Executive Highlights

Hello from Boston where we joined about 45 people in the Hyatt Regency for GTCBio's Diabetes Summit 2013. The lovely spring weather outside did not distract attendees of speakers from informative panel discussions and notable presentations. As a reminder, the conference is split into two tracks: one focusing on drug discovery and one focused on partnerships and strategic deal-making. Dr. Riccardo Perfetti (VP Global Medical Affairs, Sanofi Diabetes, Paris, France) delivered the opening keynote presentation on how the ADA/EASD's 2012 position statement affects diabetes drug developing. Dr. Perfetti believes the position statement highlights the need for better comparative effectiveness data (without which, in the future, he does not believe drugs will be able to be approved) and for more investigations into how risk/benefit ratio changes for drugs when used in combination with other drugs. Mr. Steven Burrill (CEO, Burrill & Company, San Francisco, CA) discussed the current and future state of healthcare. He highlighted that the current system disconnects patients and HCPs from the price of treatment and thus fails to incentivize patients to maintain their health. Mr. Burrill argued that payers have a disproportionately large voice regarding the value of a therapy. Dr. Edward Damiano (Boston University, Boston, MA) followed with a discussion of his work to develop a bionic pancreas. Dr. Damiano expects to complete the ongoing outpatient Beacon Hill study, which compares closed-loop control to usual care, by the end of September. He plans to conduct a camp study this summer, a longer adult outpatient study in 1H14, and a pivotal study in 2015 to enable PMA submission in 2016. During the afternoon discussion of new targets for diabetes, Dr. Faustman discussed her preclinical and phase 1 research on using the controversial bacillus Calmette-Guérin (BCG) vaccine to potentially cure (in her words) type 1 diabetes. Dr. Faustman thinks that BCG could restore insulin secretion by inducing the release of cytokine tumor necrosis factor (TNF), which has been shown to selectively destroy insulin-autoreactive T cells. Dr. Faustman's lab is currently planning a phase 2 trial of BCG.

On the track focused on partnership and deal-making, we gleaned a number of R&D updates and strategic considerations. We learned of an effort to develop an oral small molecule GLP-1 agonist by Heptares Therapeutics, a company specialized in G-protein coupled receptor (GPCR)-based therapeutics. Array is still looking for a partner for the GPR119 agonist ARRY-981; the company has shifted its focus to oncology and will not allocate the resources to carry ARRY-981 into clinical development. During this session there was lots of discussion on the type 2 diabetes treatment landscape. Dr. Lauren Shearman (Executive Director of Scientific Licensing & Acquisitions, Merck, Whitehouse Station, NJ) forecast that FDCs is "where everyone is going" and that very few new oral mechanisms would emerge in the next five years. Many speakers said that future glucose-lowering agents would have to demonstrate additional benefit beyond glycemic control in order to be successful.

Both of today's panel discussions were particularly timely, lively, and informative. In the panel discussion on investment and mergers and acquisitions in diabetes, representatives from small pharma, big pharma, and the investment community discussed strategies and trends for partnering deals. In particular, we learned quite a bit about the Merck/Pfizer partnership on the SGLT-2 inhibitor ertugliflozin that Merck just announced this morning, about SGLT-2 positioning, and about strategy in China. The panel discussion on new therapeutic targets for diabetes highlighted Dr. Douglas Melton's (Harvard University, Cambridge, MA) discovery of betatrophin's role in beta cell proliferation only several days ago. Dr. Gordon Weir (Joslin Diabetes Center, Boston, MA) noted that it's unclear if

betatrophin directly causes beta cell replication, and Dr. Denise Faustman (Harvard Medical School, Boston, MA) questioned if people with type 1 or type 2 diabetes are maximally exposed to betatrophin, which would limit the benefit a pharmacological approach with betatrophin could have.

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Detailed Discussion and Commentary

Keynote Presentation

THE MOST RECENT ADA/EASD GUIDELINES ARE CHANGING DEVELOPMENT STRATEGIES: A FOCUS ON COMBINATION THERAPY FOR THE TREATMENT OF DIABETES

Riccardo Perfetti, MD, PhD (Vice President Global Medical Affairs, Sanofi Diabetes, Paris, France)

Dr. Riccardo Perfetti discussed how the 2012 ADA/EASD position statement's new focus on combination therapy is changing how companies will need to structure development programs. In particular, Dr. Perfetti emphasized that a drug's risk/benefit profile when used alone may change when it is used in combination with another drug – it may either improve (e.g., basal insulin when used in combination with a GLP-1 agonist) or worsen (e.g., a TZD used in combination with insulin). Thus, he encouraged further study and characterization of the long-term risk/benefit profiles of combination treatments. Dr. Perfetti also stressed the need for comparative effectiveness data, saying that in the future, drug approvals will likely hinge on the ability to show effectiveness compared to the existing standard of care. Dr. Perfetti also advised that clinical guidelines are not the only guidelines that influence a drug's success – for example, he stated that the importance of reimbursement guidelines is often underestimated; they are often very different from clinical guidelines and ultimately determine whether payers will actually pay for the drug (his point being that a drug approval can be rendered irrelevant if payers decide not to cover it).

- **Dr. Perfetti highlighted critical characteristics of the 2012 position statement and outlined how it differs from the 2008 guidelines.** Interestingly, he highlighted the strong emphasis on aggressive intensification (this is a point that speakers don't often bring up – it suggests advancing from one tier of treatment to the next if the patient does not reach goal after three months of treatment initiation). Additionally, he highlighted that there are now many more choices for combination therapy, and there is now a need for comparative efficacy and effectiveness data. Another important implication for clinical development programs is that there is now the option to initiate treatment on drugs other than metformin or in combination with metformin. Presumably, metformin will remain first-line therapy in the near term, even though there are now additional options for first-line therapy outside metformin
- **Dr. Perfetti highlighted many shortcomings of clinical development data that the 2012 position statement brings to light:** 1) the need for stronger comparative data to better inform how to select a second line treatment; he stated that in the future not having comparative data in a regulatory dossier of a drug may jeopardize its regulatory or reimbursement status; 2) the need to demonstrate robust efficacy and safety in combination with other anti-diabetes therapies; and 3) the need to build combinations with complementary modes of action and better characterize mechanisms in order to identify which combinations make sense.
- **Dr. Perfetti believes that the validation of combinations will be critical.** He especially stressed that risk/benefit of a drug often changes when combined with another drug – one cannot simply add together the risk/benefit profile of each drug alone to characterize the risk/benefit of the combination.
    - **Dr. Perfetti used his experience with Lyxumia's (lixisenatide) clinical development program as an example of how combining two drugs can change the risk/benefit profile.** In anticipation of guideline changes, the lixisenatide

development program included studies of lixisenatide as monotherapy, in combination with one other OAD, in combination with two other OADs, and in combination with basal insulin. Dr. Perfetti described how GetGoal-Duo 1 followed the new position statement "100%" by randomizing patients on basal insulin to GLP-1 or placebo if they did not reach an A1c goal of 7% after three months. The risk/benefit profile of basal insulin changes when used in combination with GLP-1, he emphasized. Unlike the situation in which insulin is used on its own (e.g., intensification is associated with cardiovascular risk factors like increased body weight and hypoglycemia), when used in combination with GLP-1, the effect on weight is neutral, and there is minimal hypoglycemia.

    - **As an example of how risk/benefit can change for the worse when two drugs are combined,** Dr. Perfetti briefly reminded the audience that edema from TZDs is exacerbated when used in combination with insulin.

- **Dr. Perfetti stated that when balancing the risk/benefit profile of drug combinations, one must take the following factors into account:** mechanism of action, safety and tolerability, presence of co-morbidities, efficacy, pathogenesis of hyperglycemia, and whether the patient is lean or obese. With regard to mechanism of action – theoretically, using mechanisms that do not overlap would allow use of lower doses of each component drug. With regard to safety and tolerability, Dr. Perfetti advised the audience against undermining the importance of tolerability. Specifically, he stated that while safety allows a drug to be approved, what drives patient use is tolerability. So combinations of drugs that both cause the same side effects would not promote adherence.
- **In terms of improving our state of knowledge on comparative effectiveness, Dr. Perfetti commented on the GRADE trial,** which is scheduled to begin in April 2013 with a primary completion date in 2020. He stated that GRADE will likely help generate better comparative effectiveness data but since data are not expected until 2020 that medical associations and regulators would likely already have a good understanding of how these agents stack up. As a reminder, GRADE will compare the value of adding a sulfonylurea, a DPP-4 inhibitor, a GLP-1 agonist, or basal insulin to metformin. Since many more combinations may be in use by then, we are surprised that adding dual therapy isn't being tested in GRADE.

Questions and Answers

Q: In your experience treating patients, what is your feeling about adherence? Which therapies are patients more likely to continue?

A: That is a complex question. Adherence and compliance depend on education. Patients who have a good understanding of a drug may be more willing to follow their regimen. Patients using drugs with tolerability side effects who are not fully informed will not like it, but information gives them the possibility to inform the physician, and the physician can chose alternatives. Education is a critical component to allow for adherence. Patient empowerment is critical. In the US this is part of the culture. In China, however, diabetes is treated in a hospital setting, which does not allow management in the long term. How long can you be in a hospital setting? Let's say one week. Then you are by yourself for the next six months. Education in my view is the most critical.

Featured Presentations

THIS IS THE DAWNING OF THE AGE OF THE BIONIC ENDOCRINE PANCREAS

Edward Damiano, PhD (Boston University, Boston, MA)

Dr. Edward Damiano described his efforts to build a bionic pancreas system. (He is moving away from the term "artificial pancreas" because it says what the system is not, versus what it is.) The current system uses an iPhone 4S to run the controller, a Dexcom G4 Platinum CGM/receiver, and two Tandem t:slim pumps (one to deliver insulin and one to deliver glucagon); the system is being tested in the ongoing, outpatient Beacon Hill study. Preliminary results from the first five patients showed average blood glucose readings of 128 mg/dl on days 2-3 and on days 4-5, with low incidence of blood glucose less than 60 mg/dl. Notably, Dr. Damiano recently received the Investigational Device Exemption from the FDA to test his system in a randomized crossover study in children with type 1 diabetes at Camp Joslin (boys, n=16) and the Clara Barton Camp (girls, n=16) this summer. In addition to Beacon Hill and the camp study, he plans to conduct an adult two-week-long outpatient study (n≈50) in 1H14 and to conduct a pivotal study in 2015. Dr. Damiano expects to submit a full premarket approval application to the FDA in 2016, which would enable approval by fall 2017 so that his son (who has type 1 diabetes) can use the system when he goes to college. Dr. Damiano first presented preliminary Beacon Hill study results at the FDA-JDRF-NIH Workshop on Innovation Towards an Artificial Pancreas: see page 5 at https://closeconcerns.box.com/s/gyhzeb11sfndu5x8eg58.

- **The ongoing Beacon Hill outpatient closed-loop study involves five-day experiments in 20 adults with type 1 diabetes.** The randomized crossover design compares five days of closed-loop therapy to five days of usual care. Patients have free run of a three-square-mile area of downtown Boston. Point-of-care capillary blood glucose tests (which are blinded to the subjects) are taken during the day under 1:1 nursing conditions. At night, patients sleep in a hotel with blood glucose monitoring under 1:2 nursing conditions. Patients are required to be in the hotel from 11:00 pm to 7:00 am. The study began in February 2013 and Dr. Damiano expects to collect over 3,000 hours of data. The study is slated to complete by the end of September.
- **The system requires only the patient's weight for initialization. The system then adapts insulin dosing based on glucose information at five-minute intervals and over longer time scales.** Dr. Damiano believes that the latter is key to adapting to the higher insulin needs of adolescents and to adjust for inter-current illnesses. The system takes 6 to 12 hours after initialization to adapt to the individual and is comprised of three independent controllers: one for basal insulin needs (proportional–derivative algorithm), one for glucose excursions (model predictive control algorithm), and one for priming boluses (patients can indicate whether they are about to consume a meal, but the algorithm still controls the size of the meal-priming bolus). Patients are told about the pre-meal dosing option, but are not required to use it. Said Dr. Damiano, "we completely crush the standard of care," whether or not priming is used. Dr. Damiano explained the bolus functionality in greater detail at the recent FDA-JDRF-NIH Workshop on Innovation Towards an Artificial Pancreas: patients select if meals are more than, less than, or about equal to the number of carbs they typically eat (i.e., no precise carb counting).
- **For the five patients who have completed thus far, average blood glucose was 128 mg/dl on days 2-3 and 128 mg/dl on days 4-5 with low incidence of blood glucose less than 60 mg/dl (0.9% and 0.1%, respectively).** In individual patients, pre-meal priming may or may not have significant impact. In the case of the patient with day 2-3 blood glucose average of 133 mg/dl, Dr. Damiano explained that the drop to 115 mg/dl on day 4-5 coincided

with the patient's decision to take advantage of the pre-meal bolus functionality. Blood glucose readings under 60 mg/dl decreased from 0.9% to 0%. However, said Dr. Damiano, even if patients chose not to bolus or inconsistently bolus, the system maintains good glycemic control.

	CGM Average (mg/dl)		BG Average (mg/dl)	
	Day 2-3	*Day 4-5*	*Day 2-3*	*Day 4-5*
Individual Patients	109	110	116	108
	124	130	126	136
	132	114	133	115
	130	128	143	146
	129	122	121	133
Average	124	121	128	128

** Dr. Damiano noted that CGM tends to underestimate moderate hyperglycemia*

- **Dr. Damiano posited that patients whose blood glucose levels are harder to control may be due to previous exposure to more immunogenic animal insulins**. The ongoing outpatient study does not measure insulin pharmacokinetics; however, based on their experience from previous clinical studies, they have hypothesized that anti-insulin antibodies from prior use of more immunogenic insulins may slow absorption of the insulin in people with type 1. In these studies, patients who had only been exposed to the less immunogenic analogs typically had faster insulin absorption.
- **By moving from a laptop to a mobile, iPhone-based system, Dr. Damiano and his team will be able to collect more hours of closed-loop data in the first eight months of 2013 than in the past 4.5 years**. He emphasized that the final version of the product will not use an iPhone, but a medical grade device that can potentially communicate with a smart phone. The current system (which he described as the penultimate version) streams data from the CGM onto an unadulterated iPhone. The system's algorithm was translated from Matlab to C++ in order to embed it into the iPhone application. The iPhone is locked into the application, such that users cannot use the phone for other purposes.
- **The current system uses Lilly's formulation of glucagon and Lilly's Humalog (insulin lispro).** Dr. Damiano noted that there is no commercial path forward for his bionic pancreas with Lilly's glucagon (due to its lack of chemical stability); however, Dr. Damiano believes that a stable glucagon formulation could be approved in two-years time; several small pharmaceutical companies have developed promising formulations.
- **CGM data collected in Dr. Damiano's third clinical study (i.e., the one before Beacon Hill) suggested that the Dexcom G4 Platinum had superior accuracy amongst commercially available CGMs**. As such, the bionic pancreas in the ongoing Beacon Hill study uses the G4 Platinum. Dr. Damiano and his team conducted three clinical feasibility studies leading up to Beacon Hill. In each clinical study, CGM accuracy between the three main commercial players was compared.

CGM	MARD
2008-09	
Dexcom Seven	23%
Medtronic Guardian RT	18%
Abbott Navigator	10%
2010-11	
Dexcom Seven Plus	16.5%
Medtronic Guardian RT	20.3%
Abbott Navigator	11.8%
2012	
Dexcom G4 Platinum	10.8%
Medtronic Enlite	17.9%
Abbott Navigator	12.3%

Questions and Answers

Q: I have child who was diagnosed with type 1 diabetes at 14 months. Your approach is reality based. It's amazing how far we've come. Do you have any idea what percent of patients with type 1 diabetes will actually wear a device? This idea that digital technology will increase compliance, unless we incentivize people, I'm not so sure.

A: I don't know. We know roughly the percent of people that wear pumps. The T1D Exchange data set are showing 30-40% wear pumps in the US – this might be a little elevated due to self selection. CGM usage is slim to none: 1-3%. The first CGMs that hit the market were inaccurate devices. Unfortunately, people were colored by these early CGMs that weren't ready for prime time. That's a frustration to overcome. What will make the difference [with the bionic pancreas] is that the difference from standard of care is going to be so much greater. There will be a huge effect. It will be unconscionable for endocrinologists to not push this technology. It's hard to get people to wear these things, but when my collaborator asks why people aren't on the pump, they say, not enough benefit. So we ask, what if it was completely automated? Every one of these people – even MDIs – say they will wear it. It's how ambitious we are being that makes the difference. We want to hit a home run the first time out. That's been my strategy from the beginning and I still think that's the right way to go. Hopefully the tremendous improvement in glycemic control is what will get people to wear these devices.

Q: How do you solve the glucagon issue?

A: Technically, it is not such a hard problem. Small pharmaceutical companies have built formulations that are stable in different solutions. They use standard human glucagon. You don't have to make a glucagon analog, which has a tremendous runway through the FDA. With insulin, it's different because human insulin is so slowly absorbed. With glucagon, it's a small peptide – the 29 amino acid sequence is rapidly absorbed. You don't have to make a new molecule, just a new formulation. This will have a shorter regulatory pathway, hopefully on the order of two years.

Q: Your device is dependent on stable glucagon?

A: Yes, we will be suggesting that patients fill their glucagon reservoir with one of these new rescue glucagon formulations that are stable for three to four days in the pump.

Q: What about implanting chambers under the skin?

A: There's been a lot of work in Europe and early studies in the US. There are challenges to overcome with implanting devices in the abdomen. One of the problems is the crystallization of insulin at body temperature. You have to use more highly concentrated insulins. When the system does clog up, purging the system is a major ordeal. The problem is building insulin that is rapidly absorbed that is also stable and does not crystallize at high concentrations. There may be solutions there – there is work by Thermalin for example – but for the time being, there has never been anything FDA approved like this except for pace makers. I see this as a much bigger regulatory burden. I would love to see something reliable and safe, but it will not come in the order of four years.

Q: When you commercialize this, will it be as three components or as one product?

A: It has to be built into a single product. We can build a network of small companies. Ultimately, since it has to be a PMA, someone in the group has to take over and align with the others. It has to be one product, one integrated system. Xeris has glucagon that uses 5 mg/ml concentration, so the additional reservoir you would need for that would be quite small. Most insulin pumps are still accurate enough to deliver our smallest glucagon doses if the glucagon were as much five-fold more concentrated than Lilly glucagon (1 mg/ml). The pump wouldn't have to be that much bigger because we don't need as large a volume of glucagon as we do insulin.

Q: What about strenuous exercise, like a marathon? Can you build that into these trials? Can you build the most rigorous challenges into the trials: fight or flight, vomiting? Can you stress your system to the utmost?

A: Exercise is a tricky thing. With some kinds of exercise, you see blood glucose rise; others it's the opposite. The hardest thing in my kid was walking through the streets of London last summer – we were pumping dextrose tablets into him and running an extremely low basal and his blood sugar was running at 50 mg/dl the whole time. If he gets onto the basketball court for a game, his blood sugars rise. But in practice, with nothing at stake, with the same level of exertion, his blood sugars drop. His state of mind is critical to this. Moderate exercise at heart rates of 120-140 bpm gives rise to tremendous glucose clearance by the muscle. Activities that you might think of as not particularly challenging can sometimes pose more of a hypoglycemic threat than a marathon. The thing that is cool is that we can test our system in adolescents, who are, in fact, superhuman. Adolescents can use three fold as much insulin as adults. Our system doesn't know it's controlling the blood sugar of an adolescent or an adult. The only way we can test extremes in the insulin demands of our subjects is to design a study in both cohorts using a system that is initialized in the same way. What happens in the first 12 hours is profoundly dependent on the subject's insulin requirements. Our system's ability to adapt to such large intersubject variability gives us some confidence that we will be able to handle intrasubject variability that comes and goes rather suddenly. We do have a feature that can announce exercise. We haven't tested that infrastructure, but we will test it for the first time in the camp study to see if it is necessary. There are Achilles heels with our system – if you fast, for example, you might deplete your glycogen stores and exhaust your liver of the substrate glucagon needs to act upon in order to raise blood sugar.

STATE OF THE HEALTHCARE WORLD AND DIABETES IN THE FUTURE

G. Steven Burrill (CEO, Burrill & Company, San Francisco, CA)

In a fast-paced and engaging presentation, Mr. Steven Burrill argued that healthcare systems are beginning to focus on outcomes and value rather than on procedures and costs. He began with an overview of the healthcare landscape, noting that the world's aging population and the rise of

noncommunicable diseases are placing a significant burden on today's healthcare systems. Both factors are expected to escalate the cost of care. Diabetes in particular represents a global challenge, as 370 million people currently have the disease. In elaborating, Mr. Burrill cited two concerns: 1) nearly 50% of patients are not aware that they have the disease; and 2) diabetes led to 4.8 million deaths in 2012. Mr. Burrill highlighted that the current healthcare system does not incentivize patients to maintain their health (since payers foot the cost of treatment) and posited that placing greater responsibility with the patient would lead to better long-term outcomes. Throughout his talk, Mr. Burrill emphasized the disproportionately large influence of payers, noting that payers individually decide the value of a therapy: "Value is in the eyes of the beholder. In our world, it's the payer. Remember, the payer is God."

- **Mr. Burrill explained that an aging population and the rise of chronic care are changing the healthcare landscape.** He noted that in general, birth rates are decreasing while populations are aging; China's has roughly 465 million people over the age of 65 years – one and a half times the population of the US. Mr. Burrill also highlighted that one in three babies born today will live to be 100 years old. These trends point to a future situation where a shrinking working population will need to support a growing unemployed population (i.e., people under 20 years and over 65 years). Furthermore, while healthcare systems were originally designed to treat infectious diseases and acute sickness, they are increasingly burdened by chronic illnesses and noncommunicable diseases (which now account for 63% of deaths). Mr. Burrill remarked that this problem is by no means a problem only seen in the US.
- **Mr. Burrill then framed the "massive" global burden of diabetes, emphasizing that more than 370 million people now have the disease.** After a swift review of the related complications, he highlighted that even small countries have a significant disease burden: for example, the prevalence of diabetes has reached 37% in the Federated States of Micronesia, 30% in Nauru, and 23% in Saudi Arabia. Mr. Burrill cited two particular concerns: nearly 50% of patients are not aware that they have the disease; and diabetes led to 4.8 million deaths in 2012.
- **US healthcare spending now totals $3 trillion and is expected to reached $5 trillion in the next few years.** Mr. Burrill stated that this increase "will have nothing to do with ObamaCare" and will be driven by the US' aging population and the rise of chronic care, which will allow people with illnesses to live longer. He pointed out the declining popularity of the pharmaceutical industry, citing a recent poll that found that in general, people believe that prescription drugs account for 60% of total healthcare spending. In reality, prescription drugs represent only 11% of costs while hospital spending accounts for the majority (~40%) of healthcare expenditure. In ending this discussion, Mr. Burrill underscored the point that spending does not equal results: The US only has the sixth best healthcare system in the world despite spending more than twice the amount of healthcare (on a per capita basis) compared to other countries.
- **Mr. Burrill addressed a fundamental question: What is the patient's obligation to stay well?** He emphasized that the US healthcare system is the only place in the economic ecosystem where patients and doctors are disconnected from the payer, leading to a "menu without prices." As a result, healthcare has become highly payer-dependent: "Value is in the eyes of the beholder. In our world, it's the payer. Remember, the payer is God." Mr. Burrill commented that such a system leads to disparities in care, as payers often have differing priorities. He posited that a system that burdens patients more when they become sick may result in higher payoffs (i.e., less spending) in the long run.
    - **Mr. Burrill posed several arresting questions for the audience to consider:** 1) Who should pay for healthcare and who should decide the course of care? 2) How should

we balance individual responsibilities with societal costs? 3) Should safety and efficacy alone be the standard for approval, or should cost be a factor? 4) What does innovation mean today? And 5) How do we determine value?

- **Turning back to diabetes, Mr. Burrill gave a whirlwind overview of the "extraordinary opportunities" in diabetes therapies, as well as the associated safety concerns.** He emphasized to main points:
    - **Digital health will play a critical role in improving healthcare access and delivery.** Mr. Burrill estimated that among the seven billion people in the world, 6.2 billion have a cell phone, opening the door for remote monitoring and diagnosis of disorders. He believes that the greatest challenge will be determining which data points provide the most meaningful information.
    - **The US is moving toward a predictive, preventative, and wellness-based healthcare system, Mr. Burrill said.** To support this point, Mr. Burrill cited Tethys Biosciences, whose PreDx blood test measures seven biomarkers to assess a person's likelihood of developing type 2 diabetes within five years. He noted that the US has already adopted a focus on wellness: in general, people pay more for fitness and nutrition programs than they do for drugs.
- **Throughout his presentation, Mr. Burrill highlighted that the US is adopting a value-based healthcare system.** "Value" today is defined as achieving better outcomes at lower costs. Mr. Burrill noted that the concept of value changes across geographies ("a house has different prices in difference cities"). Value also changes over time – Mr. Burrill reminded the audience that Human Genome Sciences declined Amgen's $7 billion purchase bid in 2010 but accepted GlaxoSmithKline's bid of $3 billion in 2012 (for further details on the purchase, please see our July 16, 2012 *Closer Look* at https://closeconcerns.box.com/s/2b832e8798daac25ada2). Mr. Burrill again emphasized that value changes on a per-payer basis "Forget the guidelines, understand what the payer is and what the payer is going to do." To cite an example, he mentioned that the government CMS recently instituted a competitive bidding program for diabetic supplies (for details, please see our February 13, 2013 *Closer Look* at https://closeconcerns.box.com/s/k77ru022dpsrl4a1npfv).

Questions and Answers

Q: You've painted an interesting picture of today and the future. How long is the transition going to take? Who will lead it?

A: We're deep in it already. If you go to Kaiser and they're going to buy a drug, it's based on how they practice medicine and what their priorities are. That's the world we live in. It's based on outcomes. If you're doing your clinical trial today, you're not doing it just to prove safety and efficacy. You have to figure out for each payer out there, how they will figure out the value. You have to derive that data when you do clinical trials. You have to show that the drug increases value. If you go to the FDA, they will say, "tell me which patient populations responded." That's not in the guidelines. And Congress says that they'll only approve things that will lower costs. So that's the world we live in.

Q: How will our healthcare system go from being sickness-focused to being wellness-focused?

A: We're already there. For example, one or two years ago, Safeway – one of the largest employers in California – had healthcare costs that totaled $1.9 billion. Their profit was $1.2 billion, so to increase their profit margin they had to decrease their healthcare cost. They gave their employees an incentive: every

time they went to a fitness program, they got a 10% discount on their copay. In two years, Safeway halved its healthcare costs. As copays go up, people begin to think that it's expensive and they want to manage their health. We didn't have this incentive before. It's not a vision for the future; it's happening now. On a global basis, it's very much with us.

Q: Do you believe that it rests more with the employer versus the payer? I know that Blue Cross Blue Shield is trying to reduce healthcare costs, but it seems like it might take effect much quicker from the perspective of the employer.

A: Who pays for healthcare? The employer does, the government does, and you do. That's where it's going to come from. As soon as your copay goes up, you're going to behave differently. Don't forget – at the beginning of my presentation, I noted that we're moving from a procedures- and cost-based system to an outcomes- and value-based system. The British government will only pay for a drug if you reduce cost and improve outcomes. Germany and Australia are the same way. The US is late. The rules are being written by people outside of the US. But that's the world that we live in.

New Therapeutic Targets for Diabetes

CAN IMMUNE INTERVENTIONAL TRIALS WORK IN LONG TERM TYPE 1 DIABETICS – EXPEREIENCES FROM THE BCG VACCINE TRIALS

Denise Faustman, MD, PhD (Harvard Medical School, Boston, MA)

Dr. Denise Faustman explained why she believes beta cell function can be restored in people with established type 1 diabetes and described her preclinical and phase 1 research on using the bacillus Calmette-Guérin (BCG) vaccine to potentially reverse type 1 diabetes. Dr. Faustman thinks that BCG could restore insulin secretion by inducing the release of cytokine tumor necrosis factor (TNF), which has been shown to selectively destroy insulin-autoreactive T cells. Her proof-of-concept trial was published by PloS ONE in September 2012 (to read our coverage of the paper see our September 27, 2012 Closer Look *at https://closeconcerns.box.com/s/0v6sucnpovdly4hj2r5h) and rests on the hypothesis that reducing the insulin-autoreactive attack by T cells could allow for beta cell regeneration and insulin secretion restoration. Dr. Faustman's lab is planning a phase 2 trial of the BCG vaccine for type 1 diabetes.*

- **Dr. Faustman thinks that the late Dr. George Eisenbarth's model for the natural history of type 1 diabetes needs revision since that model indicates that peoples' pancreases do not produce insulin more than one-to-two years post-diagnosis.** Using Mercodia's ultra-sensitive C-peptide assay (a company which she emphasized she has no tie to other than using its assay), her team has detected C-peptide levels in people who had type 1 diabetes for as much as forty years. Thus, Dr. Faustman's research focuses on restoring the pancreas ("not just slowing the decay [like most studies]") in people who have had type 1 diabetes for 15-20 years.
- **The stated "take home point" of Dr. Faustman's presentation was that autoreactive T cells can be killed in humans with type 1 diabetes.** Data from rodent models and *in vitro* human blood samples suggests that that TNF can selectively destroy the pathological, insulin-autoreactive T cells. Dr. Faustman's presented data from her phase 1, proof-of-concept, double-blind study (n=6 people with type 1 diabetes on placebo or BCG, and 73 reference subjects – 57 of whom had type 1 diabetes), showing that the three BCG-treated participants exhibited higher levels of dead circulating insulin-autoreactive T cells compared to their paired healthy controls.

For more details on the trial's methodology and results see our September 27, 2012 *Closer Look* at https://closeconcerns.box.com/s/0v6sucnp0vdly4hj2r5h.

- **According to Dr. Faustman her phase 1 study was to establish safety and validate biomarkers, and her team did not expect to see an improvement in pancreatic function.** In her presentation she highlighted that the study found transient improvements in C-peptide among the people receiving BCG. She called this as a "proof-of-principle" that we can cause any "relief" in the pancreas and remarked that it was the first improvement in C-peptide levels ever seen in people with long-term type 1 diabetes.
    - **We note that this small and transient increase in C-peptide was seen in two-of-the three people who received BCG and a third person who was on placebo but had an acute Epstein-Barr Virus (EBV) infection** (causing a spike in TNF similar to that induced by BCG). The mean concentration of this peak was 2.57 - 3.49 pmol/l, whereas these people's baseline levels were ~2 pmol/l (the mean of the references subjects with diabetes was 1.65 pmol/l). Since the increase in C-peptide observed in BCG-treated individuals was small and brief, the clinical significance is unknown. Additionally, both participants receiving placebo (excluding the individual with the EBV infection) had baseline C-peptide levels in the hundreds of pmol/l, contrasting the BCG-treated participants who had baseline levels around 2 pmol/l. This could suggest a difference in disease profiles between the two groups that could confound comparisons of their C-peptide levels.
- **Dr. Faustman mentioned in Q&A that one of the three members of the study's placebo arm had an undiagnosed acute EBV infection.** (Dr. Faustman later explained that she did not have time to explain the patient during this presentation and that she will discuss him on the Summit's second day.) She did not express concern about it potentially reflecting poorly on the study's screening, explaining that EBV induces TNF secretion similar to BCG. Thus, she believes her finding that the person with EBV experienced a transient increase in C-peptide secretion lends further support to TNF improving type 1 diabetes autoimmunity and pancreatic function. She continued remark that one of the side effects of all anti-CD3 therapy for type 1 diabetes in phase 2 trials (which showed significant efficacy) had been reactivation of EBV (for example, GlaxoSmithKline's otelixizumab, which was associated with EBV infection and reactivation risk in its phase 2 trial TTEDD). In one of the phase 3 trials, the dose of anti-CD3 therapy was reduced in the phase 3 trial (we believe she was referring to otelixizumab's DEFEND-1) in order to prevent reactivation of EBV. In this trial anti-CD3 therapy did not cause reactivation of EBV and was not found to be significantly effective. Thus, Dr. Faustman implied that the reason for the anti-CD3 therapy's efficacy had been reactivation of EBV, resulting in an elevation of TNF levels.
    - **As a reminder, the EBV infection was unnoticed at the time of enrollment and was only recognized through the analysis of EBV-reactive T cells as part of the broader study of insulin autoreactive T cells.** The EBV infection was confirmed at the end of the study through the identification of antibodies in stored serum samples. Given that EBV also induces TNF secretion, data for this participant mirrored those from his BCG-treated counterparts. The paper's authors reclassified post-hoc the individual, removing him from the saline group for data analysis purposes (leaving it a smaller size of n=2).
- **Dr. Faustman's team is planning a phase 2 trial of the BCG vaccine for people with established type 1 diabetes.** The objective of this trial is to 1) stabilize or restore pancreatic C-

peptide ("not just change the decline") and 2) to define in detail long-term type 1 diabetes with longer-term follow-up. The trial will use multiple BCG doses over a year. For comparison, in the phase 1 trial, people received two injections of BCG spaced four weeks apart.

- **Dr. Faustman explained that she is using BCG – a ~90 year old tuberculosis vaccine – to cure type 1 diabetes because it induces a transient spike in TNF and has an established safety profile.** BCG is the most common vaccine in history with four billion doses having been given worldwide. Dr. Faustman remarked that she sympathizes for companies trying to establish the safety of a new drug to the FDA, because even though BCG has had more than four billion doses administered the FDA still wants substantial safety data.
- **Dr. Faustman believes that immune intervention trial in type 1 diabetes focusing on people with new onset diabetes is problematic** because there is limited drug license opportunity, the trials are extremely expensive to screen for and enroll, and these studies have had poor efficacy to date.

Questions and Answers

Comment: Your finding long-term C-peptide response in adults has been corroborated by a member of Ralph DeFronzo's group and a person from George Eisenbarth's group – they found islets of beta cells still living in people with established diabetes.

A: Even when I was in graduate school there was an old fashioned pathologist – whose name I cannot remember at the moment – who would get up and show a picture of an islet of a pancreas from a person who had type 1 diabetes for 20 years. And literally everyone would head out for coffee and say he is crazy; it might have the structure of an islet but we know it is not making insulin. Now we know the reason it was not making insulin is because the assays were not sensitive enough to recognize that it was making insulin. Finally there is a nice pairing up of the research fields.

Q: One thing that might be beneficial in one setting could be harmful in another setting. TNF is considered to potentially cause retinopathy in type 2 diabetes. Do you have a comment on this?

A: It is kind of interesting; we have to remember that type 1 diabetes and type 2 diabetes are totally different diseases. I think there is something very important to say about the pharmacology of what we are trying to do. We are trying to go in, get a spike of TNF, kill the bad T cells, and get out. You do not want to put a person on chronic antibiotics to kill an infection, similarly we want spikes of TNF see what the pancreas can do and get out.

Q: Have you considered other interventions to increase TNF?

A: There is a lot of tension after two years of doing a trial double blinded. My side that was totally blinded was cocky and thought we knew exactly which patients had received BCG. When the data was unblinded we saw that we got one person wrong. It turns out that one of our patients got an acute EBV infection. He had an acute rise of TNF from the EBV infection and a transient rise in C-peptide function. All Phase 1 and phase 2 anti-CD3 therapies were associated with causing EBV reactivation. If you go back and look at that data it is fascinating. In phase 2 trials anti-CD3 had efficacy and EBV reactivation. In one of the phase 3 trials they lowered the dose so as to not have EBV reactivation and they did not have efficacy. Now at Mass General, we are following kids with mono to see the impact on TNF. So not by design but by fault we have found in humans another ligand to increase TNF.

BETA CELL REPLACEMENT FOR DIABETES: THE PROBLEM OF BETA CELL SUPPLY?

Gordon Weir, MD (Joslin Diabetes Center, Boston, MA)

Dr. Gordon Weir began his presentation reminding the audience that beta cell replacement could be a treatment for type 2 diabetes, as well as type 1 diabetes. According to Dr. Weir, the key remaining challenges for islet transplantation are 1) developing a supply of insulin-producing cells and 2) protecting the transplanted cells from transplant rejection and autorejection. Dr. Weir believes the most-likely answers to our shortage of insulin-producing cells is embryonic stem cells or induced pluripotent cells and he highlighted the potential of ViaCyte's beta cell progenitor device, VC-01. At the Rachmiel Levine Diabetes and Obesity Symposium ViaCyte stated that they are planning to enter clinical development in 2014. Regarding, beta cell expansion, Dr. Weir sighed "that's a tough one;" however he still sounded pretty positive on the area's potential. Though he is worried if beta cell replication can be effectively stimulated pharmacologically though he expressed hope that neogenesis – which he thinks occurs in adults – can "somehow" be harnessed.

- **Discussing the recent *Cell* paper by Dr. Douglas Melton (Harvard University, Cambridge, MA) on the discovery of betatrophin, Dr. Weir offered several important questions for future research** (see the *Cell* paper at http://www.cell.com/abstract/S0092-8674(13)00449-2). Dr. Weir noted that the researchers did not demonstrate that betatrophin directly leads to beta cell replication, which he thought was "odd" though he stated, "I don't want to say that doesn't [occur], they were just eager to get the paper published." If betatrophin acts indirectly on beta cell replication, Dr. Weir indicated that the brain might be an interesting player in translating a betatrophin signal to the beta cells. Additionally, he questioned what the relationship is between betatrophin and glucose and if betatrophin causes insulin resistance. He explained that while the paper did include results from a test suggesting that betatrophin does not cause insulin resistance he felt it was a "bare bone test" that did not put the question to rest.
- **Dr. Weir described ViaCyte's beta cell progenitor device, VC-01 or TheraCyte, stating that the company "should get huge praise" for its work on turning embryonic stem cells into real beta cells.** Dr. Weir noted that curiously ViaCyte needs to put its cells into mice for them to effectively develop; when the cells are developed *in vitro* they do not become "honest" beta cells. He stated that ViaCyte is "itching to bring [VC-01] to clinic; at the Rachmiel Levine Diabetes and Obesity Symposium, ViaCyte stated that they plan to initiate a phase 1/2 trial in 2014. For more details on this trial and VC-01 see pg. 18 of our full report on the Symposium at https://closeconcerns.box.com/s/ib6v10bcvl6u4ajpmowg.
- **Dr. Weir believes that beta cell replication and neogenesis occurs in adult pancreases.** Some KOLs state that no new beta cells are generated after the age of 25 years old, including Dr. David Harlan (University of Massachusetts School of Medicine, Worcester, MA) at the Rachmiel Levine Diabetes and Obesity Symposium (for more details on Dr. Harlan's comments see pg. 8 of our full report from the conference at https://closeconcerns.box.com/s/ib6v10bcvl6u4ajpmowg). Dr. Weir noted that this hypothesis is largely founded on autopsy research. Autopsy samples from people who were younger than 20 years old, however, also have very low beta cell turnover rates. Dr. Weir therefore hypothesized that the autopsy process might hide evidence of beta cell turnover. In a rodent study, he found that pancreas samples preserved via autopsy conditions displayed significantly lower rates of turnover than control samples (kept at room temperature and then a refrigerator). Thus, he thinks if a number of conditions are met (including that beta cells in adults have 0.5% Ki67 [a protein associated with cell proliferation] and that Ki67 positivity lasts 12 hours), beta cell mass

could more than double every 100 days. He believes that new beta cells are generated through beta cell replication and neogenesis and that neogenesis could be more important in humans than it is in mice.

- **He reminded the audience that beta cell replacement could be a treatment for type 2 diabetes, as well as type 1 diabetes.** Dr. Weir explained that many people who have insulin resistance do not develop type 2 diabetes; those who develop type 2 diabetes often have only 40-60% of normal beta cell function, suggesting that type 2 diabetes is a disease of beta cell deficiency and insulin resistance. It may be easier to use beta cell replacement for type 2 diabetes since one does not need to concurrently address a person's autoimmunity.

Questions and Answers

Dr. Denise Faustman (Harvard Medical School, Boston, MA): In type 1 diabetes research, we always hog the islet transplant field. Everyone has woken up and said "type 1 diabetes is a hard field, why have we ignored type 2 diabetes all along?" Type 2 diabetes is an area where beta cell replacement might be easier due to not having the autoimmunity to address.

Dr. Faustman: We were talking about Dr. Melton's paper. The critical question is whether humans with diabetes already have this compensatory response. If humans already have high levels of this hormone then a pharmaceutical approach with this hormone will not be that useful.

A: The paper did not have a demonstration that if you put betatrophin with islets of beta cells that you get replication. It may be working through an indirect pathway. If it worked *in vitro* – in test tubes – you might be able to grow islets in culture. They did not take the protein itself and add it to islets showing that there is increased replication. I don't want to say that it doesn't work, they were just eager to get the paper published.

CELL-BASED THERAPIES TO TREAT DIABETES

Norma Sue Kenyon, PhD (University of Miami Miller School of Medicine, Miami, FL)

Dr. Norma Sue Kenyon discussed investigations into the possibility of using mesenchymal stem cells (MSC) to prolong islet allograft survival, to enhance engraftment, or reverse rejection episodes. Toxicity of immunosuppressants remains a challenge in islet transplantation (Dr. Kenyon showed data from normal cynomolgus monkeys treated with steroid-free immunosuppression demonstrating a blunted insulin response). Since MSCs have anti-inflammatory, immunomodulatory, and tissue-regenerative properties, they have been attractive candidates for the treatment of type 1 and type 2 diabetes and for the incorporation into islet cell transplant protocols. Preliminary proof of concept has been achieved in rodent and non-human primate models: cynomolgus monkey MSCs prolonged islet allografts in the liver, enhanced engraftment (vascularization), and caused reversal of rejection episodes when administered at the time of rejection (around day 110). Clinical trials are still early stage; as of April 25, 2013, there were 19 open trials for MSCs in diabetes.

PANEL DISCUSSION HIGHLIGHTS

Moderator: Richard Caroddo, MPA (Senior Business Development Executive, Medpace, Cincinnati, OH)

Panelists: Norma Sue Kenyon, PhD (Diabetes Research Institute, University of Miami, Miami, FL); Karen Segal, PhD (Senior VP, Diabetes and Metabolic Diseases, Mesoblast, New York, NY); Gordon Weir, MD (Joslin Diabetes Center, Boston, MA)

Mr. Caroddo: Betatrophin is the breaking news that you guys referenced. Do you have any comments on the next steps in development? From what I have read it looks like there have been some in-licensing deals: J&J has been mentioned through a small company called Evotec.

Dr. Weir: This got a lot of press. I think that there is going to be an explosion of work on this. It will be easy for people to get the peptide and to inject it into livers and who knows what else. There are important questions to answer; does this hormone have a direct effect on beta cells? And notice that the paper does not address this question. It is kind of odd that they do not have definitive data on that. If it does not work directly on the beta cells than how is it working? I think that the brain is particularly interesting. Is there something that triggers the brain to release factors to the pancreas? The other question is what is its relationship with glucose. Denise [Faustman] brought up a really important question: what are the levels of this in people with insulin resistance. Are we already maximally exposed? An answer to that question will help determine if we add more, whether anything good will happen. The other thing is that the paper only did one test to see if it causes insulin resistance. However, that was a bare bones test. There are too many questions on if it causes insulin resistance.

Mr. Caroddo: On iPS [induced pluripotent stem] cells, there has been a lot of publicity around those because of the Nobel Prize. Can you make any comments on the next steps in the development of possible products?

Dr. Weir: Well I may just again say that I have this preoccupation with type 2 diabetes. It's great being an academic type because I can daydream about totally impractical things. I'll bring up the idea of whether we could make iPS cells for each individual. And people say to me, "Oh my God, do you have any idea how much that would cost?" You guys are amazing at running these numbers, and I understand why you have to do that. But on the other hand, once you get some traction the prices fall. So if you think about what the reagents will cost to make iPS cells into some product, the cost of reagents is actually trivial. It's the development costs. I look at my iPhone and think about the technology that went into this thing yet you can buy it for a few hundred dollars. I don't know where the next 10-20 years will take us, but I think the idea of using iPS cells for studying pathogenesis is going to largely be academic, but I think assuming iPS cells don't have weird genetic breaks and things that make them unusable or cause cancer – which all these are important questions – but assuming you can make an honest to goodness beta cell, it seems like all kinds of things are likely to happen, and prices will fall.

Q: Do you have any perspective on how the FDA has been thinking of stem cells?

Dr. Segal: My impression with interacting with CDER [Center for Drug Evaluation and Research] is that the biologics division is extremely enthusiastic on the topic. […] They are focused on the cellular, biologic aspect of it. In my opinion they do not have enough experience with the therapeutic aspect of diabetes and they do not reach out to people who do have that background. They make comments on therapeutic trial design for diabetes that one would never see from the therapeutic area of CDER; just sort of bread and butter diabetes things – inclusion and exclusion – that are standard in diabetes clinical trials. In that

respect it is a bit of a challenge. The CDER group is small and they cover every therapeutic use of biologics including cellular therapies. I think their enthusiasm, however, outweighs their lack of background.

Mr. Caroddo: A lot of the discussion here is on treatment approaches. Have there been recent technologies that help with the diagnostic part of it? Are there any technologies that you are very excited about on that side?

Dr. Kenyon: I think there are opportunities with gene expression but the challenge is that it does not add value at this point because we do not have a way to treat people according to the findings yet. The science is ahead of what we are able to do therapeutically. Eventually, I think we will be able to much more quickly assess a person's status. Years ago I developed a test that could predict if an islet transplant was going to be rejected. It has held true. The problem is how we do not know how to reverse islet rejection. I think there is a lot of technology that will ultimately be helpful.

A NEW TARGET FOR DIABETES

William Bachovchin, PhD (Tufts University, Medford, MA)

In a fast paced presentation, Dr. William Bachovchin Executive VP, CSO, and Co-Founder of Arisaph Pharmaceuticals, described the potential for treating type 2 diabetes by inhibiting fibroblast activation protein (FAP). He opened his presentation by giving his view that several early-stage DPP-4 inhibitor candidates (Arisaph's ARI-2243 [phase 1] and DARA Biosciences/Point Therapeutics' Glu-boroPro [PT-360; preclinical]) appear to be associated with better glycemic efficacy than those currently on the market. He continued to postulate that these candidates' greater efficacy is due to them inhibiting FAP in addition to DPP-4. For background, FAP is strongly homologous to DPP-4 and, similar to DPP-4, will cleave GLP-1 and GIP. Arisaph's preclinical oral selective FAP inhibitor, ARI-3099, does not have acute benefits on glucose tolerance (after first dosing) but is associated with significantly improved glucose tolerance after four weeks of use. Dr. Bachovchin proposed that a selective FAP inhibitor could be used as a monotherapy or in combination with a DPP-4 inhibitor, or that a FAP/DPP-4 dual inhibitor could be an effective treatment option. We think that patients might adhere less well to a drug when they do not see benefits for about a month; however, it could be a more effective option in a fixed-dose combination or dual inhibitor, where the other mechanism of action provides more immediate benefit to drive adherence.

- **Dr. Bachovchin presented preclinical data suggesting that ARI-2243 and Glu-boroPro provide superior glucose control to Novartis' vildagliptin.** ARI-2243 produced a 2.5% placebo-adjusted reduction in A1c levels following eight weeks of daily dosing in ZDF rats compared with no significant change with vildagliptin (baseline A1c of ~8% for both) – given that vildagliptin is associated with significant improvements in glycemic control in humans we are surprised by these findings. In another study in ZDF rats, Glu-boroPro did not outperform vildagliptin in an acute OGGT, however it caused a placebo-adjusted A1c reduction of 1.7% after 44 days. In contrast, according to Dr. Bachovchin, vildagliptin was associated with an A1c decline of around 0.5-0.9% (baseline A1cs not provided).
- **In addition to improved A1c, ARI-2243 and Glu-boroPro were associated with** 1) a ~50% reduction in triglyceride levels, 2) improved insulin secretory profiles, 3) increased whole body insulin sensitivity index, and 4) a reduction in fasting glucose levels by 50%.
- **Dr. Bachovchin hypothesized that ARI-2243 and Glu-boroPro**'s **superior efficacy over DPP-4 inhibitors is because they also inhibit FAP.** Evidence for this includes that both ARI-2243 and Glu-boroPro are known to be inhibitors of FAP as well as DPP-4 and none of

the approved DPP-4s inhibit FAP significantly. Additionally, FAP knock-out (KO) mice demonstrate superior glucose tolerance but only in a chronic setting (similar to how ARI-2243 and Glu-boroPro had superior efficacy over vildagliptin after chronic use).

- **Arisaph has a preclinical FAP specific inhibitor, ARI-3099.** In a mouse study, four weeks of treatment with ARI-3099 was tied to a 50% reduction in AUC for the OGTT compared to control. ARI-3099 was also associated with a significant reduction in blood glucose at 20 minutes ($p < 0.01$), 40 minutes ($p < 0.01$), and 60 minutes ($p < 0.05$). Looking at the OGTT results in individual mice, Dr. Bachovchin noted that the glycemic results were robust.
- **Dr. Bachovchin stated that he would not postulate on why FAP inhibition improves metabolic parameters, however, he noted that a HFD only upregulated FAP activity in adipose tissue.** During Q&A he remarked that an FAP inhibitor's impact must differ from that of a DPP-4 inhibitor because its effects are only seen with chronic use, not following the first dose as is seen with DPP-4 inhibitors.
- **FAP KO mice have improved glucose tolerance, though not as bettered as DPP-4 KO mice** (FAP KO vs. control $p<0.05$; FAP KO vs. DPP-4 KO p-value not disclosed). FAP KO mice appear to be slightly more protected against high fat diet (HFD) induced hyperinsulinemia than DPP-4 KO mice. FAP KO mice on either chow or a HFD had a serum insulin level of ~40 ng/ml, whereas DPP-4 KO mice had a serum insulin level of ~50 ng/ml on a chow diet and ~60 ng/ml on a HFD (wild type mice serum insulin level on chow was ~45 ng/ml and on a HFD was ~110 ng/ml). FAP KO and DPP-4 KO mice are significantly (and to a similar extent) protected from HFD induced weight gain: FAP KO mice and DPP-4 KO on a HFD gained 4% of their body weight, whereas control mice gained ~7% of their body weight. FAP KO mice eat (~4 g/day) less than wild-type mice (~4.5 g/day) and more than DPP-4 KO mice (~3 g/day). FAP KO mice were also resistant to elevated serum cholesterol induced by HFD.

Questions and Answers

Q: It is a small molecule inhibitor?

A: It is a small molecule that is orally active. We have a stable of them. This data suggests that FAP may be a target for an agent that is specific for FAP. However, you might add this inhibitor to Januvia or you might use a dual inhibitor and then you would not need to use a DPP-4 inhibitor too.

Q: Has anybody looked at the distribution of FAP in humans?

A: That data is going to be published very soon. I am publishing a paper on human distribution.

Q: There have been questions raised about fibroblasts and scar formation being impacted by DPP-4 inhibitors? Have anybody studied that in FAP?

A: Not yet. Healing wounds does have more FAP in them than any other tissues, as do tumors. I think that is probably true. I am beginning to doubt if you can target FAP in the cancer environment.

Q: Can you comment on why it is only effective with chronic exposure?

A: I have some ideas but I do not think I can expand on them at the moment. Obviously, it means that it is not doing something like DPP-4 inhibitors that has a spontaneous impact. It is doing something over time.

Q: Are adipocyte macrophages involved?

A: We have not looked at that.

A NEW THERAPEUTIC OPTION FOR INSULIN DEPENDENT PATIENTS

Hakan Edstrom (President & COO, MannKind Corporation)

Mr. Hakan Edstrom reviewed MannKind's work to develop its inhaled ultra rapid-acting insulin candidate Afrezza (i.e., Technosphere insulin). Mr. Edstrom opened his presentation by recounting both the large burden of diabetes (25.8 billion people with diabetes in the US, according to CDC National Diabetes Fact Sheet 2010) and the large market potential for Afrezza (the US market for rapid acting analogs is $3 billion and growing, said Mr. Edstrom). He believes that Afrezza's time to peak action (12-14 minutes) and duration of action (~2.5-3 hours) gives it a more physiologic profile than rapid acting analogs. Further, he commented that the lower hypoglycemia, lower weight gain, and greater ease-of-use could be important market differentiators. MannKind expects to announce top line results from its phase 3 program the week of August 11, which would enable FDA filing in September/October. The company anticipates that a PDUFA date in March/April 2014 would follow. This timeline is the same as was presented in January at the JP Morgan Healthcare Conference (see page 26 at https://closeconcerns.box.com/s/rj1edd12eld3qorndbgl). Mr. Edstrom remarked that MannKind's manufacturing facility in Danbury, CT can service up to 450,000 patients at launch and can service two million patients after bringing additional capacity online (which would take six months to do post-approval).

- **Mr. Edstrom reminded the audience of MannKind's ongoing phase 3 program to vet its second-generation inhaler DreamBoat.** The company's type 1 diabetes study compares Afrezza delivered via the DreamBoat inhaler (n=133) to Afrezza delivered via the first-generation inhaler (n=133) to conventional rapid acting analog injections (n=133). The study is expected to complete May 17. The company's type 2 diabetes study compares Afrezza delivered via the DreamBoat inhaler (n=123) to placebo (n=123) in patients failing on metformin or metformin plus another drug. The study is slated for completion on June 12. Mr. Edstrom believes this study will expand the market for Afrezza by enabling earlier use of the product in patients with type 2 diabetes.

Questions and Answers

Q: What will it cost?

A: We expect it to be tier 2, which has a patient copay of ~$25. We expect it to be about same as insulin pens.

Q: Why is there less hypoglycemia?

A: The lower hypoglycemia happens because once you've digested your meal, your insulin level is back down to basal so you are not sitting there with a high amount of insulin in your blood.

Q: It doesn't affect the liver?

A: As we sit down for a meal, and the initial bolus of insulin is released, there is a signal effect to the liver. The belief is that you have such a fast uptake of insulin in the blood with Afrezza that it somehow mimics the signaling effect to the liver.

Q: Where does Afrezza fit into the treatment guideline from the ADA?

A: Our expectation is that patients will probably still start with metformin and maybe something else, but as you get to third type of option, insulin could come into play. Again, Afrezza might get an earlier use, particularly at mealtime and in transitioning patients not to a long acting, but to mealtime insulin.

Q: The trials done were in combination with metformin?

A: In our type 2 diabetes trial, those patients were on metformin. They continue their metformin therapy and then get an inhaler with Technosphere powder.

Q: The challenges of Exubera were at the dosing and pharmacy level. [Editor's note: this was Pfizer's failed inhalable insulin candidate.]

A: Afrezza will be at 10 and 20, then 30 and 40 insulin units (IUs). Ten IUs is equivalent to about 3.5 IUs of injected insulin. Our dosing is linear – that was the other problem of Exubera.

Q: In trials with Exubera, patients with type 1 diabetes showed increases in antibodies.

A: We have looked at immune responses, but there was nothing out of the ordinary. Exubera even had different kinetics for smokers – ours doesn't. We still won't recommend it for smokers, but in terms of insulin effect, it is the same.

GLYOXYLATE A POTENTIAL DRUG TARGET FOR TYPE 2 DIABETES MANAGEMENT

Dietrich Rein, PhD (Manager, Biomarker Development, Metanomics Health)

Metanomics Health is exploring the potential to use metabolite panels to detect diabetes earlier in disease progression. Dr. Dietrich Rein opened his presentation with a high-level overview of Metanomics' approach to metabolomics, which includes a pilot phase, identification phase, and validation phase to determine potential biomarkers for a disease and develop a metabolite profile. In type 2 diabetes, the company has identified over 80 metabolites associated with diabetes. Dr. Rein described one of the company's clinical cohorts for diabetes that contributed to Metanomics' identification of glyoxylate as a potential biomarker. In collaboration with the Bavarian Red Cross, Metanomics identified blood donors at high risk for diabetes and invited high-risk donors in for an OGTT to determine their diabetes status. Metanomics could then profile each individual's metabolites at the time of the OGTT and at three previous time points (~1.5 years, three years, and six years prior) by looking at the blood bank repository. Glyoxylate emerged as a potential early biomarker for diabetes (it hasn't been the strongest marker, but it is an interesting marker, said Dr. Rein). The company aims to better understand the role of glyoxylate in diabetes. Broadly, Dr. Rein believes that Metanomics company-wide efforts can help elucidate disease pathways, contribute to biomarker identification, and contribute to drug discovery.

Questions and Answers

Q: There's been a lot of interest in microflora and diabetes and obesity. What role does microflora play in glyoxylate?

A: Glyoxylate metabolism is high in gastrointestinal microflora. We did test if it comes from there by injecting glucose – it's an animal model – but we see the glucose injection stimulated the glyoxylate concentration, so we don't expect that microflora plays a role.

Q: Is there any data to suggest that glyoxylate is an earlier, better biomarker than glucose?

A: We are putting metabolite panels together from our pilot study that contains metabolites that changed earliest in the progression towards diabetes. We're working with two large cohorts where we can look at the progression. With panels of metabolites, we will be able to detect diabetes quite a few years earlier. The exact contributions of glyoxylate, we don't know yet.

TARGETING THE TRKB/BDNF AXIS FOR THE TREATMENT OF METABOLIC DISEASE

Mylène Perreault, PhD (Senior Manager and Lab Head, Pfizer, Boston, MA)

Dr. Mylène Perreault discussed the unsuccessful development of a BDNF-based therapy for metabolic disease. BDNF is a neuropeptide that binds to and activates TrkB to increase neuronal survival, plasticity, and function. Genetic studies have shown that loss-of-function in TrkB or BDNF leads to severe obesity in mouse and humans. These initial data led Pfizer to develop a TrkB agonist antibody called 29D7 that binds to TrkB and activates the downstream signaling cascade. In DIO mice this candidate potently lowered body weight by stimulating appetite suppression, with no effect on energy expenditure. Further studies showed that in ob/ob mice, 29D7 lowered blood glucose levels through pathways independent of body weight. Based on these studies, Pfizer developed a second-generation molecule called TAM-163 for human studies. TAM-163 lowered body weight in multiple rodent species, as well as in dogs. However, TAM-163 conferred the opposite effect in obese rhesus monkeys, increasing body weight by up to 35%. Subsequent studies showed that this species variance cannot be explained by differences in drug exposure or brain localization. Currently, Pfizer hypothesizes that different animals have differing neuronal compositions in the areas accessible to TAM-163; at this time, the theory has not been confirmed. Dr. Perreault ended by reviewing a single-ascending dose study of TAM-163 in healthy volunteers that found no effect of TAM-163 on appetite, food intake, or body weight. She concluded that agents targeting TrkB are unlikely to be suitable as a therapeutic approach for metabolic disorders.

Questions and Answers

Q: When we study the metabolic syndrome, we often see that the patients are at the end-stage of the disorder. They've had the disease for probably 20 to 30 years, and now we see them with obesity and diabetes. It's interesting –your rodent models were already overweight and insulin resistant and had these manifestations. The monkeys were lean and were not the typical kind of metabolic syndrome patients.

A: We tested in two strains of monkeys. Some were lean and some were obese.

Q: Were there differences in the neural physiology between the animals at the early stage of the disease versus animals at the end stage?

A: We didn't see any difference. There may be some difference in the circulating levels of BDNF, but studies need to confirm this. From lean to obese animals, we saw consistent effects.

Q: The direct question is what would the antibody do in lean mice?

A: They lose weight. We also tried guinea pigs. Every single species we looked at in the preclinical stage lost weight.

Q: Regarding the dose response, you couldn't go above 120 milligrams?

A: The trial was designed to go above 200 milligrams, but it was limited by the toxicology.

Q: There must be some endogenous regulation of BDNF. How is that affected by the drug?

A: We looked at circulating levels of BDNF after TAM-163 and 29D7, and we didn't see any effect. Again, it's not clear that circulating BDNF levels mean much in this disease state.

Comment: I think it's so valuable at these meetings to present negative data as well as positive data. It also shows the value of doing human trials at an early time point because preclinical models don't paint the whole picture.

MSIA IN DIABETES ANALYTICS

Urban Kiernan, PhD (Business Development Manager, LCD-Affinity Pipette Consumables, Thermo Fisher Scientific , Boston, MA)

In a very technical talk, Dr. Urban Kiernan posited how scientists can use next-generation technologies to re-examine old biomarkers and generate new insights. He focused on Mass Spectrometric ImmunoAssay (MSIA), a "simple and elegant" approach to purifying proteins and peptides for high-sensitivity analytical measurements. Thermo Fisher's technology uses pipettes that house a proprietary immuno-affinity column filled with antibodies. The antibodies can bind to analytes (e.g., protein of interest) in complex biological fluid and pull them out of the solution. After a series of separation and purification steps, the protein is ready for mass spectrometric analysis (e.g., identification, quantification, etc.). In discussing the clinical applications of MSIA, Dr. Kiernan focused on two examples. First, he highlighted that MSIA has an advantage over conventional immunoassay approaches because it is able to differentiate between different forms of a target. For example, though insulin has historically been a difficult biomarker to analyze, MSIA can differentiate between Apidra, Novolog, and Humalog. Second, Dr. Kiernan noted that MSIA can be used as a functional bioassay to determine DPP-4 activity. He remarked that this technology could help HCPs identify DPP-4 inhibitor users that are particularly susceptible to developing cancer as a result of the therapy.

Questions and Answers

Q: You mentioned the DPP-4 inhibitor activity assay. Then you mentioned cancer and other changes. I didn't see the link between measuring the activity level and the actual pathophysiology that you described.

A: That's a good question. We'll let the end users look at the samples to see if there is a pathophysiological link. I want to see if there is a biomarker that can identify whether the patient is going down the wrong road and if we need to take him off the DPP-4 inhibitor and put him on an alternative path. The pathophysiology is important and we'll let other people – much smarter than I am – look at that. This is one piece of data that can be added to a complex picture.

Q: I don't see the link either. Unless you say that you can identify substrates that are accumulating toxically.

A: I understand your point. This is an example of the technology being able to look at the activity of specific enzymes. This is just a point that's more applicable to what this conference is doing. There are other systems where this technology can be applied. This may be a piece, it may not be a piece. But there is a clear-cut need with the DPP-4 inhibitors in terms of identifying a biomarker to improve treatment.

Q: [Jokingly] You must have a lot of interest from the Olympics and sports authorities.

A: Actually, not so much with humans because there are legal issues involved. There was the big debacle with Lance Armstrong. But for the regulatory bodies, the less information for them the better because they don't want to get sucked into the legal aspect. There are other industries, like horse racing, that are keener on getting more information because there is less litigation involved.

CLINICAL PHARMACOLOGY AND THERAPEUTIC EFFICACY OF ANTIDIABETIC DRUGS IN THE DIABETIC MINIATURE SWINE AND NON-HUMAN PRIMATE

Alain Stricker-Krongrad, PhD (Sinclair Research Center, Columbia, Missouri)

Dr. Alain Stricker-Krongrad expounded that the miniature swine and non-human primate represent better models for type 1 and type 2 diabetes, respectively, compared to rodents. To open, he noted that mouse models of diabetes have been heavily criticized, with good reason. While most type 1 and type 2 research has been conducted in rodent models, rodent-based discoveries have been associated with high rates of failure. He concluded that rodent models have extremely limited clinical value and listed several drawbacks to their use. Dr. Stricker-Krongrad then highlighted the benefits of using diabetic miniature swine. Showing several slides of data, he explained that swine represent a valid and predictive model for subcutaneous insulin administration in type 1 diabetes for three reasons: 1) they have the same skin structure as humans; 2) insulin has identical potency in swine and humans; and 3) humans and swine metabolize insulin in similar ways. Dr. Stricker-Krongrad then remarked that while swine represent the best preclinical model for type 1 diabetes, they are poorly suited for type 2 diabetes because they react inappropriately to a high-fat diet. In contrast, non-human primates make excellent models for type 2 diabetes. Monkeys exhibit nearly identical responses as humans after a high-fat diet or SGLT-2 inhibition, and have been used to assess myriad pharmaceuticals. In closing, Dr. Stricker-Krongrad stated that animal models for diabetes should be based on scientific rationale and should be selected to answer specific clinical questions.

Questions and Answers:

Q: So you don't believe in transgenic rodents that are supposed to mimic humans?

A: If you're interested in the link between type 2 diabetes and Alzheimer's, for example, don't look at the rodent. Look at other animals like dogs or cats or non-human primates. The point is that although initial research is based on what is observed in the rodents, we shouldn't put too much weight on the data. Let's go back ten years. Ten years ago, a lot of the clinical failures were due to a lack of safety, poor metabolism, etc. So what did the industry do? It went back to the drawing board to do more safety assessments in the right species. What I'm arguing for is that instead of doing a mouse study and jumping into a phase 3 trial, let's do more exploratory work in other models.

Investment and Mergers and Acquisitions in Diabetes

PANEL DISCUSSION

Moderator: Richard Caroddo (Senior Business Development Executive, Medpace, New York, NY).

Mostafa Analoui, PhD (Head of Healthcare and Life Sciences, The Livingston Group, New York, NY); Tomas Landh, PhD (Director, Novo Nordisk, Copenhagen, Denmark); and Thomas Kuhn (CEO, Poxel, Lyon France).

Mr. Caroddo: A good place to start might be the partnering deals done within big pharma recently. For example BI/Lilly and BMS/AZ. Can you comment on your perspective on those recent deals among big pharma? Is this a trend?

Dr. Landh: So Novo Nordisk is not very famous for making large alliances in the diabetes area. Trust me, we are approached by many of our colleagues in the peer group from time to time. This has been more frequent in the last two years, indicating the increasing appetite for doing these kinds of AZ/BMS deals.

Of course, in diabetes that's going to be a challenge for us. The pipeline we have at Novo Nordisk does not really permit sharing. Of course the environment can change at any time. We're watching the whole ecosystem very carefully, from the payers to the regulatory environment. We are, of course, always adapting to that. But right now Novo Nordisk is not taking that approach, but we can clearly see an indication of increase in this type of activity.

Mr. Kuhn: I want touch on that. We've seen the Lilly and BI deal. We've seen the BMS and AZ deal. We've seen it also in Japan – there have been a lot of agreements this way. More and more are coming, even in China and in the emerging countries. I anticipate that given the market access conditions and the regulatory hurdles, there will be more and more deals. We heard this morning that AZ is pleased with its deal with BMS. They rely on these three products now. I anticipate that we'll see more similar deals among big pharma in the future.

Dr. Analoui: This morning, I saw that Pfizer and Merck announced a major collaboration on the SGLT-2 inhibitor program. The rumor is confirmed. I used to be at Pfizer, and in my tenure there, Pfizer acquired three companies adding up to $30 billion all together. Then we said we weren't going to do that anymore, then it happened. This type of collaboration can be driven by what a portfolio needs, what a market demands. It can also depend on individuals driving these deals. Big pharma is like musical chairs, someone who was at Amgen is now somewhere else where someone knew someone at Wyeth, and this discussion was ongoing in the past. There's a very difficult chemistry there. Even if we have our own quantitative method for assessing the value of an asset, we always get surprised by the personal relations angle, which surprises us. In fact you heard this morning of the $210 million private investment supporting phase 3 [for Intarcia's ITCA-650] – the largest private investment we have seen in recent years. From my perspective, it's very difficult to purely analyze from a portfolio management aspect. It's a very complex situation.

Mr. Caroddo: I know that it seems like one of the main drivers of deals among big pharma is that it's a way to minimize risk. Diabetes drug development is a risky proposition. For you guys, what do you see as the main drivers for the big pharma deals?

Dr. Landh: It's such a crowded space. Furthermore, combinations are starting to become extremely important. The offerings to the HCP and prescribers are getting more and more complex. Share of voice is extremely important. If you don't have the share of voice out there, it's not going to happen for you. When you launch, you know that the first weeks set the trajectory for success. I think this type of collaboration is as much about share of voice as it is about share of risk. That's my opinion on why we have seen such an increase in the number of collaborations.

Dr. Lauren Shearman (Executive Director Scientific Licensing & Acquisitions, Merck, Whitehouse Station, NJ): With regard to the Merck/Pfizer collaboration, it was a very strategic decision. We recognized that we had a portfolio gap in that we had not developed an SGLT-2 inhibitor internally. In the past, our franchise wasn't really keen on the mechanism. But with clinical proof of concept and Invokana [J&J's canagliflozin] getting approved by FDA, that really drove us to continue to consider that type of collaboration. A lot has to do with risk and costs. Given the CVOTs required for these types of therapies, they end up being really expensive large clinical trials, so if you can share it with someone that's great. And of course, leveraging the possibility of combination therapies is attractive. So an FDC of sitagliptin/ertugliflozin and metformin/ertugliflozin – so with the monotherapy that's three therapies that we'd get out of the partnership. Each party bringing something to the table to leverage makes it more appealing to both parties.

Mr. Caroddo: Are there any highlights or differences between this deal and the BI/Lilly deal or some of the others?

Dr. Shearman: I can't really speak to that. It's a global deal but it's worldwide ex-Japan –we realized that the drug would have a late entrance to the Japanese market because there are a lot of companies close to filing in Japan. That's one difference from some of the other collaborations. Also, the deal is just around the SGLT-2 inhibitor. No insulin, for example. So maybe it's not quite as broad as some of the other collaborations. But you know, you think of Merck and Pfizer as always competing. You always refer to them as the evil empires. We realize that we're actually more alike than we thought. It ended up being a very good collaboration. Hopefully it goes forward in a good way.

Q: For 50 or 60 years, pharma had a free ride on the Framingham study or similar studies. Those kinds of studies provided biomarkers, and all we had to do was improve cholesterol or glucose or blood pressure levels. And major classes of blockbusters got approved off of those measures. Now outcomes are being asked for, and there aren't Framingham studies to show SGLT-2 inhibition has done that so it's going to cost a lot more. So it's a strategy to reduce the risk of these bigger studies. And we heard this morning from Steve Burrill about outcomes and how important it's going to be to have those as endpoints as opposed to biomarkers.

Mr. Caroddo: Even if you look at the recent J&J approval [of Invokana], they have a whole host of post-approval studies that they have to do. They're going alone. It's pretty expensive.

Mr. Kuhn: All DPP-4 inhibitors and GLP-1 agonists have already started their post-approval trials. It's just standard now to anticipate that. There's a huge cost associated with that, as well as a risk. The study design might mitigate some risk, but you still have a risk. From a shareholder perspective, the resources are just tremendous to bring such a product to market. Combining forces can mitigate that.

Q: A question probably for big pharma folks – I'm curious on your perspective on SGLT-2 inhibitors as a class. Clearly it's not a perfect mechanism. Where do you see it being positioned in the treatment algorithm? And I'd like to hear your perspective too, Lauren, at Merck. The DPP-4 inhibitor/SGLT-2 inhibitor combination has shown impressive and durable A1c control. How do you envision this new pharmacology coming into the marketplace?

Dr. Shearman: I guess that the liabilities haven't born out too badly yet with respect to urinary tract infections. I'm hearing a lot about other infections, but it's more a tolerability issue. Given that you're getting weight loss, the drug is very appealing. Certainly it can be a second or third line therapy. I think J&J is positioning it as a second line therapy. They're going after sitagliptin. For us, we're thinking of it as a third line therapy. If someone fails sitagliptin or metformin, we can add an SGLT-2 inhibitor. But J&J is viewing it more as a second line treatment. But it will be determined by the physicians that prescribe it.

Dr. Landh: I would like to make a comment on CVOTs. I think we're facing an even more challenging regulatory environment, and we'll simply have to adapt and probably also do more adaptive launch strategies. That's something that we foresee. We've always gone with global strategies so far. As you know Tresiba was not approved here in US but has been approved in a number of other countries and regions. I think it's very important that we adapt to increased challenges. The regulatory environment changes from time to time. You really don't know if your outcomes studies will be post-approval or pre-approval. It's just that nobody can foresee that based on the data. We all try to do the best development plan of course, and this is a really big risk.

Mr. Kuhn: That's another reason why pharma companies partner. Clearly there are different regulatory considerations in different countries. And pharma companies have different experiences. Some may have more experience in the US, some in Europe. By concentrating all that, it's a win-win situation.

Mr. Caroddo: Related to that, obviously years ago, there were so many deals between small pharma and big pharma with in-licensing and acquisitions. That seems to have slowed down in the diabetes space, maybe because of the risk. Poxel, as a small company developing a diabetes drug, how do you see that changing in terms of potential partners for you? In general terms, how do you see it in terms of general partners and the appetite of the companies you could partner with?

Mr. Kuhn: Clearly we've seen a change there. I think someone said this morning, and we've really seen this, is that more and more now pharma is interested in early stage assets. So in the past we used to have this statement that clinical data were important and represented interesting inflection points. Now pharma is interested in the early stages. So there is clearly much more emphasis and focus there, much more than anticipated. Then, as you said, in contrast to that for late stage assets, in terms of ability to progress, as a biotech company you're limited by financing from progressing on a global scale into a phase 2b or a phase 3 program. So it's definitely difficult. The discussion with pharma is difficult because of your lack of back up plans.

Mr. Caroddo: From the Novo Nordisk perspective, what is your viewpoint on working with and licensing products from early stage companies? In general, do you view that as an area of opportunity? Or do you look for even earlier stage opportunities and academic opportunities?

Dr. Landh: We are always open minded to any stage. We definitely focus on pre-IP and early academic work. Hopefully, we have not missed too many opportunities in the clinical stage. If we did, I would probably lose my job, I guess. But we see even collaborative efforts pre-IP before there have been any IP generated. That's the trend for us. I think that many pharma companies are following that. We also see that there were collaborations between big pharma and medium-sized pharma a few years ago. That has dampened. Now we are trying new models. Now it's more pre-IP discussions with academia. That's where it's going now. We realize that we can do so much more in supporting them for both the translational aspect of a new target, and also in exploring new areas that we might be interested in. So we can direct them in the way we'd like to see.

Mr. Caroddo: From an investment perspective, obviously some big pharma companies have done strategies for partnering with VCs. GSK did that deal with Avalon to set up smaller companies. Merck, I'm sure, has done things setting up virtual-type companies. Is that something that will continue to happen as a way for bigger companies to spread the risk and get multiple product opportunities?

Dr. Analoui: That seems to be a strategy. The idea is creating small pockets of research that collaborates with local academic communities and also, interestingly, creating venture funds they co-invest in with other companies. And even more interestingly at that, like what Merck has done, companies are now developing two types of funds: one that is invested strictly in the line of the product or business, and something like a global health or innovation fund that Merck and others have. In such a fund, they invest generally in tools and platforms that may or may not directly benefit Merck but in general moves the ball in the right direction. That shows some open-mindedness of pushing science, since it benefits the whole of pharma companies. Similarly, there are private/public partnerships involving NIH. Those are all positive signs. Bear in mind that for some, it's very difficult for pharma to make a quantitative assessment of what the ROI is. Based on my experience, I was involved with an initiative, they tend to die very quickly. As the next bean counters come to the table, they say, "Alright this is the money to put into this particular initiative, what is the ROI?" It's very difficult to measure, and therefore they have a very short lifespan. Now coming back to give you our perspective on the M&A side, before today's discussion I looked at our database to see if I could come up with some meaningful numbers regarding diabetes. Because it's so

sparse, it's hard to say, but to give you a general landscape on what's happening in M&A in the past 12 months, definitely M&A is up in terms of multiples. When you look at multiples of 2012 compared to the first part of 2000, we have gone from 1.5X to 3.4X, which is very important. That means that buyers are willing to pay and pay more these days. The other thing that was surprising for me was that the multiples for European deals were almost half of what we pay in the US. It seems to me that either you're doing bigger deals that are more expensive or more optimistic deals. It's hard to say what the reason is. These are all positive in my view. The negative side here is still you've gone from five years from initial investment to exit to roughly nine years of investment required for companies to exit. That's the challenge we see in smaller biotech. Is there enough to support them and keep them alive to support them until exit?

Mr. Caroddo: Regarding the nine years, it seems to be on the horizon of what a traditional investor will stick around for. Is that a limitation?

Dr. Analoui: That's definitely a limitation. The typical life in healthcare is about 10 years. From coming in to getting out – if you add the due diligence and exit – at best, you're looking at 12 years. And this is the nature of life science investments. Sixty percent of investments never pay off. Maybe you lose money. Of the other 40%, some break even and some will make money for the investment. That's always the general rule. It's difficult for those coming from other fields to see these numbers – they seem quite shocking. If you look at the odds of drug development, from screening to the end of phase 3, what is the chance of success? Even if you have an FDA approval, it doesn't ensure that you will make money.

Dr. Landh: Mostafa, do they have any figures on returns or multiples for diabetes in the Saudi area?

Dr. Analoui: I do have numbers in my database. The numbers are so sparse, and taking the average creates very unrealistic numbers. The easiest way is to just share the numbers. Most of the numbers are not publicly available. Pharma does not disclose, so we have to rely on our sources or use our best guesses in these areas. That's why we don't publish these numbers – because we're not sure this is 100% comprehensively accurate.

Mr. Caroddo: Another topic is the indications associated with type 2 diabetes. In addition to the disease, you have other comorbid conditions. Do you see any of those associated areas or indications as investment areas? As the incidence of type 2 diabetes goes up, the incidence of some of these diseases will go up as well. Is there an opportunity there?

Dr. Landh: We entered the area of late complications only two years ago. We're newcomers to the field and have almost nothing in the clinical pipeline. We're very open minded to listening to big pharma in this area. We clearly see that some of the microvascular complications are difficult to pursue due to the endpoints and the lack of biomarkers. There are some challenges there. But we have announced that we're focusing on retinopathy and nephropathy. There are definitely some low hanging fruits in those areas. It's being vigorously explored by other companies so competition will be sharp, but the unmet need is enormous. Of course, we'll focus on proteins and peptides, and certain mechanisms of actions that we have not disclosed. However, when it comes to the macrovascular complications, it's difficult for us. We're not a cardiovascular company. We're in diabetes and diabetes, and more diabetes. The cardiovascular component is certainty a big part of it. But that's an area where I think we'd very much welcome a more collaborative effort. The unmet need is there – there's no doubt about that.

Mr. Caroddo: Is it a different sell, though, from a marketing point of view if you get a product to market with associated implications would that require new capabilities at Novo?

Dr. Landh: Definitely, but that's a luxury problem at that point. In a way, we also have done that for a number of years – we design any diabetic asset to have benefits for CV or complications. And that's always been something we strive for. So if we find a new blood glucose-lowering agent, we would definitely then try to identify an additional, or multiple additional, benefits for comorbidities or complications. We always do that. But we don't see ourselves launching something in the future that doesn't have these properties.

Dr. Analoui: I think that part of your question is related to whether the pharmacologic solution is the only player in this market. It seems that therapeutics is the central focus of today's conference. From our perspective, we see a lot of device approaches either for the management of diabetes or for the following complications. I think that that Ed Damiano talked about the feedback loop system that he's created for optimizing diabetes. When you look at it and see that there is a 40% lack of compliance among diabetes patient that are undertreated, you can achieve a lot by optimizing treatment. So we see a lot of efforts from our perspective. Companies are coming up with solutions in those areas. As you go downstream in the disease progression – one of the most brilliant efforts that we haven't dared to touch yet (because it's too early) is the regeneration of kidney tissue that's being done at Massachusetts General Hospital. It's so fabulous that it's hard to believe. We see those activities – anything from a software to the recreation of kidney tissue. From our perspective, we consider them as a diabetes portfolio.

Mr. Caroddo: Is anyone in the audience involved in devices or diagnostics?

Comment: I think one of the things you brought up was late stage disease affiliated with diabetes but that happens much later. Foot ulcers is one of those indications that has very few treatment options available. I didn't hear much about any of the big or small pharma companies spending lots of resources developing treatments for it. The biggest problem is an endpoint. It's very hard to reach a conclusion primarily because there's not much debate on it. For example is a person's foot closer good enough vs. getting complete closure? There have been lots of things that have not been brought up.

Dr. Landh: We're not interested because of the lack of endpoint. So we're into this loop now. We're very open minded – if there is good evidence for new endpoints, we'd go into this area as well. However, we would not go into topical treatments. That's not our focus.

Mr. Kuhn: I think another aspect of tackling microvascular complications specifically has been the years and years of work and the many failures, unfortunately. I work in pharma, and before I worked a lot on neuropathy for diabetics. We made huge investments there, and we never succeeded despite investing in one target after another. So I think nephropathy is currently where there are several cases – the endpoints are more clearly defined. You've got biomarkers, and in terms of the clinical progression, you can work into that. The potential is just enormous there like you said. So we shall see, but I think the risk is so high that pharma and even biotech are not fully ready to jump into this.

Mr. Caroddo: On the topic of diabetic foot ulcer, there's one company that's doing a pivotal study in diabetic food ulcer. I only bring this up because they're a small company. Clearly, with an indication like that, they can finance a program in that specific indication. I'm sure that if it were for the larger type 2 population, they wouldn't be able to finance it. It's an example of a specialized indication where a company could go alone.

Comment: We took a different tactic. We have an integrated practice unit, an IPU, or what Michael Porter calls organizing around the condition. We created a composite disease severity index. Every patient with a type 2 diabetes diagnosis, when they come through they get a phenotypic diagnosis. We're building an IT platform that is an EHR-coded diabetes registry, which allows it to be mobilized. We're creating a population where you can study

biomarkers and a real world patient population for new drugs. Or for old drugs you can see where they work. We're on the other end of things, but we think there's going to be a meeting of some sort.

Comment: I hear your points that the endpoints are not very clear. What we've seen is that the interest in the small companies have been a little higher on those comorbid conditions, primarily because there is a lot of flexibility, regulatory-wise, for defining the endpoints and defining your disease outcomes. There have been some success stories, primarily because it doesn't take a lot of investment to do a medical device trial, for example. Since the endpoints are not very defined, you know very quickly with a small population if it's working. When we went to the FDA for discussion, we saw a lot more flexibility in terms of accepting different approaches. But we're seeing very few of those from companies that have more experience than the smaller companies.

Dr. Shearman: I was just going to say that we have a similar strategy to Novo Nordisk with regard to diabetic foot ulcers. We're also not interested in topicals, but we have a more opportunistic view on it. If someone has phase 3 data, we are interested in looking at it.

Mr. Caroddo: One other topic to address is emerging markets. Tomas, we were discussing Novo Nordisk in China earlier. Maybe if you guys could speak to if you see certain countries or regions as drivers of investments or acquisitions that you might make. Or is it just part of an across the board strategy?

Dr. Landh: So we invest heavily in China, of course. There's no doubt about that. We've done that since 1989. It's a long-term investment that has paid off fairly well in diabetes. Quite often, that's new to a certain extent – we are more and more forced to make investments in emerging markets to have market access. This is of course both good and bad, I would say. It's something that we oblige to. But that's new when you enter emerging markets in particular. You can see this trend in the Mediterranean area, in North Africa, and in the Arabic regions. Diabetes is common in Africa. There's much more undiagnosed diabetes of course. There's an enormous untapped opportunity in Novo Nordisk getting people to be under control and compliant. Any innovation in that space would help so much, even more so in emerging markets. Because there, you have the issue where people can't afford to buy 30 days of insulin supply. There is no way. You have to be innovative in that space. There's a lot of room for innovation and opportunity.

Mr. Caroddo: My understanding is that Novo Nordisk has done it more as an in-house approach to setting up operations and marketing in countries as opposed to doing any kind of joint venture partnerships.

Dr. Landh: As I said, we are not very famous for these kinds of partnerships. When we can do it on our own, we try to do that.

Mr. Caroddo: Mostafa I know this is a bit of a general question, but do you see investment opportunities revolving around specific countries?

Dr. Analoui: Again, we haven't made any investment in those markets. This is based on my personal experience. It's clear that diabetes is growing much faster than many other areas. I have a couple of observations. You know that in India, there has been a lot of progress in creating different types of insulin. Biocon is probably the poster child there. They've managed to create so much insulin that they're selling it to their western counterparts. That's a good sign. There's a positive parameter in those areas: most healthcare systems in those areas are managed by the government. So they can tolerate a little bit more expensive therapies and solutions for the population. What makes it difficult is the lack of general education and adherence with treatment. These are based on my personal experiences.

Comment: I actually had five trips to mainland China in the last year. One was to see a diabetes hospital that they are building in a third-tier city. I started to get some understanding of the Chinese system and the emerging market that's there. And then another opportunity I had, because I'm an infectious disease specialist, was to do a consult in an infectious disease ward in Ganzhou. What we found is that it's very different on the ground from what we hear here in the US. Most people there cannot afford the types of drugs we can afford, and the providers and hospitals don't even have access to the drug. This patient had scrub typhus, and they didn't even have IV doxycycline. What we're told, and what is actually happening, is sometimes different. What is definitely happening is capitalism driving a fee-for-service model like in the US a few decades ago. The hospital worries about making the money and the patient is discharged with no structure to manage care at home. From a capitalistic standpoint, that's what's driving the emerging market there. They're really not interested in some things we're interested in, like improving health and improving wellness. So there's a real disconnect there. It's like we're talking about two different incentives.

Dr. Landh: It's extremely important to meet with the Chinese government, both local and central. We can help them a lot. We have academic programs. We're really trying to educate both the HCP and physicians and the patients – the whole value chain. It's extremely important that we take that responsibility once we've been granted a marketing authorization in China. We have a responsibility. They want to give care to everyone in China. But it's 1.3 billion people. That's not easy, especially from a logistics perspective. We can help them.

Comment: In spending time with them, they are very suspicious of Americans and very suspicious of anything western. So that approach, "let me help you understand this," is sometimes rebuffed because they believe that they are the Middle Kingdom. So part of this is that "we don't need to be told what to do." It's a fascinating culture, and I'm speaking from experience.

Dr. Landh: That's not the approach you should take, of course, you should try to take a much more humble approach and a "let's do this together" approach. If you do it in the right way, it's very successful

Comment: And it's not just how you frame it, they have a long history of distrust of the West, and it's hard to get over. And I'm speaking from an American standpoint here from interactions with many different people. Many people coming from the West say doing business in China is challenging. Companies can suddenly be nationalized. I know people like Novo Nordisk have been doing this for a long time. But unless you have, it can get very dicey.

Comment: I've been to China more than 40 times. At one point, I owned a pharma company there; it was a disaster. What we know is that China had a national healthcare system not unlike a place like Cuba. That has essentially been destroyed in the last 12 years. They put in a new system built around doctors writing prescriptions for expensive medications. That system now has 900 million people without healthcare. We think we have problems with our healthcare system – China's got it in spades. It is going to be a huge problem going forward. It is a system that is designed in a capitalist model and it's designed for the 300-400 million people that, on a world standard, are lower-middle class.

Innovative Partnering & Licensing Strategies

SURVIVAL OF THE FITTEST: INNOVATION HURDLES AND CONTEMPROARY DEAL MAKING IN TYPE 2 DIABETES AT HEPTARES THERAPEUTICS

Daniel Grau (President, Heptares Therapeutics, Hertfordshire, UK)

Daniel Grau introduced us to Heptares' two discovery-phase diabetes programs: Heptares aims to develop a small molecule oral GLP-1 agonist for type 2 diabetes and a GPR39 agonist. Mr. Grau stated that Heptares solved the structure of a Family B G-protein coupled receptors (GPCRs), the family of which the GLP-1 receptor is a member, and that they have identified novel binding sites that are applicable to GLP-1 agonism. Thus, Heptares aims to develop a small molecule GLP-1 agonist to fit the GLP-1 receptor and could be taken orally. Grau described GRP39 as an emerging GPCR target that requires zinc as a cofactor. He stated that a number of animal models have suggested it has the potential to be disease modifying in that it is not just protective of beta cell function, but promoted neogenesis of beta cells (he did present specific data on this front).

PARTNERING OPPORTUNITY: NEXT GENERATION GPR119 AGONIST, ARRY-981

Brad Fell, MS (Senior Research Investigator, Array BioPharma, Boulder, CO)

With Array's shift in focus to oncology, the company has decided to license out its GPR119 agonist, ARRY-981. ARRY-981 is an incretin secretagogue and a glucose-dependent insulin secretagogue. Brad Fell presented Array's preclinical data on the compound in hopes of catching the eye of a sourcing director in the audience, stating that if Array had the funds to allocate to diabetes, it would have taken this into phase 1 on its own. Array has completed preclinical studies for ARRY-981, and it is ready for IND submission (this is the first update we have heard on the compound's status since Array announced the commencement of preclinical studies). For more background on ARRY-981, please see our report on Mr. Fell's presentation at GTCBio 2012 on page 6 of our GTCBio 2012 Day #2 report at https://closeconcerns.box.com/s/33372abe83f27cc95102.

- **Mr. Fell stated that ARRY-981 is different from previous clinical candidates in structure, has shown superior efficacy in preclinical trials, and has improved physiochemical properties** (Mr. Fell stated that "poor physiochemical properties have plagued this field"). In terms of structure – whereas GSK, Arena, and Metabolex's candidates were structurally very similar, ARRY-981 is structurally distinct. Mr. Fell says this has given ARRY-981 an advantage in terms of solubility, which has translated into a favorable PK profile. Additionally, Array has demonstrated efficacy of ARRY-981 with mixed-meal tolerance tests and oral-glucose tolerance tests in ZDF rats to address the issue seen with Arena/J&J's candidate (see below). Preclinically it has shown durable and superior glucose-lowering in 28-day studies in ZDF rats and DIO mice compared to other GPR119 agonists, and the 3 mg dose has demonstrated additive efficacy in combination with metformin, sitagliptin, and dapagliflozin (with a synergistic effect on nonfasting glucose in combination with metformin). It has also been shown to lower triglycerides.
- **Mr. Fell stated that "the clinic has not been kind to GPR119."** Four clinical candidates have been dropped or have had rights returned: AZ returned the option to Prosidion's PSN-821 in 2012 after a phase 2 study in type 2 diabetes; Sanofi returned rights to Metabolex's MBX-2982 in 2011 after a phase 2 study; J&J returned rights to Arena's APD-597 in 2011 after a phase 1 study in type 2 diabetes patients in which modest single-dose AUC glucose lowering did not translate into meaningful 24-hour weighted mean glucose lowering after 14 days (J&J also stated that it

was not effective in the presence of food); and GSK halted development of GSK1292263 in 2011 after a phase 2 study in type 2 diabetes in which the compound did not reduce 24-hour glucose profiles on day 14 despite reductions in AUC glucose on day 1. To our knowledge, companies continuing to develop GPR119 agonists include Zydus Cadila (ZYG19, phase 1) and Neurocrine/BI (preclinical).

Questions and Answers

Dr. Tomas Landh (Novo Nordisk, Copenhagen, Denmark): What was the primary reason for letting these diabetes assets of yours go?

A: We had, and we have had, a number of different therapeutic areas we've worked on. We felt that in order to be competitive, we needed to focus. We partnered 11 projects with different people. Seven, well six are in phase 2, one in phase 3. The projects we've kept in house and pushed into clinic are oncology projects. So we felt that as a company we should focus on those. That's it. So we're now an oncology company.

MERCK'S PARTNERING STRATEGY IN METABOLIC DISEASES

Lauren Shearman, PhD (Executive Director of Scientific Licensing & Acquisitions, Merck, Whitehouse Station, NJ)

Dr. Lauren Shearman reviewed many facets of Merck's partnering strategy in diabetes. Most interestingly, she discussed Merck's expectations for the future of the diabetes landscape, what Merck sees as the unmet needs in diabetes, and identified Merck's strongest areas of interest in next generation oral therapies. Notably, Dr. Shearman commented that fixed-dose combination (FDC) is "where everyone is going" and that very few new oral mechanisms would emerge in the next five years. Like many others today, Dr. Shearman expressed the sentiment that new diabetes therapies need to do more than "just" lower glucose, whether it be reducing risk of macrovascular or microvascular complications, protecting beta cell function, or simplifying current treatments.

- **Dr. Shearman discussed expectations for the future of the diabetes landscape.** She forecast that metformin would remain the mainstay first line therapy with sulfonylureas (SFUs) continuing to decline; that safety concerns would continue to impact the TZD class, limiting the impact of pioglitazone going generic; that the DPP-4 inhibitor class would continue to grow and increasingly displace SFUs and TZDs; that GLP-1 agonists would continue to grow, primarily in obese patients and those failing oral therapy; that insulin analog use would continue to grow, especially in emerging markets; and that very few new oral mechanisms would emerge in the next five years. She speculated that perhaps GPR40 agonists could make an entry, but beyond that there does not seem to be an obvious next wave of oral therapies.
- **In Merck's view the unmet needs in diabetes include** new therapies that can be used in combination with existing agents to improve glycemic control; therapies with improved durability that prevent or reverse beta cell failure; therapies that reduce risk CVD or other comorbidities; therapies that prevent the onset, delay progression, or reverse microvascular complications (though one could also argue that achieving good glycemic control would effectively achieve the prevention of microvascular complications); insulins with improved benefit/risk profiles (e.g., with regard to hypoglycemia and weight gain); therapies that simplify treatment and improve adherence (she stated that fixed-dose combinations is "where everyone is going"); and obesity agents that are safe, efficacious, and well-tolerated.

- **Dr. Shearman highlighted glucose-dependent insulin secretagogues, novel insulin sensitizers, and novel gut peptides as Merck's areas of focus in developing next generation oral agents.** Merck publishes its areas of interest twice a year (in January around JPM and in June around ADA) that can be found at www.merck.com/licensing.

NOVO NORDISK PARTNERSHIP AND DEVELOPMENT STRATEGY

Tomas Landh, PhD (Novo Nordisk, Copenhagen, Denmark)

Dr. Tomas Landh discussed Novo Nordisk's R&D strategy and focus. He stated that Novo Nordisk does not "entertain drug discovery of small molecules anymore" and focuses solely on protein development, since this is where its expertise lies. Notably, he relayed that Novo Nordisk's strategy is to use phase 1 studies as more of an exploratory development stage as opposed to only advancing compounds to phase 1 that it has an interest in pursuing commercially. After phase 1 experience in the clinic, Novo Nordisk continues to tweak and mutate candidates to optimize PK/PD. He described the research strategy at Novo Nordisk as "focus, focus, focus, on insulin and GLP-1 in diabetes and obesity." Novo Nordisk's is now heavily focused on oral delivery of these peptides and is also interested in the concept of tailored tissue selectivity (Dr. Landh says he would like to see an insulin that targets the liver). In line with sentiments expressed by others at this meeting, Dr. Landh stated that glucose-lowering is no longer enough; diabetes drugs must have some additional benefit. Worryingly, Dr. Landh stated that the number of new targets being investigated for diabetes has been declining. Novo Nordisk has created new strategies to encourage innovation: 1) the Diabetes Innovation Award program, which awards $150,000 or $500,000 competitive research awards; and 2) Novo Nordisk is hosting diabetes research summits in which academics are invited to submit ideas in a discussion-based setting.

--- by Nina Ran, Jessica Dong, Hannah Deming, Kira Maker, and Kelly Close