannabis ( $\Delta^9$ -THC or tetrahydrocannabinol, also known more commonly as marijuana). CB<sub>1</sub> receptors are primarily found in the brain but also peripherally in metabolically active tissues in the gut; these receptors are involved in the inhibition of GABA (another neurotransmitter). Cannabis is a well-known appetite stimulant so it is logical to think that an antagonist to this receptor should be an appetite suppressant. The first drug in this class is rimonabant (**Accomplia**; Sanofi-Aventis). Unfortunately, while it is an effective adjunct to diet and exercise in reducing weight for individuals with associated Type-2 diabetes and high cholesterol, it also triggers depression in a significant percentage of patients. While it received an 'approvable letter' from the FDA and was approved in Europe, the FDA sent the company back to do further trials and the EMEA has just requested that the drug be withdrawn from the market. Merck and Pfizer had been developing similar drugs in MK-9470 and CO 945598 respectively, both of which were in Phase III clinical trials. Merck and Pfizer have also announced that they have discontinued their programmes in this drug class.

Another drug candidate in this category is tesofensine being developed by NeuroSearch which is about to enter Phase III clinical trials. Tesofensine is a triple neurotransmitter potentiator which has shown promise in a proof of concept Phase IIb trial displaying a dose-responsive loss of weight of up to 12.6 percent versus 2 percent in the placebo group.

Another set of drugs in this category are two drug combinations involving naltrexone (opioid agonist) and bupropion (anxiolytic) on the one hand (**Contrave**; Orexigen Therapeutics) and phentermine and the anti-convulsant topiramate (**Qnexa**; Vivus) on the other. Both focus on combining differential effects on multiple neurotransmitter pathways to take advantage of weight reducing effects while being dosed to avoid the known side-effects of this drug; the pharmacological equivalent of tiptoeing through a room full of broken glass! Both are in Phase III so the jury is still out on whether these 're-positioned' strategies bear fruit.

### ***Gut signaling pathway approaches***

As highlighted earlier there are a number of signaling hormones produced by the gut that are intimately involved in telling the brain the status of energy stores and the state of hunger or satiety of the system. A new class of drugs is being developed to modulate these systems through two types of actions:

- orexigenic action involving hormones such as ghrelin: endorphins and others are involved in signaling to the brain hunger so their blockage with antagonists should result in appetite suppression;
- anorexigenic action implies signaling pathways that signal satiety: their activation with agonists should promote appetite suppression as well.

In this class of drugs there are a number of potential market participants with pipeline candidates aimed at modulating or stimulating hormones involved in signaling satiety or hunger. The focus appears to be on trying to stimulate anorexigenic action. One such drug was under development by US based Nastech (now called MDRNA having changed its focus from nasally delivered drugs to siRNA based therapeutics) in conjunction with London-based Thiakis out of Imperial College. PYY<sub>3-36</sub> is the native anorexigenic peptide which was formulated in Nastech's nasal delivery system. Unfortunately, the Phase II clinical trial completed this year did not meet its primary endpoint of dose-response and failed to show a statistically significant difference in weight loss versus placebo and Abbott's **Meridia**. The same drug is also being tested in combination with another drug in this category called pramlintide (**Symlin**; Amylin Pharmaceuticals), an amylin (an anorexigenic which is co-secreted with insulin and acts to inhibit the level of glucose in the blood and delay gastric emptying) agonist aimed at signaling the state of satiety; the latter is currently in Phase II clinical trials.

Another very active area of drug development is in the area of Neuropeptide Y receptor agonists and antagonists. Neuropeptide Y is a peptide neurotransmitter actively involved in the appetite pathway and acts to stimulate greater food intake. There are five receptor subtypes (Y1 –Y5) of which two, Y1 and Y5, are known to be active in eliciting feeding behaviour and Y2 and Y4 are involved in establishing a state of satiety; it follows that blockage of the former and stimulation of the latter are valid appetite suppressant strategies. 7TM Pharma out of Denmark has two candidates in PI/IIa clinical trials for the treatment of obesity. The lead compound obineptide (TM 30338) is a PYY<sub>3-36</sub> and PP (pancreatic polypeptide) analogue that acts as an agonist on both the Y2 and Y4 receptors. The company also has a follow-up Y4 receptor agonist TM 30339. Both showed safety and indications of efficacy in Phase 1 trials. Finally, Shionogi USA has a Y5 receptor antagonist in Phase II (S2367) clinical trials.

Other drugs in this category are the approved diabetic drugs GLP-1 agonists (**Byetta**; Eli Lilly) and an amylin secretagogue (**Symlin**; Amylin Pharmaceuticals), approved as therapies for the treatment of Type-2 diabetes. Both are injectable and both are highly effective at normalising glucose metabolism but both also have appetite suppressant activity and can result in weight loss. Novo Nordisk's liraglutide, another GLP-1 agonist, is at the FDA, with a panel meeting expected in April of 2009.

### ***Lipid metabolism modifiers***

In this category one clearly finds orlistat (**Xenical**: Roche), a lipase inhibitor approved for the management of obesity as an adjunct to lifestyle therapy (i.e., reduced calorie diet). Although the drug attained sales of just under US\$1 billion at its peak its gastrointestinal side-effects, centered on diarrhea and incontinence, and its high price made its use rather unpopular. More recently, it has been relaunched by GSK as an over the counter drug called **Alli** with some considerable success. Another drug developed by the UK's Allzyme called **Cetilistat** is currently in a series of 12 month Phase III clinical trials with and without co-morbidities (such as Type-2 diabetes).

## **2-OHOA: a novel mechanism for the assault of obesity**

### **Background**

In the field of clinical research, there occasionally are developments that emerge that produce surprising, sometimes astonishing discoveries. The beneficial effects of the so-called 'Mediterranean Diet' have been touted and reviewed extensively in the scientific literature and in the popular press. Few people who care about these issues can claim to ignore the fact that this diet appears to be associated, in the populations that use it, in a significantly lower incidence of so-called 'Lifestyle' metabolic-linked diseases. We also know that this diet is very rich in olive oil (which itself is rich in oleic acid – about 80%) but also in other omega-type mono- and polyunsaturated fats. Whether the low incidence of these diseases is solely based on this diet or whether a significant genetic component is at play here is unknown but the concept that there is some 'magical' pharmaco-metabolic effect of oleic acid is certainly worthy investigation as a potential therapeutic strategy.

As it turns out, the effect is real. Oleic acid on its own has a specific effect on the cellular membrane at high doses and is thought to alter its structure and trigger a signaling system which can be linked to these beneficial effects; the link rationale does exist. Researchers in Spain discovered that a hydroxylated derivative of oleic acid has similar and additional effects versus the native compound except at much lower concentrations. This is the basis for a novel therapy for the treatment of obesity. The biochemical and metabolic basis for this is that the type of hydroxylation ( $\alpha$ -hydroxylation) on 2-OHOA is not readily digestible by the normal pathway ( $\beta$ -hydroxylase action) resulting in the accumulation and slow disposal of the compound leaving it free to exert other effects. In contrast, oleic acid is almost directly used as an energy source and metabolised rather rapidly.

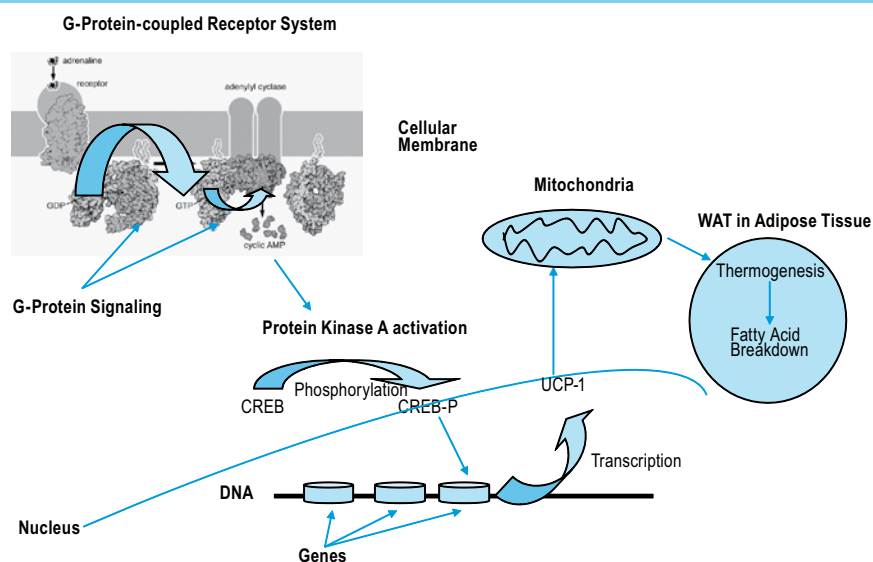


### Putative obesity mechanism

On the one hand, G-protein activation induces a chain reaction that activates a transcription factor called CREB (or cyclic AMP response element binding) which binds to DNA and is responsible for activating a number of important metabolic hormones. Simplistically, the Spanish group has shown that 2-OHOA activates a protein called UCP-1 in a CREB-dependent fashion and that this UCP-1 activation occurs in white adipose tissue (WAT) which seems to have acquired brown adipose tissue (BAT) characteristics<sup>12</sup>. UCP-1 is a protein that induces **thermogenesis** which is a process through which mammalian bodies produce heat via the breakdown of fat stores (which is particularly important in hibernating animals). The activation of this protein normally occurs in BAT<sup>13</sup> but the finding that it can be induced by 2-OHOA in WAT while surprising, could reasonably explain the reduction in adipose tissue mass and reduction in body weight seen in animals treated with this drug.

There is an additional, possibly related, putative mechanism which this group has uncovered through the observation that animals treated with 2-OHOA show a marked downregulation of an enzyme called SCD-1 or Steroyl-CoA desaturase-1, a rate-limiting enzyme in the conversion of saturated long chain fatty acids into MUFA's. Several papers have shown that either the inhibition<sup>14</sup> or knockout<sup>15</sup> of SCD-1 function resulted in loss of weight or prevention of obesity. The mechanism behind this is just beginning to be understood. The blockage or unavailability of SCD-1 has multiple effects in liver, WAT and BAT. The putative effects of blocking this enzyme include increasing insulin sensitivity, upregulating UCP-1 (inducing thermogenesis) and affecting lipid metabolism in a way that appears to result in weight loss and the prevention of obesity.

### G-protein coupled signaling



Source: Objective Capital & adaptations from published sources

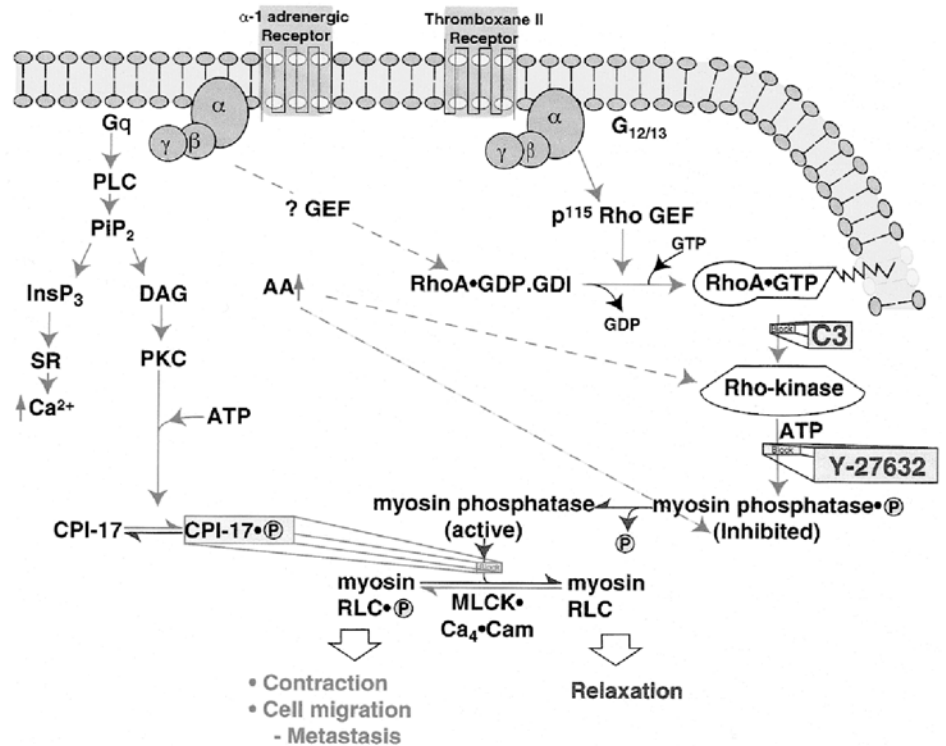
<sup>12</sup>Voegler et al., *Intl. J. Obesity* (2008); **32**:464-473

<sup>13</sup>The physiological function of BAT, which is present in hibernating mammals and neonates, is to generate heat whereas WAT functions as an energy storage through the deposition of fat.

<sup>14</sup>Jiang G. et al., *J. Clin. Invest.* (2005); **115**:1030-1038

<sup>15</sup>Ntambi J et al. (2002); **99** (17):11482-11486

## Molecular mechanisms of hypertension



Source: Solmyo A. & Solmyo A.; *Journal of Physiology* (2000), 522.2, 177–185

### Hypertension mechanism

Hypertension, which is characterised by a consistent abnormal rise in blood pressure, is linked to an increase in peripheral vascular resistance which is due to fundamental functional and structural changes in the physiology of the arterial cell wall. The phosphorylation of the myosin (muscle protein) light chain is the fundamental driver of this process. While all of this is not completely elucidated, there is considerable evidence that two separate mechanisms are at work here: one to induce contraction and the other to induce relaxation of the vascular wall. As seen in this rather complex diagramme, both are driven by G protein-coupled receptor-driven mechanisms (in this case through adrenaline and prostacyclin receptors) and both end up in the same place (the phosphorylation of the myosin light chain). The relaxation mechanism is driven via a RhoA/Rho-Kinase based mechanism and the other through a lipid signaling mechanism involving phospholipase and culminating in the blockage of the aforementioned phosphorylation to contract the cell wall.

The same Spanish group at the University of the Balears has shown in an SHR model that after the administration of 2-OHOA, a sustained, time-dependant and dose-dependant reduction in systolic and diastolic blood pressure was seen. In this paper<sup>16</sup>, the group looked at two potential mechanisms that might be underlying this impressive hypotensive effect. On the one hand it found that 2-OHOA activated Protein Kinase A a key G-coupled receptor induced pathway that is impaired in the SHR model in its ability to induce vasorelaxation. This

<sup>16</sup>Alemanya, R. et. al; *J. Lipid Res.*; 47:1762-1770

observed effect was confirmed through reversal using antagonists and supports the notion that the drug is acting through an active pathway. They also looked at the Rho Kinase pathway that we described above and found that it too was up-regulated which should potentiate the relaxation pathway involving the phosphorylation of the myosin light chain. The authors concluded that ‘the sustained antihypertensive action of 2-OHOA is apparently caused by the upregulation of the vasodilatory AC/cAMP/PKA pathway and downregulation of the vasoconstrictory Rho kinase pathway’.

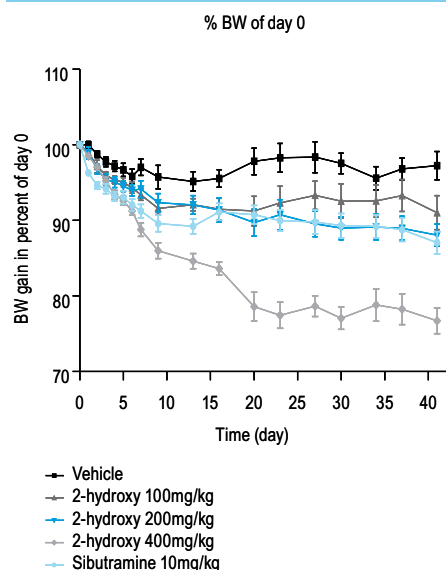
In conclusion, where does all of this leave us? Obesity and hypertension are frequently co-morbidities and weight loss in itself can have a hypotensive effect (BP drops by 1mm HG per Kg lost up to a total of 10 kg). **What we have is a drug that may not only reduce body fat (with implications for co-morbid hypertension) but also embodies a potential mechanism for reducing blood pressure as well.** While this is early data, if validated, the implications for the potential commercial success of this drug are explosive.

### Clinical status and strategy

How does the drug compare to drugs already on the market? Bridge conducted animal toxicology and efficacy studies as part of its preclinical programme testing the dose responsiveness of 2-OHOA in a standard obesity animal model. The effect of 2-OHOA is both dose and time dependent in a dose range of 100 mg/kg all the way to 400 mg/kg. There were no signs of toxicity at any dose and at 400 mg/kg 2-OHOA resulted in a 24 percent drop in weight versus a 13 percent drop for sibutramine (Meridia; Abbott Labs). Should this data hold up in humans, the obesity data combined with the effects on blood pressure bode well for the drug.

Bridge are conducting a dose-ranging study in dogs to push the dosage of 2-OHOA to where it becomes toxic. Currently the dosage studied is at 900 mg/kg and the plan is to push that up again. Once this study has been completed, the preclinical package itself will be complete and the company will submit this to the US (2-OHOA is sourced from a US GMP certified manufacturer), and/or European regulators to initiate what will be a Phase Ib or Phase IIa study in healthy obese individuals. The protocol of this study will probably be constructed along the lines of other obesity studies currently being conducted. This will be a placebo-controlled randomised double blind trial with between 25-50 healthy but obese patients with hypertension. The primary endpoint would be weight loss over 90 days but the secondary endpoints would focus on surrogate markers of increased insulin sensitivity and reduction in hypertension. It is likely that such a study would be completed by the end of 2009 or beginning of 2010. This would pave the way for a Phase II/III trial in 2011/12, a filing in 2014 and a market approval in 2016.

### 2-OHOA dose-response vs sibutramine



Source: Bridge BioResearch, Rheoscience Preclinical Data

## **Licensing strategy**

Very simply put, the Phase IIa study that is contemplated will be a Proof of Concept or PoC study which would ready the compound for outlicensing. The company plans to employ a standard licensing strategy which would focus on finding a partnership with a major pharma or by dividing up regions amongst various regional/speciality companies. These transactions are projected to trigger upfront and milestone payments as well as a fixed royalties upon marketing which, in this case, would be somewhere in the 15 percent range.

## **The current obesity market: dynamics, regulation and reimbursement**

### **Market dynamics**

The current market for anti-obesity drugs was somewhere in the range of US\$0.5-1 billion in 2007. However, the European Medicines Agency has requested the withdrawal of Sanofi-Aventis's Accomplia as patients on the drug were twice as likely to have suicidal thoughts as the general population; not an adverse effect that is appropriate for a weight loss drug! Alli, the GSK OTC brand of Roche's Xenical (orlistat) was approved for OTC sales by the FDA early this year and has had brisk sales (US\$80 million we believe) but it too has started to run into trouble as repeat sales have been hard to come by.

We believe that the potential market for anti-obesity drugs is almost too large to contemplate. We estimate from publicly available prevalence data that as many as 390 million people are clinically obese worldwide and a combined total of around 1.4 billion people are either pre-obese (overweight) and obese. Our obesity growth rates are somewhat more modest than those estimated by the WHO which is predicting a doubling of the global obese population to close to 700 million by 2025. Our more model prediction of 550-600 million seems to us to be large enough!

Given the size of the current market, it is obvious that the market potential for these drugs is not being fulfilled. Why is this so?

The fundamental reason for lack of success and market penetration is rather simple: price, significant side-effects, modest efficacy and, last but not least, lack of reimbursement. While drugs such as amphetamines/sympathomimetic agents are effective, the abuse/dependency or side-effects that accompany these are not acceptable in longer term treatment. The lipase inhibitor orlistat (Xenical; Roche) and the SNRi (Serotonin and Noradrenaline) dual reuptake inhibitor sibutramine (Meridia; Abbott) are both accompanied by significant side-effects that are unacceptable for daily continuous use.

## 2-OHOA and obesity market model

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
<b>Global population</b>														
US	300	303	306	309	312	315	318	322	325	328	331	335	338	341
Japan	125	126	128	129	130	131	133	134	135	137	138	139	141	142
Western Europe	393	397	401	405	409	413	417	421	426	430	434	438	443	447
RoW	5,726	5,783	5,841	5,900	5,958	6,018	6,078	6,139	6,200	6,262	6,325	6,388	6,452	6,517
<b>Total</b>	<b>6,544</b>	<b>6,609</b>	<b>6,676</b>	<b>6,742</b>	<b>6,810</b>	<b>6,878</b>	<b>6,947</b>	<b>7,016</b>	<b>7,086</b>	<b>7,157</b>	<b>7,229</b>	<b>7,301</b>	<b>7,374</b>	<b>7,448</b>
<b>Prevalence of obesity (%)</b>														
US	25.0%	25.3%	25.5%	25.8%	26.0%	26.3%	26.5%	26.8%	27.1%	27.3%	27.6%	27.9%	28.2%	28.5%
Japan	3.0%	3.0%	3.0%	3.0%	3.1%	3.1%	3.1%	3.1%	3.1%	3.1%	3.2%	3.2%	3.2%	3.2%
Western Europe	14.0%	14.1%	14.3%	14.4%	14.6%	14.7%	14.9%	15.0%	15.2%	15.3%	15.5%	15.6%	15.8%	15.9%
RoW	4.5%	4.5%	4.6%	4.6%	4.7%	4.7%	4.8%	4.8%	4.9%	4.9%	5.0%	5.0%	5.1%	5.1%
<b>Total</b>	<b>6.0%</b>	<b>6.0%</b>	<b>6.1%</b>	<b>6.2%</b>	<b>6.2%</b>	<b>6.3%</b>	<b>6.3%</b>	<b>6.4%</b>	<b>6.5%</b>	<b>6.5%</b>	<b>6.6%</b>	<b>6.7%</b>	<b>6.7%</b>	<b>6.8%</b>
<b>Combined prevalence overweight/obese (%)</b>														
US	60.0%	60.6%	61.2%	61.8%	62.4%	63.1%	63.7%	64.3%	65.0%	65.6%	66.3%	66.9%	67.6%	68.3%
Japan	25.0%	25.3%	25.5%	25.8%	26.0%	26.3%	26.5%	26.8%	27.1%	27.3%	27.6%	27.9%	28.2%	28.5%
Western Europe	15.0%	15.3%	15.6%	15.9%	16.2%	16.6%	16.9%	17.2%	17.6%	17.9%	18.3%	18.7%	19.0%	19.4%
RoW	20.0%	20.4%	20.8%	21.2%	21.6%	22.1%	22.5%	23.0%	23.4%	23.9%	24.4%	24.9%	25.4%	25.9%
<b>Total</b>	<b>21.6%</b>	<b>22.0%</b>	<b>22.4%</b>	<b>22.9%</b>	<b>23.3%</b>	<b>23.7%</b>	<b>24.1%</b>	<b>24.6%</b>	<b>25.1%</b>	<b>25.5%</b>	<b>26.0%</b>	<b>26.5%</b>	<b>27.0%</b>	<b>27.5%</b>
<b>Prevalence of obesity (millions)</b>														
US	75	77	78	80	81	83	85	86	88	90	92	93	95	97
Japan	4	4	4	4	4	4	4	4	4	4	4	4	4	5
Western Europe	55	56	57	58	60	61	62	63	65	66	67	68	70	71
RoW	258	263	268	274	279	285	290	296	302	308	314	321	327	334
<b>Total</b>	<b>391</b>	<b>399</b>	<b>407</b>	<b>415</b>	<b>424</b>	<b>432</b>	<b>441</b>	<b>450</b>	<b>459</b>	<b>468</b>	<b>477</b>	<b>487</b>	<b>497</b>	<b>507</b>
<b>Combined prevalence pre-obese/obese (millions)</b>														
US	180	184	187	191	195	199	203	207	211	215	220	224	229	233
Japan	31	32	33	33	34	35	35	36	37	37	38	39	40	40
Western Europe	59	61	63	64	66	68	70	73	75	77	79	82	84	87
RoW	1,145	1,180	1,215	1,252	1,290	1,329	1,369	1,410	1,453	1,497	1,542	1,589	1,637	1,686
<b>Total</b>	<b>1,415</b>	<b>1,456</b>	<b>1,498</b>	<b>1,541</b>	<b>1,585</b>	<b>1,631</b>	<b>1,678</b>	<b>1,726</b>	<b>1,775</b>	<b>1,827</b>	<b>1,879</b>	<b>1,933</b>	<b>1,989</b>	<b>2,046</b>
Target average drug cost per month(*)	50	55	60.5	66.6	73.2	76.9	79.2	81.5	84.0	86.5	89.1	91.8	94.5	97.4
Average number of months of treatment	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Total average annual cost per treatment	600	660	726	799	878	922	950	979	1008	1038	1069	1101	1134	1168
Estimated discount to current treatment costs	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
<b>Estimated annual price for 2-OHOA (US\$)</b>	<b>\$600</b>	<b>\$660</b>	<b>\$726</b>	<b>\$799</b>	<b>\$878</b>	<b>\$922</b>	<b>\$950</b>	<b>\$979</b>	<b>\$1,008</b>	<b>\$1,038</b>	<b>\$1,069</b>	<b>\$1,101</b>	<b>\$1,134</b>	<b>\$1,168</b>
<b>Total market potential for 2-OHOA in combined obesity/overweight markets (US\$ billions)</b>														
<b>Global potential (obesity/overweight)</b>	<b>\$687</b>	<b>\$779</b>	<b>\$882</b>	<b>\$1,000</b>	<b>\$1,133</b>	<b>\$1,226</b>	<b>\$1,301</b>	<b>\$1,380</b>	<b>\$1,464</b>	<b>\$1,554</b>	<b>\$1,649</b>	<b>\$1,750</b>	<b>\$1,857</b>	<b>\$1,970</b>
<b>Key markets (US, Japan, Western Europe, 10% of ROW)</b>	<b>\$123</b>	<b>\$139</b>	<b>\$157</b>	<b>\$178</b>	<b>\$201</b>	<b>\$218</b>	<b>\$230</b>	<b>\$244</b>	<b>\$259</b>	<b>\$274</b>	<b>\$291</b>	<b>\$308</b>	<b>\$326</b>	<b>\$346</b>
<b>Total market potential for 2-OHOA in obesity only markets (US\$ billions)</b>														
<b>Global potential (obesity/overweight)</b>	<b>\$235</b>	<b>\$264</b>	<b>\$296</b>	<b>\$332</b>	<b>\$372</b>	<b>\$399</b>	<b>\$419</b>	<b>\$440</b>	<b>\$462</b>	<b>\$486</b>	<b>\$510</b>	<b>\$536</b>	<b>\$564</b>	<b>\$592</b>
<b>Key markets (US, Japan, Western Europe, 10% of ROW)</b>	<b>\$96</b>	<b>\$107</b>	<b>\$120</b>	<b>\$135</b>	<b>\$152</b>	<b>\$162</b>	<b>\$171</b>	<b>\$179</b>	<b>\$188</b>	<b>\$198</b>	<b>\$208</b>	<b>\$218</b>	<b>\$229</b>	<b>\$241</b>

(\*) Based on the monthly cost of Sanofi Aventis's rimonabant (Accomplia)

(\*\*) Based on Business Insight and Objective Capital estimates

Source: WHO, US CDC, literature data and Objective Capital estimates

None of these drugs have been able to trigger significant reimbursement from either national or insurance sources; as unreimbursed compounds, they tend to be too expensive to achieve broad market penetration. In any case, drugs like sibutramine are not favoured by physicians due to their side-effect profile (nausea, dry mouth, constipation, etc) and the weight loss experienced with these drugs has been too modest to motivate users to remain on them for any length of time. What is required in this market is a drug that triggers sustainable weight loss benefits (with appropriate lifestyle changes) with beneficial effects on co-morbidities (diabetes, hypertension, etc), an appropriate cost/benefit ratio and is viewed as a medical therapy worthy of reimbursement.

The extensive pipeline demonstrates that this market has not only attracted attention from pharma companies but is being actively pursued by many.

### **Regulatory environment**

With the experience of Xenical and Meridia behind them, regulatory agencies have issued guidelines for the approval of weight management drugs. The FDA issued guidelines in 2007 requesting that for drugs to be submitted they must demonstrate one of the following criteria over a year of testing:

- have a statistically significant difference in mean weight of at least 5 percent between the treated and placebo group; and
- that a minimum of 35 percent of the patients in the treatment group lose an amount of weight that is equal to or greater than 5 percent and that this proportion of total treated be double that of the placebo group and statistically significant.

We believe that in order to pass muster at the FDA and elsewhere, a drug for this disease must have a relatively clean side-effect profile as evidenced by the rejection of Sanofi-Aventis' Accomplia which was eventually withdrawn in Europe as well. The rationale for such a high bar is evident. Obesity is usually accompanied by co-morbidities such as diabetes, hypertension and other conditions. It is not considered desirable for other morbidities to be added to the mix.

### **2-OHOA competitive profile**

It is too early to tell where 2-OHOA will fall in the mix of products that are in the general obesity pipeline. The accompanying table outlines the various mechanisms being pursued from the current ones already outlined to the new combinations and mechanisms. Clearly the CB-1 receptor antagonists are under a cloud as Accomplia exits the market. Second generation lipase inhibitors are aimed at improving the side-effect profile of Meridia and could be useful. The combinations depicted in the accompanying table are aimed at manipulating the central nervous system to affect feeding behaviour or appetite. There are some novel mechanisms in the works such as Y receptor agonists being developed by 7TM in Denmark, selective serotonin receptor agonists, amylin agonists, etc. All will need to prove significant safety profiles in addition to a sustainable weight loss that meets the guidelines.

## Pipeline of obesity therapies by mechanism of action

	Stage of development	Companies	MoA <sup>1</sup>
<b>Catecholamine modulation</b>	Phase III	NeuroSearch, Arena & Others	Brain serotonin receptor agonist stimulates the release of norepinephrine or dopamine (or both)
<b>CB-1 antagonists</b>	Phase III/withdrawn	Sanofi, Merck & Pfizer	Brain CB1 receptor suppression which reduces appetite
<b>GLP-1 agonists</b>	Phase III	Eli Lilly, Novo, Corcept, Amylin	GLP-1 mimic which stimulates the release of insulin from the pancreas, lowers blood sugar, induces state of satiety and delays gastric emptying
<b>Amylin agonists</b>	Phase II	Amylin, Natestch	Amylin mimics acting on brain and gut to lower food intake and delay gastric emptying
<b>Neuropeptide Y receptor agonists</b>	Phase II	7TM	Potentiates brain neuropeptide Y receptors helping to induce a state of satiety which reduces food intake and leads to weight loss
<b>Combinations</b>			This category takes advantage of the differential properties of these individual drugs and combines them to achieve putative increased efficacy and overcome the deficiencies of monotherapy
<b>Amylin agonist/Leptin agonist</b>	Phase II	Amylin	
<b>Catecholamine release/Antiepileptic</b>	Phase III	Vivus	
<b>Catecholamine uptake inhibitor/Opioid agonist</b>	Phase III	Orexigen	
<b>Catecholamine uptake inhib./anticonvulsant</b>	Phase II	Orexigen	

<sup>1</sup> Mechanism of Action

Source: published sources and Objective Capital

The putative anti-hypertensive and insulin sensitising properties of 2-OHOA along with its ability to induce weight loss and appetite suppression all point to a very unique profile. The only drugs that compare favourably to this are the GLP-1 and amylin based approaches but these are injectable versus the oral route for 2-OHOA. It is too early to tell how the drug will be positioned in all of this but, if 2-OHOA can achieve in human clinical trials the safety and efficacy that it has demonstrated in preclinical models (which historically have proved relevant), the potential of this drug could be, in our view staggering. A large proportion of obese patients have either hypertension or diabetes and often both. A drug approved for weight loss but with beneficial effects on those co-morbidities would be highly desirable from a medical point of view and likely to attract reimbursement. This in turn should lead to a significant market penetration.

## Projected 2-OHOA revenues

In the accompanying table we have depicted a revenue model that derives from the market model which we outlined above. Our revenue numbers are based on a current market penetration of under 5 percent which we project to expand as new, safer drugs achieve market entry. We have also focused our analysis on major markets despite the fact that these drugs could find significant usage in advanced developing countries as well as in Russia and Eastern Europe. We have priced the drug against the known level of rimonabant (Accomplia; Sanofi-Aventis) although we believe that a cost benefit analysis which includes its anti-hypertensive and diabetes benefits should translate into a higher price point (possibly twice to three times that). Finally, we have used market penetration rates that are relatively standard and achieve an 9-10 percent market penetration taking into account the possibility that this may be a crowded market by the time we estimate this drug reaches the market in 2016.

### Projected revenue for 2-OHOA

Period	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Total market potential for 2-OHOA in obesity only markets (US\$ billions)																
Global potential (Obesity/Overweight)	\$235	\$264	\$296	\$332	\$372	\$399	\$419	\$440	\$462	\$486	\$510	\$536	\$564	\$592	\$622.1	\$653.6
Key markets (US, Japan, Western Europe, 10% of ROW)	\$96	\$107	\$120	\$135	\$152	\$162	\$171	\$179	\$188	\$198	\$208	\$218	\$229	\$241	\$253.3	\$266.1
Market penetration rates																
Key market penetration (in US\$ billion)	\$6	\$6	\$8	\$9	\$12	\$14	\$16	\$19	\$22	\$26	\$30	\$35	\$40	\$47	\$54.9	\$64.0
Penetration rate	4.5%	4.6%	4.8%	5.3%	5.8%	6.4%	7.0%	7.7%	8.5%	9.3%	10.2%	11.3%	12.4%	13.6%	15.0%	16.5%
Current and prospective market forecast **	\$1	\$1	\$2	\$2	\$2	\$3	\$4	\$4	\$4	\$4	\$4	\$4	\$4	\$4	\$4.6	\$4.7
Current/Proj. market penetration	18%	19%	21%	21%	21%	22%	22%	21%	19%	16%	14%	12%	11%	10%	8%	7%

### 2-OHOA - projected revenue

#### Core model

Estimated market penetration	2.0%	5.0%	7.0%	8.0%	9.0%	9.0%	9.0%
Estimated full priced sales (US\$ millions)	\$233	\$691	\$1,128	\$1,502	\$1,970	\$2,295.8	\$2,676.0
Estimated discount pricing	25%	25%	25%	25%	25%	25%	25%
<b>Total core model projection for 2-OHOA</b>	<b>\$174</b>	<b>\$518</b>	<b>\$846</b>	<b>\$1,127</b>	<b>\$1,477</b>	<b>\$1,721.8</b>	<b>\$2,007.0</b>
<b>Total core model projection for 2-OHOA (£m)</b>	<b>£113</b>	<b>£334</b>	<b>£546</b>	<b>£727</b>	<b>£953</b>	<b>£1,111</b>	<b>£1,295</b>

#### Optimistic model

Estimated market penetration	3.0%	6.0%	8.0%	9.0%	10.0%	10.0%	10.0%
<b>Estimated full priced sales (US\$ millions)</b>	<b>\$349</b>	<b>\$829</b>	<b>\$1,289</b>	<b>\$1,690</b>	<b>\$2,188</b>	<b>\$2,550.9</b>	<b>\$2,973.3</b>
Estimated discount pricing	25%	25%	25%	25%	25%	25%	25%
<b>Total core model projection for 2-OHOA</b>	<b>\$262</b>	<b>\$622</b>	<b>\$967</b>	<b>\$1,267</b>	<b>\$1,641</b>	<b>\$1,913.2</b>	<b>\$2,230.0</b>
<b>Total core model projection for 2-OHOA (£m)</b>	<b>£169</b>	<b>£401</b>	<b>£624</b>	<b>£818</b>	<b>£1,059</b>	<b>£1,234.3</b>	<b>£1,438.7</b>

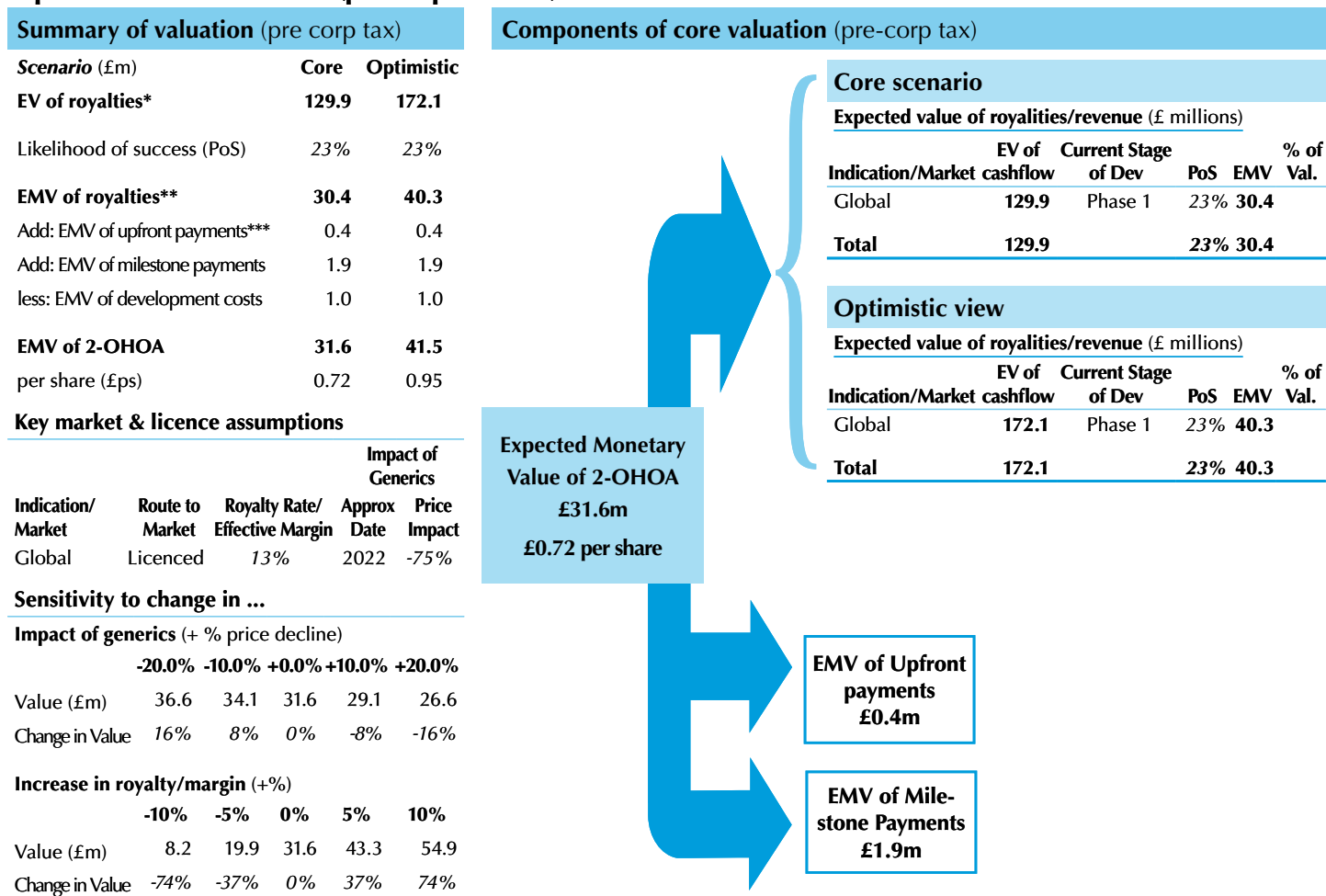
\* Base on the monthly cost of Sanofi Aventis's rimonabant (Accomplia)

\*\* Based on Business Insight and Objective Capital estimates

Source: WHO, US CDC, literature data and Objective Capital estimates

The results are a revenue projection that would reach around US\$1.4-1.6 billion, a modest revenue estimate in what is a blockbuster market. We believe that for a drug of this profile this might represent only 25-30% of its potential. Nevertheless, at this stage we believe that a prudent approach to estimating the market potential for this drug is called for but investors should keep in mind that the potential is several time larger with the right profile and right partner.

## Expected value of 2-OHOA (pre-corporate tax)

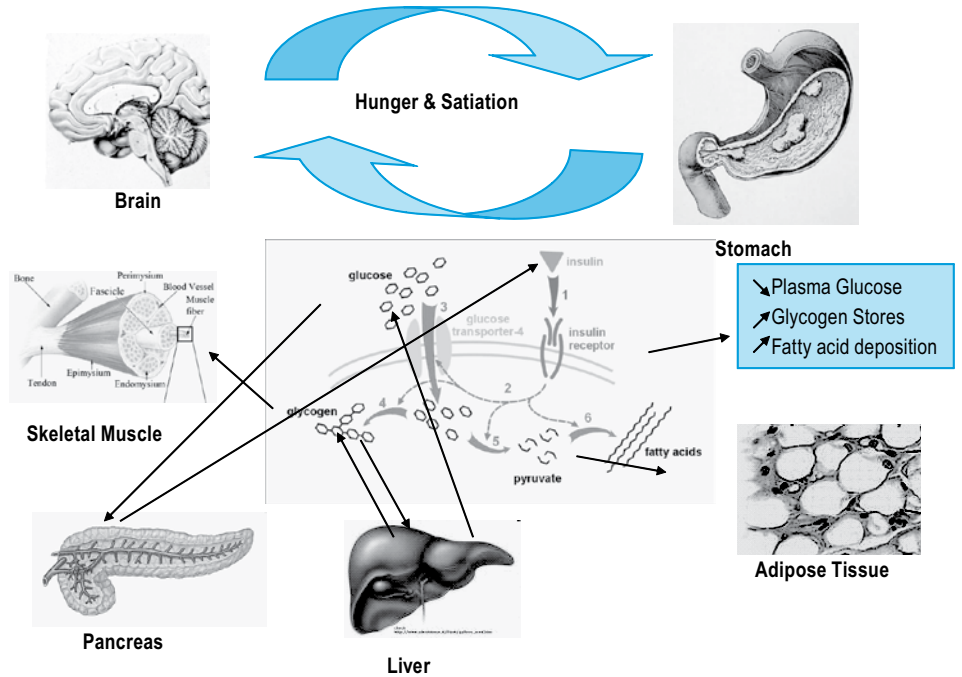


\* The expected value (EV) of royalties has been calculated assuming our explicit revenue forecasts, a period of further growth until generics enter the market, and a period of further market growth and decline as competing products enter the market.

\*\* Expected monetary values (EMV) refer to risked values

\*\*\* upfront, milestone and development costs have been risked based on the probability of being received/incurred

## Insulin actions



Source: Objective Capital adapted from published sources

## Overview of Type 2 diabetes: products and markets

### Metabolism fundamentals

Glucose metabolism is fundamental to life. It is, along with fatty acids, one of the principal fuels upon which cell metabolism is built and is subject to a stringent regulatory mechanism that maintains the integrity of life itself. Any breakdown in this regulatory mechanism creates serious problems as both too much and too little glucose trigger significant pathological effects. Insulin is the central anabolic (blood glucose reducing) hormone, which together with glucagon (the catabolic or blood glucose increasing), regulate the levels of glucose in the blood. As indicated in the accompanying graphic insulin acts by inciting cells (binding to the insulin receptor on the cell surface) to absorb glucose (through the indicated transporter system) as metabolic fuel. Any malfunction in this system wreaks havoc in the system and results in a serious degradation of physiological function and ultimately organ failure and death.

### Glucose metabolism breakdown: the genesis of diabetes

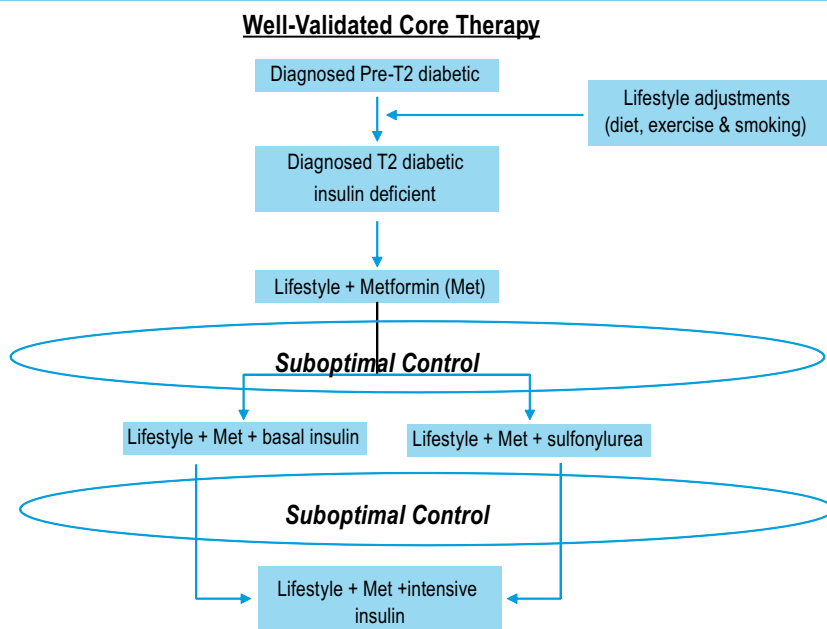
There are two main form of diabetes that affect the production and action of insulin. One involves the inability of pancreatic beta cells to synthesise insulin. This disease, known as Type 1 is a disease that is autoimmune in nature. The autoimmune reaction that ensues kills pancreatic beta cells and impairs insulin production.

The second type of diabetes involves a reduced sensitivity of cells to insulin; also called 'insulin resistance' as well as impaired insulin secretion. This disease, which is called Type 2 diabetes involves insulin resistance but is also accompanied by insufficient insulin secretion which often results in the need to provide insulin replacement therapy in the latter stages of the disease. Type 2 diabetes is termed a 'lifestyle disease' which results primarily from obesity and the stresses that this confers upon metabolism and the integrity of the cellular glucose control mechanisms. A possible aetiology for this disease is thought to stem from both excess circulating glucose ("glucotoxicity") and excess circulating fatty acids that are released from adipose tissue ("lipotoxicity"). This toxicity impairs the insulin sensitivity of metabolically important cells in skeletal muscles, liver and fat tissue in achieving glycaemic control.

### Treatment goals in T2D

The primary goal in treating this disease is to achieve normal glycaemic control through better absorption of glucose into cells through the active glucose transport mechanism. Today, the treatment goals have changed somewhat and the focus is not only on normalising blood glucose but rather HbA1c, a form of 'glycosylated' (i.e., with glucose attached) haemoglobin which is a longer term indicator (2-3 months) of glucose levels. A number of therapeutic strategies have been developed to achieve glycaemic control.

### Current classical T2D strategies



Source: Adapted from Nathan D. et al; Diabetes Care (2008) 31(12):1-8

However, as outlined in the December 2008 issue of *Diabetes Care*<sup>17</sup> in the newest consensus joint statement from both the American Diabetes Association and the European Association for the Study of Diabetes, the core, best-validated treatment algorithm for Type 2 diabetes is outlined in the schematic above. Other less validated regimens, using glitazones such as pioglitazone (**Actos**; Takeda) and GLP-1 analogues (such as exenatide/**Byetta**; Amylin Pharmaceuticals and Lilly) are used as well. However, glitazones such as rosglitazone (**Avandia**; Glaxo) have been shown to increase the risk of heart problems and GLP-1 analogues are associated with the incidence of pancreatitis. The following outlines existing classes of drugs in use for the treatment of T2D.

**Metformin (Glucophage**; Pfizer as well as multiple generics), a biguanide, appears to act by activating the enzyme AMP kinase which is central in insulin signaling. It acts by reducing the amount of gluconeogenesis (glucose production) in the liver, enhances insulin sensitivity, increases peripheral glucose uptake and reduces glucose absorption from the gastrointestinal tract. It is by far the most widely used oral anti-diabetic drug either as a single agent or in combination with other drugs primarily due to the fact that it does not trigger weight gain; in fact it is an effective appetite suppressant which makes it a first line treatment for T2D patients that are overweight. It is highly effective, with reduced weight gain, in combination with other drugs (TZD's and DPP-4 inhibitors).

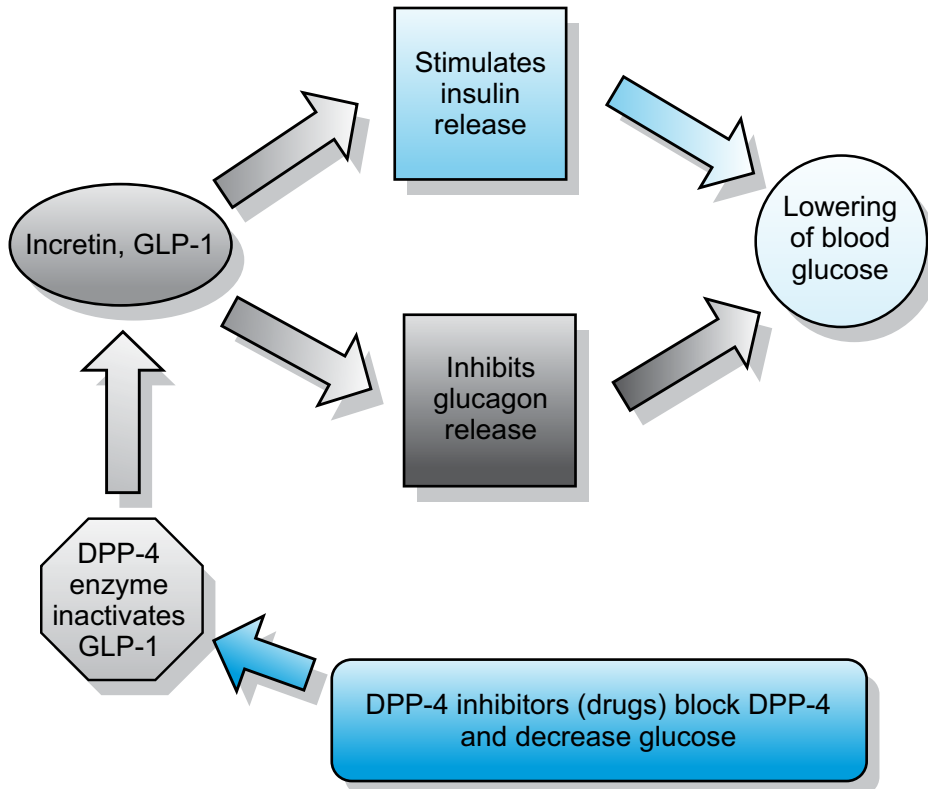
#### ***Enhanced insulin secretion***

One strategy is to enhance the degree of insulin secretion using what are called insulin secretagogues. **Sulfonylurea** compounds are a class of insulin secretagogues that act by binding to the cell surface ATP-sensitive potassium channels of pancreatic beta-cells thereby affecting the polarization of the membrane opening calcium channels and increasing the level of intracellular calcium. The increased calcium has the effect of increasing the fusion of insulin-containing granules with the cell's membrane and increasing its secretion. **Meglitinides** are another class of drugs that act in a similar fashion.

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<sup>17</sup>Nathan D. et al.; *Diabetes Care*; (2008);31(12): 1-11

## Incretins and DPP-IV inhibitors



Source: Wikipedia

Newer secretagogues such as **GLP-1 Agonists**<sup>18</sup> and **DPP-IV inhibitors** act via the activation of a class of gastrointestinal hormones called *incretins* of which GLP-1 is a member. As indicated in the accompanying diagramme, GLP-1 both stimulates insulin and inhibits glucagons resulting in a lowering of blood glucose. DPP-IV<sup>19</sup> inhibitors block this enzyme which is responsible for inactivating GLP-1 thereby inhibiting its effects on insulin and glucagon. GLP-1 agonists, such as amilyn, Lilly's **Byetta**, are injectable whereas DPP-IV inhibitors such as Merck's **Januvia** are oral drugs.

Bridge's recently-acquired isosteviol (STX03) fits within the category of insulin secretagogues but acts through a completely different molecular mechanism than the aforementioned drug classes. While its mechanism is not completely elucidated, it is thought to act by increasing acetyl-CoA (ACC) carboxylase gene expression which triggers an increased secretion of insulin. It also appears to increase the uptake of glucose into the cell; both of these mechanisms would act to lower blood glucose.

<sup>18</sup> Agonists are the opposite of antagonists. These are substances that activate or potentiate the action of a target biological substrate.

<sup>19</sup> DPP-IV is the enzyme Dipeptidyl peptidase IV.

### ***Insulin sensitisation***

Although metformin is also an insulin sensitiser, a number of new classes of drugs have emerged over the past 15 years to claim this therapeutic category.

**Thiazolidinedione (TZD)**<sup>20</sup> are a class of drugs introduced in the 1990's that bind to PPAR- $\gamma$ <sup>21</sup> a transcription factor that regulates a number of insulin-responsive genes involved in the modulation of both glucose and lipid metabolism. The result is a decrease in insulin resistance (through sensitisation). However, the withdrawal of Rezulin due to the increased incidence of hepatitis leading to liver failure coupled with potential cardiovascular risks has put somewhat of a cloud over this class of drugs. The above mentioned increase in cardiovascular risk with the use of this category of drugs has seen them fall rapidly out of favour resulting in rapidly falling revenues.

### ***Modification of glucose metabolism***

**$\alpha$ -Glucosidase inhibitors** block the action of this enzyme and result in the blockage of dietary sugar breakdown resulting in a lowering of measured HbA1c, post-prandial<sup>22</sup> and fasting glucose levels with minimal systemic absorption, the absence of induced hypoglycaemia and no weight gain. This class of drugs can be used in combination with metformin and sulphonylureas.

### ***Amylin secretagogues***

Equally characteristic of T2D is the lack of amylin secretion. Amylin is a peptide hormone secreted at the same time as insulin from pancreatic  $\beta$ -cells (ratio of 1:100) which is thought, in the same way as its brain located cousin the beta-amyloid protein (active in Alzheimer's disease), to have pro-apoptotic<sup>23</sup> activity; a function which may be of significance in the progression of T2D. Amylin analogues have been developed primarily by Amylin Corporation and one, pramlintide, has been approved by the FDA under the brand **Symlin** to lower glucose in both T1D and T2D patients. It is the only drug approved to lower blood glucose in T1D other than insulin itself. It delays gastric emptying which has the effect of slowing the rate of glucose absorption following a meal but it also inhibits the secretion of glucagons which reduces the production of glucose by the liver (through gluconeogenesis) after a meal.

As the above suggests, the issues surrounding T2D therapy have been approached from many different angles however there are problems with many of these approaches whether through side-effects, hypoglycaemia, and oedema or weight gain. The profile of STX03 has some unique properties which may make it a drug of choice in the armamentarium to treat this disease.

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<sup>20</sup>also called glitazones.

<sup>21</sup>the peroxisome proliferators-activated receptors, which are key transcription factors regulating gene expression.

<sup>22</sup>prandial is the medical terminology for a meal and is the common word used when describing pre or post metabolic events surrounding a meal and related to the administration of a drug such as insulin.

<sup>23</sup>a form of induced cell death.

## The Diabetes Mellitus market

The WHO has declared diabetes to be a global disease of epidemic proportion affecting as many as 150 million people worldwide and projected to more than double by 2025<sup>24</sup>. Diabetes is a collection of diseases consisting primarily of Type 1 diabetes mellitus (T1DM) and Type 2 diabetes (T2D). T1DM is estimated to represent about 10 percent of the market with T2D accounting for the remainder<sup>25</sup>. The primary treatment for T1DM is insulin in its various formulations whereas T2D treatment is based primarily on oral anti-diabetics (OAD) and a smaller number of injectable agents (e.g., the amilyn and GLP-1 agonists).

We have outlined in the accompanying tables a summary of the key anti-diabetic product sales based on IMS data for 2007 for the seven major markets (US, Japan, UK, France, Germany, Spain and Italy) and an overview of the total market in that year and projections for 2011. From these projections, we estimate that growth through 2011 will be in the 20 percent range driven by strong prevalence data and some very interesting pipeline candidates making their way to market in that period (generating an estimated US\$8 billion in revenues). The underlying OAD growth appears rather tepid at 3 percent per annum but that does not include the bulk of the US\$9 billion we are estimating for pipeline products most of which are for the OAD/IAD<sup>26</sup> market. Out of the twelve compounds to be launched in the 2007-2017 period (which does not include STX03), only two are insulin-related products and are new dosage forms which will likely cannibalise existing products.

What one can conclude from this analysis is that the dynamics of the diabetes market, overall, remain very strong. Population dynamics in this market are reminiscent of the projected WHO growth rates which are in the 5% per annum range. As seen in the accompanying table, our 2020 estimate is just below the WHO estimate at 334 million afflicted with all forms of diabetes.

<sup>24</sup> King H. et al, *Diabetes Care* (1998); 21: 1414-1431

<sup>25</sup> Rodbard HW and the AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. *Endocrine Pract.* (2007);**13** (suppl. 1):3:68

<sup>26</sup> Oral Anti-Diabetics and Injectable Anti-Diabetics separate from the insulin market.

## Market profile of diabetes

7 major markets (US\$m)	2007	2012	
OAD market segment			
α-Glucosidase inhibitors	727	600	
Amilyn	50	250	
Biguanides	780	1,000	
DPP-IV inhibitors	597	2,200	
DPP-IV inhibitors/Metformin	74	250	
TZD/Glitazones & combinations	6,000	5,500	
GLP-1 agonists	592	200	
Meglinities	569	400	
Sulfonylureas	908	990	
Sulfonylureas/biguanide combo	166	200	
<b>Total</b>	<b>10,463</b>	<b>11,590</b>	<b>3%</b>
<b>Insulin</b>			
Animal insulins	5	5	
Fast acting human insulin analogue	2,811	3,600	
Intermediate acting human insulin analogue	676	600	
Human insulin analogue combination	1,844	2,150	
Human insulin analogue-long acting	2,507	3,700	
Other brands + generics	2,200	6,000	
<b>Total</b>	<b>10,043</b>	<b>16,055</b>	<b>15%</b>
<b>Pipeline</b>	<b>0</b>	<b>9,000</b>	
<b>Total Market (7 MM)</b>	<b>20,506</b>	<b>36,645</b>	
<b>Total Market (Global)</b>	<b>28,090</b>	<b>50,199</b>	<b>20%</b>

*Source: IMS and Objective Capital estimates*

In such a market, there is considerable room for a new market entrant, particularly one with a very interesting twist attached to it!

## Isosteviol and diabetes market model

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
<b>Global Population</b>														
US	300	303	306	309	312	315	318	322	325	328	331	335	338	341
Japan	125	126	128	129	130	131	133	134	135	137	138	139	141	142
Western Europe	393	397	401	405	409	413	417	421	426	430	434	438	443	447
RoW	5,726	5,783	5,841	5,900	5,958	6,018	6,078	6,139	6,200	6,262	6,325	6,388	6,452	6,517
<b>Total</b>	<b>6,544</b>	<b>6,609</b>	<b>6,676</b>	<b>6,742</b>	<b>6,810</b>	<b>6,878</b>	<b>6,947</b>	<b>7,016</b>	<b>7,086</b>	<b>7,157</b>	<b>7,229</b>	<b>7,301</b>	<b>7,374</b>	<b>7,448</b>
<b>Prevalence of diabetes (%)</b>														
US	6.5%	6.6%	6.6%	6.7%	6.8%	6.8%	6.9%	7.0%	7.0%	7.1%	7.2%	7.3%	7.3%	7.4%
Japan	7.1%	7.2%	7.2%	7.3%	7.4%	7.5%	7.5%	7.6%	7.7%	7.8%	7.8%	7.9%	8.0%	8.1%
Western Europe	7.4%	7.5%	7.7%	7.9%	8.0%	8.2%	8.3%	8.5%	8.7%	8.8%	9.0%	9.2%	9.4%	9.6%
RoW	2.5%	2.6%	2.6%	2.7%	2.7%	2.8%	2.8%	2.9%	2.9%	3.0%	3.0%	3.1%	3.2%	3.2%
<b>Total</b>	<b>23.5%</b>	<b>23.8%</b>	<b>24.2%</b>	<b>24.5%</b>	<b>24.9%</b>	<b>25.2%</b>	<b>25.6%</b>	<b>26.0%</b>	<b>26.3%</b>	<b>26.7%</b>	<b>27.1%</b>	<b>27.5%</b>	<b>27.9%</b>	<b>28.3%</b>
<b>Prevalence of diabetes (millions)</b>														
US	20	20	20	21	21	22	22	22	23	23	24	24	25	25
Japan	9	9	9	9	10	10	10	10	10	11	11	11	11	11
Western Europe	29	30	31	32	33	34	35	36	37	38	39	40	42	43
RoW	143	147	152	157	161	166	171	176	182	187	193	199	205	211
<b>Total</b>	<b>201</b>	<b>206</b>	<b>212</b>	<b>218</b>	<b>225</b>	<b>231</b>	<b>238</b>	<b>245</b>	<b>252</b>	<b>259</b>	<b>267</b>	<b>274</b>	<b>282</b>	<b>290</b>
<b>Split of Type 2/Type 1 diabetes</b>														
Type 1	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
Type 2	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%
<b>Type 2 diabetes patient population (millions)</b>														
US	18	18	18	19	19	19	20	20	21	21	21	22	22	23
Japan	8	8	8	8	9	9	9	9	9	10	10	10	10	10
Western Europe	26	27	28	29	29	30	31	32	33	34	35	36	37	39
RoW	129	133	137	141	145	150	154	159	163	168	173	179	184	190
<b>Total</b>	<b>181</b>	<b>186</b>	<b>191</b>	<b>197</b>	<b>202</b>	<b>208</b>	<b>214</b>	<b>220</b>	<b>227</b>	<b>233</b>	<b>240</b>	<b>247</b>	<b>254</b>	<b>261</b>
Estimated rate of diagnosis for T2D	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%
<b>Estimated target T2D population</b>	<b>126.4</b>	<b>130.0</b>	<b>133.8</b>	<b>137.6</b>	<b>141.6</b>	<b>145.7</b>	<b>149.9</b>	<b>154.2</b>	<b>158.6</b>	<b>163.2</b>	<b>167.9</b>	<b>172.8</b>	<b>177.8</b>	<b>182.9</b>
Target average drug cost per month(*)	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
Average number of months of treatment(**)	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Total average annual cost per treatment	600	600	600	600	600	600	600	600	600	600	600	600	600	600
Estimated discount to current treatment costs	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
<b>Estimated Price for isosteviol (\$US\$)</b>	<b>600</b>	<b>600</b>	<b>600</b>	<b>600</b>	<b>600</b>	<b>600</b>	<b>600</b>	<b>600</b>	<b>600</b>	<b>600</b>	<b>600</b>	<b>600</b>	<b>600</b>	<b>600</b>
<b>Total market potential for isosteviol (US\$ billions)</b>														
Global potential	\$76	\$78	\$80	\$83	\$85	\$87	\$90	\$93	\$95	\$98	\$101	\$104	\$107	\$110
<b>Key markets (US, Japan, Western Europe, 10% of ROW)</b>	<b>\$27</b>	<b>\$28</b>	<b>\$29</b>	<b>\$29</b>	<b>\$30</b>	<b>\$31</b>	<b>\$32</b>	<b>\$33</b>	<b>\$33</b>	<b>\$34</b>	<b>\$35</b>	<b>\$36</b>	<b>\$37</b>	<b>\$38</b>

(\*) Average cost of OAD's from ORAL PHARMACOLOGICAL AGENTS FOR TYPE 2 DIABETES: SULFONYLUREAS, MEGLITINIDES, METFORMIN, THIAZOLIDINEDIONES, a-GLUCOSIDASE INHIBITORS, AND EMERGING APPROACHES; Chapter 14 - Joseph L. Evans, Ph.D. and Robert J. Rushakoff, M.D. August 26, 2002 in DIABETES AND CARBOHYDRATE METABOLISM. Ira D. Goldfine and Robert J. Rushakoff - Editors, Endotext.com.

Source: literature data and Objective Capital estimates

## STX03: a very novel approach to T2D

### Background

It has been known for a long time that the South American plant *Stevia Rebaudiana Bertoni* conferred metabolic benefits to the native population who drank it in a tea form. More recently, the leaves of this plant have been harvested for their inherent sweetness (3000 times sweeter than sugar) which, although slow to emerge, lasts longer than sugar itself. Coca Cola and Cargill have developed this product trademarked **Rebiana** (Cargill's brand is **Truvia** and Pepsi's version is **Pure Via**) with it slated to hit the market in 2009 in a number of markets. As with all artificial sweeteners, the testing and approval process has been lengthy. The main extracted products of this plant are stevioside and rebaudioside but the building block for this new generation of sweeteners is steviol, a breakdown product of stevioside. Another company, Blue California, claims to have developed an economical industrial synthetic route for rebaudioside A which it plans to produce commercially in 2009<sup>27</sup>. These sweeteners have yet to be approved by the FDA as food additives but Stevia-based sweeteners are very prevalent in Japan and represent 40 percent of the market. A recent report from the WHO<sup>28</sup>, concluded that:

*The Committee concluded that stevioside and rebaudioside A are not genotoxic in vitro or in vivo and that the genotoxicity of steviol and some of its oxidative derivatives in vitro is not expressed in vivo. The no-observed-effect level (NOEL) for stevioside was 970 mg/kg bw per day in a long-term study evaluated by the Committee at its fifty-first meeting.*

*...stevioside has shown some evidence of pharmacological effects in patients with hypertension or with type-2 diabetes at doses corresponding to about 12.5–25 mg/kg bw per day (equivalent to 5–10 mg/kg bw per day expressed as steviol)...*

*...A temporary ADI of 0–2 mg/kg bw was established for steviol glycosides, expressed as steviol, on the basis of the NOEL for stevioside of 970 mg/kg bw per day (or 383 mg/kg bw per day expressed as steviol) in the 2-year study in rats and a safety factor of 200. This safety factor incorporates a factor of 100 for inter- and intraspecies differences and an additional factor of 2 because of the need for further information.*

***In fact, the only hesitation that this analysis had about the safety of steviol as a food additive was the reported anti-hypertensive effect of this substance in Type-2 diabetics which they hypothesized could result in hypotension in certain normotensive subjects!***

Hence, all in all, the extensive testing of extracted steviol, stevioside and its cousin rebaudioside as sweetener additives appears to show that it is deemed to be safe. Steviol (the API of STX03) is a de-glycosylated metabolite of stevioside, the native substance in the *Stevia* plant. The extensive safety testing of stevioside and steviol bodes well for the further development of STX03.

<sup>27</sup>see Blue California website ([http://www.bluecal-ingredients.com/whatsnew/pr\\_20071113.php](http://www.bluecal-ingredients.com/whatsnew/pr_20071113.php))

<sup>28</sup>Benford D.J. et al. In Safety of certain Food Additives (2006) (section on Steviol Glycosides) WHO Food Additives Series: 54; p117-144

STX03 stems from the work of three Endocrine specialists based at the Aarhus University Hospital in Denmark. Dr Jeppeson is a recognised expert in the stevioside field who along with Professors Hermansen and Dr Gregerson were able to first demonstrate the insulinotropic, and anti-hypertensive properties of this class of compounds. They went on to form a company called Stevia Pharmaceuticals which was recently partly acquired by Bridge.

### **STX03: a novel OAD with anti-hypertensive properties**

Steviol (and its cousin isosteviol) are both derived from the native parent compound stevioside, the predominant glycoside in the plant *Stevia Rebaudiana Bertoni*. Steviol is derived from stevioside through the de-glycosylation of the latter in a very simple chemical reaction. Steviol and isosteviol are the metabolites in the gut of stevioside breakdown<sup>29</sup>. The resulting compound, STX03, had been found, in a glucose independent fashion, to exert both insulinotropic and glucagonostatic<sup>30</sup> effects in the presence of high levels of glucose (this equals and increases its insulin sensitivity to glucose). This in turn results in an increased uptake of glucose into skeletal muscles. There are several available OAD's that have similar effects but STX03 differentiates in several important ways from drugs that are on the market by:

- reducing blood pressure;
- a positive effect on lipid metabolism;
- preserving pancreatic ( $\alpha$ - and  $\beta$ -) islet cells through a lipotoxicity and glucotoxicity-protective effect;
- not inducing any observed weight gain.

As mentioned earlier, this compound is part of a family of compounds whose toxicity has been extensively tested as food additives and are the subject of a full evaluation submitted to the WHO<sup>31</sup>.

### **STX03: putative mechanism of action?**

The field of metabolic drugs is a very complex one and it usually is a tall order to present with any degree of certainty the precise mechanism through which a drug of this type acts. Metabolism is the central core of the life of a cell and evolution has created what one might call a fault-tolerant network of reactions that are finely regulated so as to be ready to react swiftly to a wide variety of metabolic stimuli. Glucose is one of the main fuels of the system so we should expect that its actions, transport, metabolism and transformations are key components to the life of a cell. As explained above, there is a complex system of regulation in place for dealing with plasma glucose involving an elaborate set of hormones dominated by insulin and glucagon. The breakdown of this system results in a set of diseases called diabetes.

<sup>29</sup>also, steviol has been found to be converted by gut bacteria into isosteviol

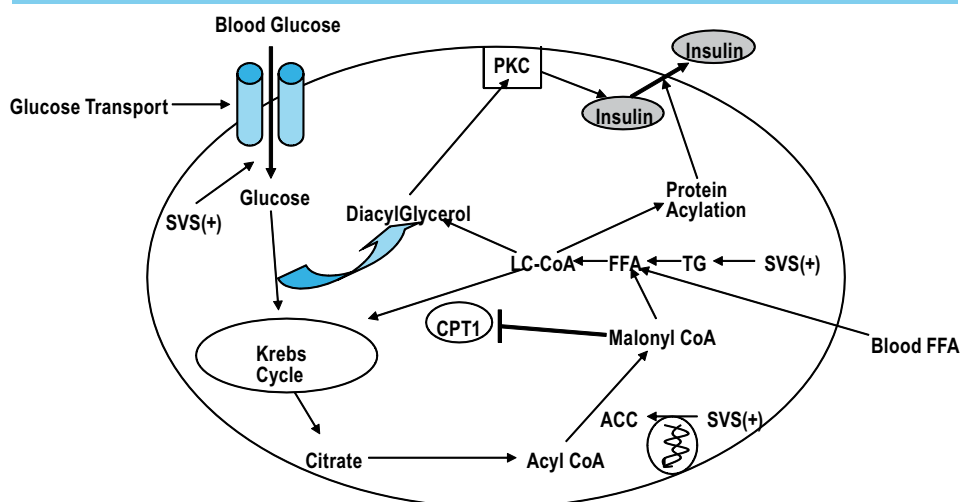
<sup>30</sup>increased insulin release and glucagon suppression

<sup>31</sup>see WHO reference above

The original observation that stevioside (the parent of STX03 or isosteviol) lowered blood pressure acted as a catalyst to look at the metabolic effects of this class of compounds. Stevioside itself is metabolised by the bacterial flora of the gut into steviol and isosteviol. The metabolites themselves are not further processed in the gut and are absorbed into plasma to exert an effect. It is known that steviol is converted to isosteviol in the gut and that it is isosteviol that is absorbed into plasma to exert its effect. However, stevioside itself when given orally does not raise the level of these metabolites in plasma by itself.

The precise MoA of isosteviol/STX03 is not known at this time but it is believed that it exerts its effect principally through the increased activity of a key metabolic enzyme called acetyl CoA carboxylase or ACC. The Aarhus group had earlier shown, *in vitro*, that stevioside acted to prevent the effects of glucose toxicity (i.e., in the presence of repeated stimulation with glucose) through increased ACC activity via a mechanism that results in the increased active transport of glucose into the cell and insulin secretion. This improvement in  $\beta$ -cell insulin sensitivity (though an improvement of GSIS<sup>32</sup>) was shown to result from the activation of free fatty acid metabolism and the accumulation of long chain Coenzyme A (shown in the diagramme as LC-CoA) as a substrate for the protein acylation process that triggers insulin release (via a Protein Kinase C (PKC) driven mechanism)<sup>33</sup>. Concomitantly in the same study, the observed increase in glucose feeds into this scenario by increasing the synthesis of malonyl CoA through the actions of ACC-1 (the isoform of the enzyme active in this pathway), stimulating the conversion of triglycerides into free fatty acids (FFA) which combine with malonyl-CoA to generate LC-CoA. Normally, an enzyme called carnitine palmitoyl-transferase-1 (CPT1) will recycle these into the metabolism but the accumulation of malonyl-CoA inhibits this process. In parallel to this, the glucose transported into the cell is transformed into pyruvate which generates acetyl CoA which goes on to activate the cells membrane potential by closing ATP-dependent potassium channels and increasing the levels of intracellular calcium.

### Stevioside effects on insulin sensitivity



Source: Objective Capital adapted from Chen J. et al, *Am J, Physiol Endocrinol. Metab.*;292:E1906-E1916

<sup>32</sup>Glucose-Stimulated Insulin Secretion.

<sup>33</sup>Chen J. et al, *Am J.Physiol Endocrinol Metab* 292: E1906-E1916

Now all of this is rather complex but the summary of it is that three processes conspire to increase  $\beta$ -cells insulin sensitivity:

- the accumulation of LC-CoA through blockage of the CPT-1 driven oxidation/metabolism process;
- the availability of this excess LC-CoA is a signaling mechanism to processes involved in exocytosis (or the cellular expelling mechanism) which is the way in which insulin is released;
- finally the conversion of glucose to pyruvate and then to acetyl CoA which influences the closure of ATP-dependent membrane potassium channels which depolarises the cell's membrane, opens up calcium channels, results in an increase in intracellular calcium and promotes the expelling of insulin containing granules.

It is in this way that stevioside, the parent compound of STX03, increases the cell's insulin sensitivity to glucose through GSIS.

As a metabolite of stevioside and then steviol, isosteviol (STX03) exhibits a more consistent absorption and bioavailability profile than its cousin. The conversion of steviol to isosteviol is acid dependent and the genetic variability of gut acidity translates into variable absorption into the plasma and hence, bioavailability. It follows that one would expect a more consistent effect on all of the parameters that have been shown to be affected by the two original compounds tested. This should lead to more consistent levels of the drug with its concomitant effect on insulin sensitivity, blood pressure with the added benefit of increasing HDL, a rather unique and important characteristic in this patient population. The principals of Stevia Pharmaceuticals surmised that it was likely that the deglycosylated derivative of the parent compound would act through similar mechanisms.

### **STX03: the data**

In looking for an ideal candidate for the treatment of Type-2 diabetes and possibly the concomitant treatment of co-morbid hypertension, the group at Aarhus conducted an *in vivo* animal experiment to test the effects of isosteviol (STX03) in a mouse diabetic model. The results were impressive indeed and outlined in a recently published paper<sup>34</sup>. Stevioside had been tested in early human clinical trials for both lowering of blood pressure in mild hypertension and the ability to lower blood sugar in T2D patients. Both trials showed early promise but the acid-dependant conversion of steviol into isosteviol made the absorption/bioavailability profile of the former too variable; isosteviol is absorbed unchanged into the blood making it a better candidate to go with.

The group then turned its attention to the development of STX03, the precise mechanism of action of which remains unclear at this time. It is likely that this drug's actions will parallel those of stevioside and steviol although in the only study published on the drug, STX03 also seems to have an effect on lipid metabolism (through the lowering of triglycerides), a unique and attractive property for a putative medication in the T2D arena.

<sup>34</sup>Nordentoft I et al; *Diab. Obesity & Metab.*(2008) **10**(10):939-949

This study was carried out in a diabetic mouse model called KKAY which progresses more rapidly from the pre-diabetic insulin resistance stage to full blown diabetes in a relatively predictable, developmental staged, age-dependant fashion, reaching the insulin-deficient stage at 12 weeks of age. The study was carried out over 14 weeks (i.e., two beyond the full blown diabetic stage) with an interim plasma measurement at 9 weeks and a full blown blood workup followed by islet isolation and gene expression analysis.

Three groups of animals were studied: a normal control, a KKAY control (untreated) and a treated one. The objective was to look at the effect of isosteviol given orally on fasting glucose, plasma insulin, insulin sensitivity index and plasma triglycerides. Additionally, using a gene microarray, the level of genes that are implicated in insulin expression,  $\beta$ -cell function and insulin signaling pathways were measured to study the development of insulin resistance during its use in the animal.

The results are summarised in the table below.

### Summary of preclinical animal and *in vitro* data on isosteviol (STX03)

<b><i>In Vivo</i> Data</b>	<b>Function/Measurement</b>	<b>Effect versus Untreated at 9 weeks vs 5 weeks</b>	<b>Interpretation/Meaning</b>
Plasma Glucose	degree of Insulin-induced metabolism	Decrease of 38% (p<0.01)	Improved Insulin Function
Plasma Insulin	measure of Insulin resistance	Decrease of 65% (p<0.001)	cells less resistant to Insulin action
Insulin Sensitivity (Glucose-Insulin Index)	Sensitivity of cells to insulin action	Increased (p<0.01)	Improved sensitivity to Insulin
Plasma Triglyceride	Measure of Lipotoxicity	Decreased	Better Lipid metabolism/reduced damage to glucose metabolic function
Body Weight	idem	Decreased (~13%)	improved sugar and fat metabolism resulting in loss of weight
Food Intake	idem	No difference	Effects seen are independent of CNS-related Hunger/Satiation pathways
<b>Microarray Data</b>			
Glut2, Beta2/NeuroD/Pdx1	Glucose Transport/Insulin Expression/ beta-cell maturation	Upregulated	Improved Glucose transport and Insulin function
C/EBPalpha/11-beta-HSD-1	Breakdown of fat in adipose tissue/ Gluconeogenesis	Downregulated	reduced Release of toxic fat and synthesis of Glucose to go into Plasma
IR/visfatin/Ins2/Akt1	Insulin signalling pathways	No effect	Indicates normal signalling functionality unaffected by drug action
Foxa2/Pax6/Nkx2.2/Nkx6-1	beta-cell development factors/ somatostatin function	upregulated (1.9-2.6x)	consistent with increased somatostatin function
somatostatin	Insulin Sensitization/inhibitor of Insulin Secretion	upregulated	consistent with increased insulin sensitisation and decreased transport into plasma
Ins1	Insulin Gene	No effect	might be due to an artifact of the microarray system
<b><i>In Vitro</i> Data</b>			
Pdx1/Beta2/NeuroD/Glut2/Ins1	Insulin Expression/Beta cell maturation/Glucose transport	Upregulated	Improved glucose transport and insulin function
C/EBPalpha/11-beta-HSD-1	Breakdown of fat in adipose tissue/ Gluconeogenesis	Downregulated	reduced fat breakdown/lower lipotoxicity/ reduced damage to glucose metabolic function
IR/Visfatin/AKT1	Insulin Signalling Pathways	Little effect	Indicates normal signalling functionality unaffected by drug action

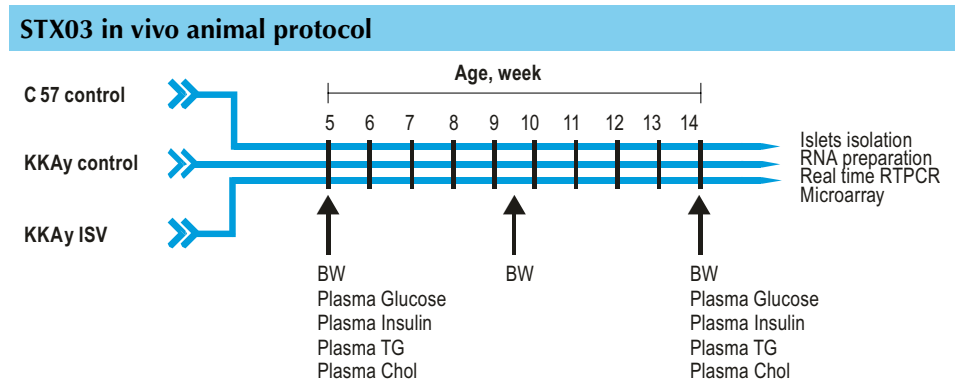
Source: Objective Capital, adapted from Nordentoft I. et. Al. in *Diab. Obesity & Metabol.* 2008 Sep;10(10):939-49

As can be seen, the animals treated with isosteviol showed a statistically significant reduction in plasma glucose, triglyceride and insulin as well as a dramatic decrease in the insulin sensitivity index (which translates into increased insulin sensitivity). The increase in insulin sensitivity coupled with an effect on lipid metabolism, if corroborated in humans, would establish a drug profile of major significance for this drug. This latter fact, if translated into humans with the increase in insulin sensitivity and decrease in triglyceride levels, could be of major significance in establishing a unique profile for this drug. In this study, the level of gene expression of all known genes implicated in Insulin expression,  $\beta$ -cell function and insulin resistance were, for the most part, increased or decreased in a statistically significant fashion versus the untreated KKAY control mouse, in a manner consistent with the improvement in overall  $\beta$ -cell function implying that isosteviol confers protection against both gluco- and lipo- toxicity prevalent in this model.

The increase in both insulin expression and insulin protein content seen in isosteviol treated animals prompted this group to look at whether or not isosteviol was able to stimulate GSIS functionality. To do so it isolated islet tissue to examine whether GSIS was being stimulated and compared it to the action of its cousin steviol which this group had previously demonstrated had a potent insulinotropic effect on isolated mouse islets<sup>35</sup>. At high doses of glucose, a maximal effect on insulin secretion was obtained and at low doses, no such stimulation was seen. When compared to steviol, at low concentrations, isosteviol was significantly more potent, at high concentrations, there was not significant difference.

The fact that isosteviol is highly insulinotropic at a high glucose concentrations but not at low concentrations is highly significant as regards the potential for hypoglycemia during treatment of patients, a major drawback of other insulin sensitizers such as glitazones (e.g., TZDs) and metformin.

Finally, animals treated with isosteviol (STX03) experienced an average loss of body weight of 13 percent.



Source: Bridge BioResearch

<sup>35</sup>Jeppeson PB et al; *Metabolism* (2000);**49**:208-214

### Data implications for drug profile

As analysts it is rare to be confronted with truly unique and important data from a preclinical study. In this regard, we usually look at preclinical data with a healthy dose of scepticism as safety and efficacy in many animal models do not necessarily translate into humans. Obesity models and diabetic models are reasonably indicative of safety and efficacy in man but only clinical trials will verify whether this is the case here. Nevertheless, the efficacy profile of isosteviol that is emerging from this study, if confirmed, is truly unique. Its effects on insulin expression and secretion along with putative effects on lipid metabolism, are a very powerful combination which fits well with the multifactorial risk issues that are prevalent in this patient population. If that is not enough, the putative inactivity of the drug at low glucose concentrations (as demonstrated *in vitro*) and the loss of weight observed, if translated into humans, would provide a unique improvement on the side-effect profile of some of the most commonly used OADs (metformin and TZDs).

In other words, a therapeutic and side-effect profile based on this preclinical work could make STX03 a formidable competitor in the T2D market. The combination of efficacy in the core indication (insulin sensitisation) combined with metabolic improvements (weight loss, triglyceride lowering) and a lack of potential for hypoglycaemia are the basis for a potent multifactorial T2D medication worthy to compete with the best of breed on the market or coming to market over the coming years.

### Competitive positioning

As we have noted earlier, the T2D market has been a very active one and many companies have marketed products or have pipeline candidates on their way to market. The rollout of medical therapy after diagnosis is broadly as follows:

- first intervention is 'lifestyle-related' with diet, weight control and exercise;
- if all fails first line treatment is generally metformin;
- when this stops working, a number of other drugs (glitazones, sulfonylureas, etc ) are used alone or in combination with metformin in an attempt to control blood glucose;
- third line treatment today would be to add incretin mimetics (Byetta) or DPP-IV/Januvia as monotherapy or more likely as combination with metformin and others.

In this scenario, the patient is on an inevitable treadmill towards insulin over a shorter or longer period of time. The approach with most potential (although not approved for this at this time) would be a combination of metformin or Actos and a DPP-IV inhibitor (Merck's **Januvia**) potentially as first line therapy particularly if DPP-IV inhibitors can be shown to be  $\beta$ -cell sparing. The only other approach which could attain a more competitive position in the market would be a once a

week injectable form of exenatide (**Byetta**) and the upcoming Liraglutide from Novo Nordisk, where weight loss, potential  $\beta$ -cell sparing activity, improvement in lipid profile, effective glucose lowering, low incidence of hypoglycaemia and restoration of good insulin sensitivity are a potentially very useful profile. The problem remains that this is an injectable and the drug does have some significant adverse effects (nausea, vomiting, dizziness, headaches, etc). In fact most of these drugs have one drawback or another and there is still considerable room for a 'cleaner' more effective approach.

The only other potential competitive force here is bariatric surgery which has shown significant potential not only in weight loss, but also in reversing the course on T2D in patients. It does not work in all patients and is not the most common medical approach.

However, none of this has the potential to modify the course of the disease and prevent both the micro- and macro-vascular complications of T2D which will ultimately lead to early mortality.

The factors that require control are multiple and include weight, blood pressure, blood glucose and lipid profile in addition to protecting  $\beta$ -cell function and implies the need for a more holistic approach to this disease. Hence a drug with the profile of STX03 would fit beautifully into this category of holistic approaches particularly when combined with lifestyle adjustments such as diet and increased exercise. Its lack of hypoglycaemia potential, combined with weight loss, a decrease in Triglycerides and a reduction in blood pressure, could make this one of the drugs of choice for early treatment. Most type 2 diabetics are hypertensive and the threshold for intervention for this co-morbidity is much lower than in non-diabetic patients. The key is to be able to treat early when pancreatic  $\beta$ -cell function is still at an early stage of degradation and STX03 holds the potential to provide protection against such progressive degradation.

Hence, if the  $\beta$ -cell protective effects, weight loss, blood pressure lowering, insulin sensitising functions of STX03 can be confirmed in the human clinicals, the emergence of such a treatment could have significant implications for the treatment of diabetes. It is possible that a drug of this kind could have the potential to be disease modifying rather than simply slowing down the progression of the disease.

### **STX03 revenue model**

When faced with a profile of the power we have seen in preclinical work, it is tempting to go off the deep end and extrapolate in a way that reasonable observers would consider to be out of control! Our experience tells us that nothing is ever what it seems in this field and that the road to an established profile is a long and tortuous one; filled with very large potholes and potentially insurmountable obstacles. Having pinched ourselves to remain humble in the face of such uncertainty, we are nevertheless moved to speculate on the potential for this drug which is on the verge of entering a Phase IIa trial, probably in early 2009.

Based on published data on T2D drug costs for the US we have estimated an average price of around US\$80. Taking into consideration that drug prices can be significantly lower outside of the US, we have discounted this price by around 40% as the basis for pricing. We believe that this is potentially a gross underpricing of what a drug of this profile might cost but the profile is not yet established clinically in humans so we will hold our powder dry until the Phase II data is in. The reason that this may be the case is that patients with T2D are co-morbid with hypercholesterolaemia (i.e., high cholesterol), tend to be overweight or obese and have hypertension (we have not even mentioned the BP-lowering properties of this drug as we are faced with an embarrassment of riches already!). A drug profile that is aimed at all of these has a cost/benefit analysis that would translate into a much higher price and should attract significant reimbursement as part of a prevention programme. Nevertheless, we prefer to remain on the conservative side at this time.

Similarly, our market penetration numbers are standard for this industry. We are estimating a modest 5-7 percent penetration of the market in what is a fiercely competitive market with major, very valid competition. By the time STX03 hits the market, it is likely that Byetta LAR, a once a week amylin agonist injection will be on the market. Better DPP-IV inhibitors will have made their way into patients and other novel approaches may have also transitioned from the clinical trial realm through the regulatory maze to market. Hence, we believe that it is prudent not to get too carried away despite the potentially attractive profile of this product. The result is that we believe that a product of this nature could reach a revenue level in the US\$1.8-2.3 billion range after five years; a very modest number for a potentially explosive, market-disruptive drug profile.

### Projected revenue for isosteviol (STX03)

Period	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Estimated target T2D population	126.4	130.0	133.8	137.6	141.6	145.7	149.9	154.2	158.6	163.2	167.9	172.8	177.8	182.9	188.2	193.6
Target average drug cost per month*	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
Average number of months of treatment**	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Total average annual cost per treatment	600	600	600	600	600	600	600	600	600	600	600	600	600	600	600	600
Estimated discount to current treatment costs	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Estimated price for isosteviol (US\$)	600	600	600	600	600	600	600	600	600	600	600	600	600	600	600	600
<b>Total market potential for isosteviol (US\$billions)</b>																
Global potential	\$76	\$78	\$80	\$83	\$85	\$87	\$90	\$93	\$95	\$98	\$101	\$104	\$107	\$110	\$113	\$116
Key markets (US, Japan, Western Europe, 10% of ROW)	\$27	\$28	\$29	\$29	\$30	\$31	\$32	\$33	\$33	\$34	\$35	\$36	\$37	\$38	\$39.1	\$40.1

#### Isosteviol - projected revenue

##### Core model

Estimated market penetration	0.4%	2.5%	4.5%	5.0%	5.3%	5.4%	5.5%	5.6%
Estimated sales (in US\$millions)	\$117	\$752	\$1,390	\$1,585	\$1,724	\$1,803	\$1,885	\$1,970
<b>Estimated sales (in £ millions)</b>	<b>£76</b>	<b>£485</b>	<b>£897</b>	<b>£1,022</b>	<b>£1,112</b>	<b>£1,163</b>	<b>£1,216</b>	<b>£1,271</b>

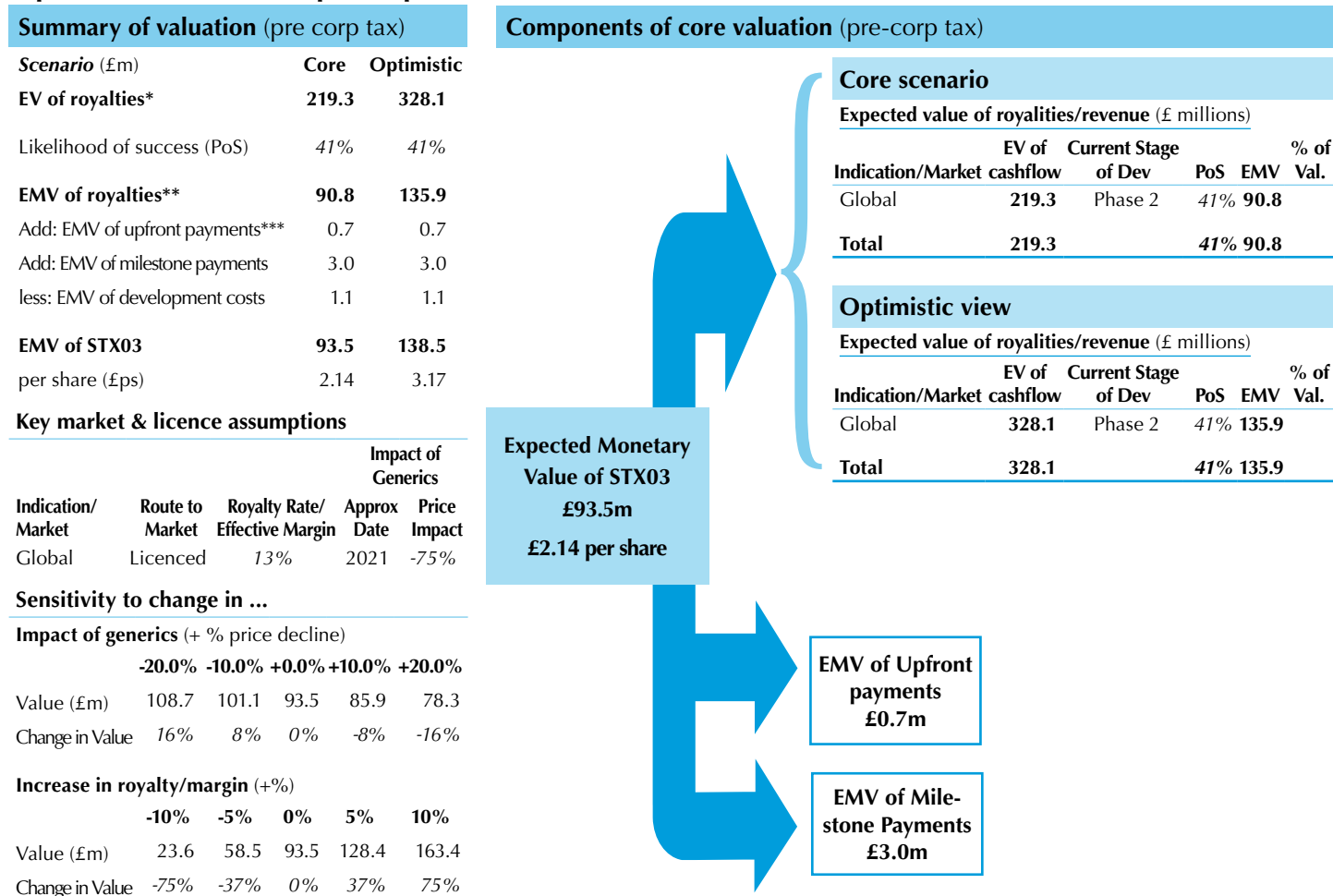
##### Optimistic model

Estimated market penetration	0.6%	3.5%	6.0%	6.5%	6.7%	6.9%	7.1%	7.1%
Estimated sales (in US\$millions)	\$176	\$1,053	\$1,853	\$2,060	\$2,180	\$2,304	\$2,433	\$2,497
<b>Estimated sales (in £ millions)</b>	<b>£114</b>	<b>£679</b>	<b>£1,195</b>	<b>£1,329</b>	<b>£1,406</b>	<b>£1,486</b>	<b>£1,570</b>	<b>£1,611</b>

\* Average cost of OAD's from Diabetes and Carbohydrate Metabolism, Goldfine I & Rushakoff R., Editors, Endotext.com. Other published information

Source: literature data and Objective Capital estimates

## Expected value of STX03 (pre-corporate tax)\*\*\*\*



\* The expected value (EV) of royalties has been calculated assuming our explicit revenue forecasts, a period of further growth until generics enter the market, and a period of further market growth and decline as competing products enter the market.

\*\* Expected monetary values (EMV) refer to risked values

\*\*\* upfront, milestone and development costs have been risked based on the probability of being received/incurred

\*\*\*\* valuation shown before Bridge's share

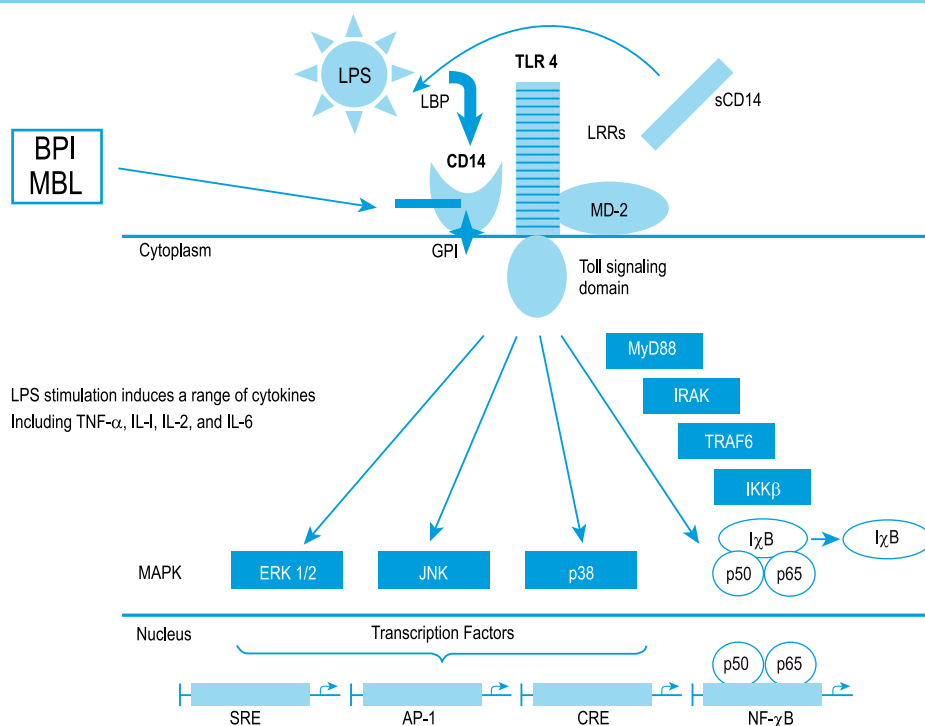
## CD14 profile, development and licensing

CD14 is part of a family of mediators that are ligands for the Toll-like receptor family involved in a signaling process of innate immunity and inflammation in cells. As shown in the accompanying diagramme, CD14 is involved in the activation of the Toll-like receptor number 4 or TLR4 which itself triggers a signaling cascade which eventually leads to the release of DNA transcription modulators that activate the transcription of various inflammatory substances called cytokines. Diabetes is amongst a family of autoimmune diseases driven by these mechanisms which are known to underlie the progression of these pathologies.

In diabetes, it is believed that a more fatty diet leads to an increase in gram-negative bacteria and the release of an endotoxin called LPS or lipopolysaccharide. LPS has the ability to bind to membrane-bound CD14 which then activate the TLR cascade. This binding can be inhibited by several other endogenous factors but in fact, soluble CD14 does bind LPS and has been shown in animal studies to increase glucose tolerance and improve the animal's triglyceride profile. This implies that CD14 binding and sequestration of LPS might reduce the persistent inflammation that causes progressive insulin resistance.

As an early programme of Bridge, this has now been superseded in importance by the STX03 programme (as has the parallel BPI and MBL; LPS blocking programmes). Nevertheless, this is a separate and possibly useful approach which the company might pursue by looking for a 'repositioned' CD14 small molecule mimic which could then be tested in a small Phase I/II proof of concept clinical trial before being licensed early to a potential partner.

### CD14 driven inflammatory pathway



Source: Bridge BioResearch Corporate Presentation

## Expected value of CD14 (pre-corporate tax)

### Summary of valuation (pre corp tax)

Scenario (£m)	Core	Optimistic
<b>EV of royalties*</b>	<b>96.0</b>	<b>97.1</b>
Likelihood of success (PoS)	5%	5%
<b>EMV of royalties**</b>	<b>4.8</b>	<b>4.9</b>
Add: EMV of upfront payments***	0.2	0.2
Add: EMV of milestone payments	0.4	0.4
less: EMV of development costs	0.3	0.3
<b>EMV of STX03</b>	<b>5.0</b>	<b>5.1</b>
per share (£ps)	0.11	0.12

### Key market & licence assumptions

Indication/Market	Route to Market	Royalty Rate/Effective Margin	Approx Date	Price Impact	Impact of Generics
Global	Licensed	5%	2024	-50%	

### Sensitivity to change in ...

Impact of generics (+ % price decline)					
	-20.0%	-10.0%	+0.0%	+10.0%	+20.0%
Value (£m)	5.5	5.3	5.0	4.7	4.5
Change in Value	11%	5%	0%	-5%	-11%

### Increase in royalty/margin (+%)

	-10%	-5%	0%	5%	10%
Value (£m)	0.2	0.2	5.0	9.8	14.6
Change in Value	-96%	-96%	0%	96%	192%

### Components of core valuation (pre-corp tax)

**Expected Monetary Value of CD14**  
**£5.0m**  
**£0.11 per share**

#### Core scenario

Expected value of royalties/revenue (£ millions)					
Indication/Market	EV of cashflow	Current Stage of Dev	PoS	EMV	% of Val.
Global	96.0	Identification	5%	4.8	
<b>Total</b>	<b>96.0</b>		<b>5%</b>	<b>4.8</b>	

#### Optimistic view

Expected value of royalties/revenue (£ millions)					
Indication/Market	EV of cashflow	Current Stage of Dev	PoS	EMV	% of Val.
Global	97.1	Identification	5%	4.9	
<b>Total</b>	<b>97.1</b>		<b>5%</b>	<b>4.9</b>	

**EMV of Upfront payments**  
**£0.2m**

**EMV of Milestone Payments**  
**£0.4m**

\* The expected value (EV) of royalties has been calculated assuming our explicit revenue forecasts, a period of further growth until generics enter the market, and a period of further market growth and decline as competing products enter the market.

\*\* Expected monetary values (EMV) refer to risked values

\*\*\* upfront, milestone and development costs have been risked based on the probability of being received/incurred

## Business Strategy

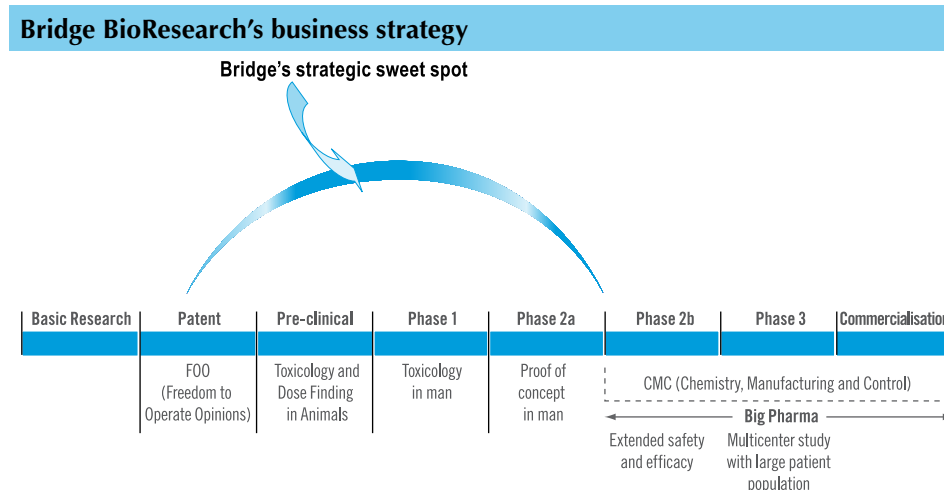
As the name of the company implies, Bridge aims to act as a bridge between academic or quasi-academic benchtop/preclinical development of drugs in the metabolic area to PoC development prior to licensing to medium-large, global, regional or speciality pharma companies. Bridge invests at an early stage and attempts to bring the drug candidate through early clinical development prior to when clinical development costs escalate significantly. Bridge, in common with many emerging pharma and biotech companies, positions itself to receive upfront and clinical development milestone payments from its partners and, after the launch of the drug, royalty payments for the life of the drug.

The cost of developing a drug will range between US\$500 million and US\$1.5 billion and take as much as twelve years from the conceptual stage to commercialization. While the risk of failure tends to decrease particularly between Phase I and Phase II. Bridge positions itself as the developer in that period where significant de-risking of drug development occurs.

Using a 'virtual' business model, Bridge keeps its staff costs low and outsources all preclinical and clinical work to CRO's who can then conduct, under its supervision, 'low cost' trials in appropriate countries and clinical settings. Drug materials are 'farmed' out to specialty manufacturers who then create a 'scaled-up' process capable of generating GMP<sup>36</sup>-level materials. All clinical work is done according to the highest regulatory standards at recognised clinical centres.

### Due diligence, licensing and intellectual property

The basis upon which Bridge is willing to acquire or license a particular property is not only dependent on the validity of the target and the potential of the compound itself, but also very much on the intellectual property position of the products. In common with many companies using this business model, Bridge conducts extensive scientific, clinical and IP due diligence before it agrees, definitively, to take on a project.



Source: Bridge BioResearch Corporate Presentation

<sup>36</sup>Good Manufacturing Practice or GMP material is a standard that is laid down by regulatory authorities for clinical-grade materials.

## 2-OHOA

The licensing of this lead candidate in January 2006 is based on a Patent Licensing Agreement with the University of the Balears Isles in Spain with a licensing fee of 12.5 percent of net revenues to Bridge subject to minimums. Bridge received a favourable freedom to operate (FTO) opinion from consulting patent lawyers. 2-OHOA is covered by a family of patents<sup>37</sup> covering the use of 2-OHOA and derivatives as anti-tumour, anti-hypertensive and weight-reducing agents. The priority dates of these patents are 2001 which implies that they would expire in 2022 without any of the extensions that are granted in certain jurisdictions (usually five years in the US for example). The FTO opinion covers both the hypotensive and anti-obesity indications of this drug.

## Stevia Pharma compounds

In May of 2008, Bridge acquired a 50.066 percent majority interest in Stevia Pharmaceuticals based in Denmark. The primary pharmaceutical assets of this entity were a series of compounds derived from the main active component of the plant *Stevia*, stevioside. The intellectual property of the company covers the use of stevioside derivatives, steviol and isosteviol as treatments for insulin resistance and any other diseases associated with insulin resistance<sup>38</sup>. The priority date of this patent is 2000 with an expiry date in 2021 without the exclusivity extension available in various jurisdictions. The FTO opinion received confirms the validity of these patents for the treatment of T2D.

In this transaction, Bridge has an option to acquire further shares to bring its interest up to 60.5 percent under certain conditions involving the stage of clinical development and the achievement of approval to enter a Phase IIa trial and upon the commencement of patient recruitment.

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<sup>37</sup>WO 05/041691/EP1435235/US2005014831

<sup>38</sup>WO 2008/031439

# Financials

Profit & Loss					
Year ending 31 Dec (£m)	2006A	2007A	2008E	2009E	2010E
<b>Revenues</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>
Upfront payments	0.0	0.0	0.0	0.0	2.5
Milestone payments	0.0	0.0	0.0	0.0	0.0
Licensing/royalty revenues	0.0	0.0	0.0	0.0	0.0
<b>Net revenues</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>2.5</b>
Cost of sales	0.0	0.0	0.0	0.0	0.0
<b>Gross profits</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>2.5</b>
Gross margins	NM	NM	NM	NM	NM
Other operating income	0.0	0.0	0.0	0.0	0.0
<b>Administrative expenses</b>	<b>0.3</b>	<b>0.4</b>	<b>1.4</b>	<b>2.4</b>	<b>2.6</b>
Depreciation	0.0	0.0	0.0	0.0	0.0
Amortisation	0.0	0.0	0.2	0.2	0.2
Wages and staff costs	0.1	0.1	0.3	0.4	0.4
Share-based payments	0.0	0.0	0.1	0.0	0.0
R&D	0.1	0.3	0.6	1.4	1.5
Other costs/income	0.2	0.0	0.3	0.5	0.5
<b>Loss from operations</b>	<b>(0.3)</b>	<b>(0.4)</b>	<b>(1.4)</b>	<b>(2.4)</b>	<b>(0.1)</b>
Net interest income	0.0	0.0	(0.0)	(0.1)	(0.2)
Interest expenses	0.0	0.0	0.0	0.0	0.0
Pretax income (Loss)	(0.2)	(0.4)	(1.4)	(2.6)	(0.4)
Taxes	0.0	0.0	0.0	0.0	0.0
Rate	NA	NA	NA	NA	NA
<b>Net income (Loss)</b>	<b>(0.2)</b>	<b>(0.4)</b>	<b>(1.4)</b>	<b>(2.6)</b>	<b>(0.4)</b>
EPS (in pence)	(0.7)	(0.9)	(0.0)	(0.0)	(0.0)

Balance Sheet					
Year ending 31 Dec (£m)	2006A	2007A	2008E	2009E	2010E
<b>Non-current assets</b>					
Intangible assets	3.2	3.3	3.1	3.4	3.7
Tangible assets	0.0	0.0	0.0	0.0	0.0
Investments	3.0	3.0	3.6	4.1	4.1
<b>Total</b>	<b>6.2</b>	<b>6.3</b>	<b>6.7</b>	<b>7.5</b>	<b>7.7</b>
<b>Current assets</b>					
Trade and other receivables	0.0	0.5	0.0	0.0	0.0
Cash & equivalents	0.0	0.2	(1.2)	(4.5)	(5.2)
<b>Total</b>	<b>0.1</b>	<b>0.6</b>	<b>(1.1)</b>	<b>(4.5)</b>	<b>(5.1)</b>
<b>TOTAL assets</b>	<b>6.3</b>	<b>6.9</b>	<b>5.6</b>	<b>3.0</b>	<b>2.6</b>
<b>Current liabilities</b>					
Other trade payables	0.1	0.1	0.1	0.1	0.1
Other payables	0.0	0.0	0.0	0.0	0.0
<b>Total</b>	<b>0.1</b>	<b>0.1</b>	<b>0.1</b>	<b>0.1</b>	<b>0.1</b>
<b>Net current assets</b>	<b>6.3</b>	<b>7.0</b>	<b>5.6</b>	<b>3.0</b>	<b>2.7</b>
<b>Net assets</b>	<b>6.2</b>	<b>6.9</b>	<b>5.5</b>	<b>2.9</b>	<b>2.6</b>
<b>Shareholders' equity</b>					
Share capital	0.3	0.3	0.0	0.0	0.0
Share premium	6.3	7.3	0.0	0.0	0.0
Total share capital	6.6	7.6	7.7	7.7	7.7
Retained earnings	(0.3)	(0.8)	(2.2)	(4.7)	(5.1)
<b>Total equity</b>	<b>6.2</b>	<b>6.9</b>	<b>5.5</b>	<b>2.9</b>	<b>2.6</b>

## Cash flow statement

Year ending 31 Dec (£m)	2007A	2008E	2009E	2010E
Operating loss	(0.4)	(1.4)	(2.4)	(0.1)
Depreciation and amortisation charges	0.0	0.2	0.2	0.2
Share-based payments expenses	0.0	0.1	0.0	0.0
Income tax credit received/(paid)	0.0	0.0	0.0	0.0
<b>Net cash from operations</b>	<b>(0.4)</b>	<b>(1.1)</b>	<b>(2.3)</b>	<b>0.1</b>
<b>(Increase)/Decrease in trade and other receivables</b>	<b>(0.4)</b>	<b>0.4</b>	<b>0.0</b>	<b>0.0</b>
<b>(Decrease)/Increase in trade and other Payables</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>
<b>Net cashflow from operations</b>	<b>(0.8)</b>	<b>(0.7)</b>	<b>(2.3)</b>	<b>0.1</b>
<b>Cashflow from investing</b>				
Property plant & Equipment	(0.0)	(0.0)	(0.0)	(0.0)
Purchase of intangible fixed assets	(0.1)	(0.1)	(0.5)	(0.5)
Purchase of investments	0.0	(0.5)	(0.5)	0.0
Net cash from investing activities	(0.1)	(0.6)	(1.0)	(0.5)
<b>Cash flow from financing activities</b>				
Issue of ordinary shares	0.4	0.0	0.0	0.0
Net interest received	0.0	(0.0)	(0.1)	(0.2)
Net cash from financing	0.4	(0.0)	(0.1)	(0.2)
Net Increase (decrease) in cash flow	0.5	(1.3)	(3.4)	(0.6)
<b>Opening cash equivalents</b>	<b>0.2</b>	<b>0.2</b>	<b>(1.2)</b>	<b>(4.5)</b>
<b>Closing cash equivalents</b>	<b>0.7</b>	<b>(1.2)</b>	<b>(4.5)</b>	<b>(5.2)</b>

Source: *Objective Capital*

## Appendix: Management

### **Directors, Senior Management and Scientific Advisory Board**

#### **Tor Norup Svensson, Executive Chairman, Danish (aged 45)**

Tor Svensson holds a Masters Degree in Science of Economics from the University of Copenhagen, Denmark (1987) and an MBA from the Kenan-Flagler Business School at the University of North Carolina at Chapel Hill, USA (1989). He completed post-graduate studies in finance at Universidad de Los Andes in Colombia and at IESA business school in Venezuela. He lectured International Business courses at Coker College in the US. For two years he was Vice President of Merrill Lynch International Bank in London. Prior to this he served as the Global CEO and Managing Director for the Gaia Titan Group (fund manager with \$0.5 billion under management) with offices in London, New York, Hong Kong, South Africa and India. Tor was Marketing Associate for Sonoco Products in the US (Fortune 500 packaging company). Tor has worked for the Danish Ministry of Foreign Affairs and for Nordea, the largest Scandinavian Bank. He has provided investment advice to Antfactory, Credit Agricole Indosuez, and UBS.

#### **Soren Stenderup, Managing Director and Chief Executive Officer, Danish (aged 51)**

Soren Stenderup graduated from the Aarhus School of Business and Foreign Language in 1984, and then completed a Danish Pharma Industry Post Graduate Course. Soren has ten years of international sales and marketing experience in branded goods with Elizabeth Arden and Quaker Oats, before subsequently moving to sales and marketing positions with big pharma companies, GlaxoSmithKline and F. Hoffman-la Roche. He founded his own company in 2003 representing Indian Biotech companies in Northern Europe as well as advising on business development within healthcare for both private and government clients. He has specific experience of developing and executing marketing strategies for obesity drugs aimed at European GPs.

#### **Dr Anders Bogh Jensen, Chief Scientific Officer, Danish**

Anders Bogh Jensen is a biochemist with a master thesis focusing on yeast genetics from the Institute of Molecular Biology, University of Copenhagen in 1989. He then worked as a research assistant at the Carlsberg Research Laboratory. After that he was awarded a four year European Union, BRIDGE mobility fellowship for carrying out his post graduate research training at the Dept. of Plant Molecular Genetics, CID, CSIC, Barcelona, Spain in the field of stress and hormone controlled gene regulation (1994 PhD thesis in molecular biology and genetics). During his PhD, he also spent time in laboratories in France and England.

He has worked as an associate professor at the Institute of Molecular Biology on map kinase signalling using bio-imaging as a tool to identify key transcriptional components by reverse genetics. These studies were supplemented with frequent visits to Cold Spring Harbor Laboratory and CSIC Barcelona. He also spent time at the University on modernizing biology teaching, developing advanced PhD courses and organizing meetings on novel aspects on plant molecular biology. These activities have formed the basis for a broad network within US and European laboratories.

He served as the head of Poalis A/S agro division, a plant based Biotech company. He has a long-standing scientific expertise in the field of biotechnology, genetics and molecular biology with numeral publications in leading journals including Cell. In addition he serves as Industrial representative board member at The Danish Society for Biochemistry and Molecular Biology.

#### **Peter Guldberg, Financial Officer, Danish**

Peter Guldberg has a strong financial analytical background from being a proprietary trader and risk manager with leading financial institutions in Europe and the US. Recently, Peter worked for Citadel Investment Group in London where he was Associate Director, specialising in Convertible Arbitrage in Europe. He was jointly managing the European Convertible Bond desk in London employing four people and was a member of the ten person firm-wide trading committee from 2002 to 2004. Prior to Citadel, Peter was responsible for trading \$650 million worth of convertible bond positions at Alexandra Investment Management in New York, where he also developed a proprietary valuation model. At Arnhold & S. Bleichroeder in New York he was Vice-President, responsible for Convertible Bond Trading. For McLeod Young Weir/ScotiaMcLeod Inc. and RBC Dominion Securities / Kitcat & Aitken London Peter held a number of senior positions, including as Vice President, in Equity Sales, Convertible Bond Trading, Derivatives Structuring and Fixed Income Proprietary Trading. Peter completed his education in Denmark and graduated from Niels Brock's School of International Business with a BBA.

#### **Graham May, Company Secretary and Legal Advisor, UK**

Millers Associates conduct all legal, accounting and company secretarial functions for the Company. The principal officer at Millers Associates who represents the company is Graham May, a qualified lawyer, admitted as a solicitor in 1979 following a law degree at Cambridge University. He is conversant with all areas of law, with an initial background in commercial property transactions for the London Legal Department of the National Coal Board Pension Schemes. Graham's international experience included 7 years practising as an attorney-at-law in the Cayman Islands in the areas of banking, insurance, trusts and mutual funds. Since 1989 he has practised as a lawyer in the U.K. financial services industry, first with currency fund managers, Gaiacorp U.K., and then as Managing Director of that group's London subsidiary, renamed Titan Capital Management, where he was instrumental in developing the worldwide investment management business. Having co-ordinated the sale of Titan in 2002 – 2003, he set up Mottram Partners, a legal, accounting and compliance subsidiary of a plc. Following the break-up of the plc, he jointly established Millers Associates to continue the business of advising plc's and private companies in all aspects of law and company secretarial procedures. He is a consultant solicitor with the City firm of Paul Roberts Solicitors, the solicitors to the company.

### **Tryphonas Stavrou, Chief Accountant, Bridge BioResearch, UK**

Tryphonas Stavrou has 12 years' accounting experience since completing his graduate and post-graduate diplomas in accounting at North London University. His accountancy background is varied, from practicing with the London firm of G. N. Papas & Co to operating his own accounting/taxation consultancy business for several years. He acted for four years at Titan Capital Management as Finance Officer, responsible for all accounts and FSA financial matters. Since 2003 Triph has been providing accounting services to diverse clients in accounting and taxation through Mottram Partners and, more recently, Millers Associates, in which he is a director and principal.

### **Scientific Advisory Board**

**Professor Mike Cawthorne** (English) has since 1994 been Professorial Research Fellow and Director of Metabolic Research, University of Buckingham. From 1968 to 1994 he was employed by Beecham and SmithKline Beecham as Manager, then Director and then Group Director, Diabetes and Obesity research. He was awarded the Society of Medicines Research award for drug discovery in 2001 for recognising the need to target insulin resistance in diabetes and the successful discovery and development of rosiglitazone. He is a Member of MRC College of Experts, a frequent author of academic and research papers and presently consults for pharmaceutical and biotech companies and is on the Scientific Advisory Board of Inpharmatica, Carex and Probiodrug.

**Professor Denis Richard** (Canadian) is full Professor of Anatomy and Physiology at Laval University. Together with serving as Director of the Laval Hospital Research Centre, and Director of the Center for Research on Energy Metabolism at Laval University, he is the recipient of the Merck Frosst/CIHR Research Chair in Obesity, the only Chair devoted to obesity research in Canada. He is active with several societies and associations, including the North American Association for the Study of Obesity: IASO representative on the Council (2002- now); The International Association for the Study of Obesity (IASO): Awards Committee Member, and the Canadian Obesity Network: Board of Directors and Theme Area Coordinator (Behavioural and Biological Determinants); as well as Centre de Recherche en prévention de l'obésité (Fondation Lucie et André Chagnon): Laval Hospital representative on the Administrative Board. He earned his philosophy doctorate in Physiology at Laval University and received further postdoctoral training in nutrition and physiology at the Dunn Nutrition Unit at the University of Cambridge, Cambridge, England.

**Dr Danapal Naidu** (Indian) has been Deputy Chairman of AEC Edu Group Pte Limited ([www.aec.edu.sg](http://www.aec.edu.sg)) since 2001. He was attached to the Family Planning Board of Singapore in the Ministry of Health and currently is the founder, chairman and medical doctor at the Harley Street Healthcare and Wellness Clinic in London. A gynaecologist, Dr Danapal obtained his postgraduate training from London's Royal College of Obstetrics and Gynaecology. Prior to starting his own practice, he spent several years as Assistant to The Queen's Gynaecologist, Sir George

Pinker. He is also the director of the Apollo Group of Hospitals in India and Sri Lanka. Dr Danapal graduated as a medical doctor from India and later pursued his specialisation in the United Kingdom.

**Professor Karsten Kristiansen** (Danish) has extensive experience in the administration, planning and organizing of research projects, including in Metabolic Disorder treatment discovery. At SDU, he heads up a research group comprising nine professors and doctorate students. Mr Kristiansen is participating in several European research projects and international scientific collaborations. He is a member of the Danish Academy of Natural Sciences, visiting Professor and Senior Advisor of the Beijing Genomics Institute, Chinese Academy of Sciences, member of the scientific advisory board of Kunming Primate Center, Chinese Academy of Sciences, and member of the scientific advisory board of the Institute of Bioinformatics, Bangalore, India. Further he is member of several industrial and governmental scientific advisory boards. After graduating with a Masters Degree in Science from the University of Copenhagen in 1972, with a thesis Methods for Protein Sequencing, he has been a guest researcher at the Max-Planck-Institut für Molekulare Genetik in Berlin and at the Institut de Biologie Physico-Chimique, Fondation Edmond de Rothschild, in Paris. Mr Kristiansen is a Reviewer for the French INSERM and the British Association for International Cancer Research.

**Dr Jose Manuel Fernandez-Real** (Spanish) was born in Sarria, Lugo, Spain. After developing the residence in endocrinology in Barcelona, he began research on insulin resistance in 1991 while he worked as a physician in Girona Hospital. He has been there since and he has created a new lab in endocrinological investigation in the hospital. He is also Assistant Professor in the University of Girona. His research strategy is based in large part on the analysis of molecular and genetic determinants of insulin resistance and inflammation using state-of-the-art techniques of study of insulin sensitivity. José Manuel Fernández-Real is author or co-author of more than 100 scientific articles. He has received several prizes and awards: Research Grant Awards from the European Association for the Study of Diabetes in 2002; Award from the Spanish Society of Diabetes in 2000 to the best young investigator in Diabetes; Awards from the Spanish Society of Endocrinology and Diabetes in 2002 and 2004; Award from the Catalan Academy of Medical Sciences in 2002, Prize for Professional excellence in 2005. He was founder of Mellitus S.L., a university based spin-off that converted into one of the main bio-techs in Spain, and is now a subsidiary of the company.

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**Steven Zimmer**, M. Sc. (Molecular Biology)  
Steven has more than 25 years experience in analysis, corporate finance and as a portfolio manager in biotech and pharma including working for DLJ, CSFB and Robert Fleming in London, NY and Switzerland.

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