DIABETES CLOSE UP

We had luck enough to sit down and talk with Dr. Jay Skyler this week to hear his 2006 ADA impressions…and to talk about lots of other exciting goings-on in the diabetes arena. A past President of the American Diabetes Association, Dr. Skyler is today a professor of medicine, pediatrics, and psychology at the University of Miami and associate director of the Diabetes Research Institute. Dr. Skyler's academic and clinical experience is vast. and he's a major figure on the global diabetes stage – in addition to being on the board of directors at Amylin and DexCom, and having been on the board of directors at MiniMed, before its 2001 acquisition by Medtronic, he sits on well over a dozen scientific advisory boards at various pharmaceutical and medical device companies throughout the U.S. and Europe. We have long admired Dr. Skyler's commitment to diabetes, and were thrilled that he agreed to be the focus of our seventh in-depth DCU interview.

Kelly Close (KC): Thanks *so* much for talking to us Dr. Skyler! We're doing a post-ADA newsletter and wanted to get your thoughts on the meeting. What are your big picture take-aways? What did you think of the science and the products?

Jay Skyler: I was actually disappointed in the meeting, disappointed because I've kept up with all the new things in diabetes and therefore there was little or nothing new that I saw at ADA that I didn't already know about. You know, I like ADAs where I get some *really* exciting stuff. Maybe all that means is that I'm *too* close to things, because everybody else I know loved it!

KC: Let's talk about DPP-4 inhibitors a little bit, for a start. What did you think of Novartis' vildagliptin data?

JS: I actually thought that vilda [vildagliptin] did better than sita [sitagliptin] in A1c lowering in most of the abstracts. That's a hard thing to analyze because they start out at different points, making analysis tougher. And you know they're not done in the same population nor in the same country. The other thing that makes it hard to compare is that Vilda was willing to go up against active comparators, and sita (until the very end) didn't go up against anything but placebos. And placebo's a pretty good straw man. Also, sita did all of it's studies at QD, and vilda did most of its studies at BID and they did some studies that showed that you seemed to get a similar effect at BID as you do at QD for the same total amount, 100 QD versus 50 BID. So you can see it's really hard to make comparisons.

KC: So talk to us a little bit about what you think will happen. Do you think the drugs will be approved – with or without panel? Will they get reimbursement? Do you think patients will want to use them even though the drugs are weight neutral at best?

JS: You wouldn't think they're weight neutral if you read the press release!

KC: Trial design can be tricky to assess.

JS: You know there's only the one study that has showed a little bit of weight loss. I look at DPP-4 inhibitors fundamentally as weight neutral. It is really tough, as you point out, to show in a trial a drug that is basically weight neutral but to use it in a trial doing a diet and exercise program. I would have preferred to see the drug going just against a placebo there, because then you can figure out the real effects. My general impression from the totality of the data on DPP4s is that they are weight neutral. They are not weight loss, despite the press release that said otherwise.

KC: So on Byetta - everyone has a story about weight loss, but it's our sense that it was mostly endocrinologists who were talking about it.

JS: Yes, it's not been marketed very heavily outside of endocrinologists. By second quarter this year, it was already evident that there was going to be a potential shortage if it was expanded, so a broad PCP launch hasn't happened. The launch of Byetta went even better than was expected and they just had to hold back.

KC: Wow. Do you think that makes primary care doctors more excited to get it because they can't have it? If some PCPs do go straight to using DPP4s, and this assumes the reimbursement is there—then do you think that it will delay them from moving some patients to Byetta?

JS: Doctors always delay injectables. But once they get used to it, I think that they're going to want to have the weight loss effects of Byetta. And the patients are going to go nuts, they will be demanding it. That's where there is a real dilemma.

KC: What do you think about the company's decision to urge endocrinologists not to put new patients on Byetta right now?

JS: I don't think they have a choice. Ideally what you want to do is be able to keep your existing patients treated and you can't risk not having that be the case.

KC: There's a worry that part of the shortage is from too much off-label use of Byetta to treat obesity. What do you think about that?

JS: I don't think that's true. I just don't see much off-label use going on from what I can tell as I talk to people. And it's probably not a wise drug to use off-label in non-diabetic people because it causes glucose-stimulated insulin secretion. You may then over-secrete insulin and get hypoglycemic because you've already got endogenous insulin and you don't need to accelerate anything. There's also a theoretical danger because you would be altering gastrointestinal flow concurrently. You don't want to cause any late hypoglycemia, and that could theoretically happen in non-diabetic people taking Byetta.

KC: One of the big messages from the launch has certainly been that people care a lot about weight loss, and there certainly aren't any other drugs out there that are significantly affecting weight loss. Do you think the FDA would ever be willing to expedite review of Symlin for obesity because there is so much interest in obesity but no good drugs out there now?

JS: That's an interesting question. I've never heard the FDA talk about expediting a drug for obesity. On the other hand if there's an approved drug, you'd be looking for another indication. There isn't any precedent for that and I would have no reason to speculate on it but I like the way you think.

KC: Well, because there's so much safety data for Symlin it seems it might makes sense.

JS: Yes, that is absolutely true.

KC: So one thing about Byetta, aside from weight loss, is that A1cs are definitely improving too. The question is are A1cs improving more in real life because patients are more motivated or is it just the drug? What is your real-life experience?

JS: I think people are more motivated. My clinical experience has been that people who get on Byetta really get enthusiastic about their diabetes because they're losing weight and controlling their glucose at the same time, and they've never had that happen before. That gives them a high.

KC: That has to be excellent to see! What is it doing for doctors? To have a medicine that is motivating patients, that must make life a little different for them as well.

JS: I think doctors are thrilled with it too. It goes across the spectrum. And it's very different than anything we've had in the past because of that. Everything we've had in the past has been more of the same—this is clearly and distinctly different.

KC: What do you think about the open-label data at Amylin? You know that was exciting because three years out they still showed the sustained A1c drop of a point and the slope of the weight loss line was still going down!

JS: The sustained effect is theoretically what you would expect, particularly if you are improving beta cell function. And there is no reason to believe that the weight loss would a priori stop.

KC: Could you say that at three years you view it as a proxy for beta cell preservation or even beta cell regeneration?

JS: I don't know that I'd go into beta cell regeneration, but preservation of beta cell function is something that one might expect to see. And I think that this may be supportive of that. Three years may be enough time to draw a conclusion. You're walking on thin ice and on the fringes there, but it definitely could be.

KC: What do you think the impact would be of TZDs on beta cell preservation? How do you think the average endocrinologist is thinking about TZDs right now? And how do you think about them?

JS: Well, you probably are aware that I am the antichrist for TZDs.

KC (laughing): Yes. Tell us about that.

JS: Well, it goes back to Rezulin. That was clearly a problem in terms of causing liver disease, and everybody else was enthusiastically supporting it and I couldn't figure out why. I developed the view we can treat diabetes and control glucose with insulin and don't need a TZD for glucose control. And why take a risk of liver when I don't need to? And so that's why I never started using Rezulin when everybody else was.

Now, I am the first to admit that the other TZDs are not Rezulin with its liver disease effects. The others don't have that, thank goodness. On the other hand, what the others do have as part of their mechanism of action is that you invariably will gain weight if the drug works. And my patients who have to buy new clothes don't care whether it's a metabolically good drug. They care that they're buying new clothes. And so I've just never really seen a good argument for why TZDs ought to be used.

KC: So much of the focus with Amylin is on Byetta - did you see anything interesting about Symlin at the meeting?

JS: I thought it was nice that Symlin can be used without mealtime insulin. Lantus plus Symlin could be a really exciting play in the management of type 2 diabetes, controlling postprandial glucoses adequately while not having to worry very much about anything else.

KC: What about inhaled insulin? I know that you were pretty enthusiastic about inhaled insulin when it got approved. You know, it's six months later and it's about to be launched. What advice would you have for Pfizer? How do you think it will play? Do you think it will be reimbursed?

JS: Well, you've thrown out some of the $64,000 questions, for which I don't know the answer. The barriers to adoption of Exubera are several. One is reimbursement. What is it going to cost and where is it going to be reimbursed? Is it going to require prior authorization? All those things that add to the burden of reimbursement, and if a managed care company is looking at it are they going to actually reimburse something where the only benefit is patient acceptability? That's one issue.

A second issue that is faced is who's going to schedule the pulmonary function tests—nd who's going to pay for them? I don't think we know the answer to that and logistically it is not easy.

KC: Why wouldn't Pfizer just say they would pay for it?

JS: Even if that happened, I think you face another set of problems because the recommendation is to perform pulmonary function tests at baseline, then every six months during the first year, and every year thereafter. And if each time it's done in a different lab and the technique is a little bit different and the value looks low, well, that might be a technical difference. How do you distinguish that, and interpret that adequately? Or do you mistakenly blame Exubera? I think that's a dilemma that they haven't quite thought through that they need to face.

The third issue is: how long will it take to teach somebody how to use the Exubera inhaler? Now if you just inhale, that's easy, but that's not the only thing you need to teach. You need to teach people how to take the device apart, how to change the transjector, and how to clean the device. And none of those things are either intuitive or easy. So that's another round of hurdles.

All these things are limiting factors for Exubera. Some of these are subtle, but they're perhaps important. The other subtle thing is that the obvious place to launch the product is among endocrinologists. Products for diabetes that have failed to launch to endocrinologists in the past have ended up kicking themselves in the butt.

KC: Can you think offhand of any examples of those?

JS: One example of it would be the first-round launch of [then Aventis'] Amaryl. When they first came out with Amaryl they went directly to the primary care community. Nothing happened. They had to end up re-launching it later and then redoing the entire launch. Prandin never got traction in the diabetes community and therefore failed to make it in the primary care community as well. There are several examples of that. You need to get the diabetes people on board because historically it's been well demonstrated that the place where primary care doctors get most of their education is when they talk to their local endocrinologist and they say, "Well, what do you think of this?"

KC: Right.

JS: If the local guy looks at you and says, "I don't know what you're talking about," then the product goes nowhere, so you have to launch to the endocrinologists. That can be a problem though because the

diabetes guys don't have patients that are likely to be suitable or the best candidates for something like Exubera; those candidates are in the offices of PCPs. These are hurdles that have to be overcome in order to really use the drug well. So when people ask "What will Exubera's uptake in the community be?" I actually don't know the answer to the question. I think that it has an enormous potential and the really important part of that potential is that you might be able to lower the average national A1c and the impact of that in terms of the overall healthcare system would be absolutely phenomenal. If you heard Bob Rizza's presidential address in trying to program out what the meaning of those kinds of things are, it's huge.

KC: So the big potential is lowering the population's A1c, but if you don't get endocrinologists really behind it then it's hard for the PCPs to do it alone. Who do you think will most excited and positive about Exubera?

JS: I think the diabetes community is behind it in general. But when you go out to the community endocrinologists they may not have very many patients relative to the number of patients in the PCP offices. That's where there's a little bit of a disconnect, but it's something they're going to have to overcome, and they will hopefully.

KC: Some want to see Exubera being used in a large population for a few years before they really make a decision about whether it's really safe. What did you see in the trials in terms of safety signals?

JS: There's always the potential that there are safety signals that you don't know see, and there's no way to handle that except for over time, but time eventually will answer that. The question is should we be worried about that in this particular setting, and I am less worried about that here than I am in other places. I think that the one thing that we have learned is that there's a greater safety database here than there is for most other drugs. For example, I am more concerned about the DPP-4 inhibitors.

KC: Yeah, so let's talk about that. Can you outline the safety issues with DPP-4 inhibitors for us?

JS: DPP4 the enzyme works on at least 62 known peptides. And, you know, that looks like a side effect waiting to happen in many ways because we don't know what lurks behind when the effects on some other peptide become manifest in some people. So I'm more worried about that than I am about Exubera, which I think we know an awful lot about and which has been in very long-term trials relative to other products. So I am actually pretty confident Exubera doesn't have anything that we know about in this kind of timeframe. The problem comes if you have something that takes 10 or 12 years to develop, but there is nothing one can do to answer that question at this juncture.

KC: How important is tolerability for primary care doctors? You know, if the FDA approves the drug people generally believe that it's safe. So doctors may just generally believe that the inhaled insulin is safe, right? What about DPP4 inhibitors?

JS: Well, tolerability seems great so far. There is no signal that I've seen talked about with the DPP4s that suggest that there's any problem at all. I don't think that's a big deal at all for PCPs.

KC: So is really good tolerability an incentive to use a drug?

JS: Yeah, I think PCPs like that!

KC: Whereas the endocrinologists are more willing to work people through the first month or so of treatment.

JS: Endos want to do what's right and what sounds scientifically rational. PCPs want to do what's easy to implement and that is good for their patients. I think the one thing that people forget about sometimes is that most PCPs really care about what's good for their patient. That's what the business of being a doctor is all about. And so they really care about that and they listen to their patients a lot. And so what happens is that if the patient in any way says that they're concerned about, say, injection in this case, they're going to walk away from it. And that's where I think Exubera has a great chance; it resonates with patients.

KC: Do you think it resonates so much that they would actually pay for it?

JS: Some would. Not many. I think that there has gotten to be the expectation in the healthcare system that things always get paid for. And actually I think that's a pity in some respects because we've changed the dynamic of how we think about the healthcare system. Let's look at ruboxistaurin for a moment. Ruboxistaurin is a drug that has great potential in preventing diabetic complications. But the studies that were done occurred in late diabetic complications, because doing them early would have taken too long and they would not have been able to get them to market in a reasonable period of time. So when the studies were designed, they said, "Okay, we're going to design studies that are here to look at vision in late diabetic retinopathy." And that's the last place we should be doing these studies! I would have taken the DCCT number of subjects, I would have taken the DCCT protocol, and said okay, let's use the same endpoint. Let's do 1,441 patients, start them at the same place. We ought to get improvement in complications the same way there was in the DCCT. The problem is it will take an average of six years to get there in 1,441 patients. There's no motivation to do that because the study takes so long that the companies are not willing to invest in doing that. What we need to do, I think, is convince Congress to support that, maybe to put in a much longer exclusivity period for a drug.

KC: That would be great.

JS: Then the manufacturer can recoup the necessary investment to really get these kinds of potentially disease-changing drugs to market. Otherwise, there's very little incentive to do so. And particularly in a system that we have now in which we have an emphasis on drugs becoming generic, Congress has bent over backwards to make things available generically. The innovators spend a huge amount of money to develop the drug and get a relatively short period of exclusivity, therefore they have to make all their money back during that short period of exclusivity. Therefore they have to charge a higher price than they otherwise would in order to recoup their investment. That raises the price of the drugs. And when it becomes generic, the price base is so high that the generic guy, even though it's not costing him anything to develop it, reduces the price by 25 percent, steals the market, and the poor innovator is left to hang out and dry. I think it's a horrible system that we've developed.

KC: It’s hard to argue with that. I think I’ll switch gears—can you say anything about what you learned from the meeting in terms of measuring things like inflammation or oxidative stress? There seems to be a lot of focus on that. How might that help us going forward?

JS: You know, it has nice correlation and it looks intriguing. But we need clinical trial data that's prospective to prove the point. I'd want to see a trial designed where one is measuring, along the way, those endpoints and that they really are considered as an important feature of it. You then also would design a control group where you don't impact other endpoints but you have similar improvement in A1c. I think those are hard trials to design, by the way.

KC: Were there any other trials that you saw where you found the results very surprising?

JS: I don't think I saw anything surprising.

KC: [laughs] We're curious what you thought about the competitive data on the GLP-1 front.

JS: The data on liraglutide continues to show what it's shown before. It still fails to have much impact on postprandial glucose. I'm not sure why that is, but it's probably got something to do with the magnitude of the effect. But as long as it continues to lack that impact it's going to get classified as a drug that has doesn't quite compete.

KC: Byetta is being tested at both ends of the spectrum, in monotherapy and in combination with insulin. Which end do you think is more important to invest in?

JS: Both, but I think it's going to be used with insulin no matter what, so if I were investing, I'd invest in the monotherapy end and in the pre-diabetes component of it. That's where people will want to see more data. But I think both are important. I view that we have had in type 2 diabetes for the longest time, an insulin-o-centric viewpoint, then an insulin-resistance-centric point of view, which is probably too extreme in that direction. And I think that, from a therapeutic standpoint, we ought to be having a GLP1-centric point of view and more use, if they're safe, of DPP4 inhibitors. Going forward, treatment is going to be much more focused around the endocrine pathways for the treatment of the disease. So I think it goes on both ends.

KC: Do you think that the DPP4s should be used as a monotherapy or that we should use then in combination?

JS: My therapeutic paradigm over the last year has turned out to be that I start with metformin. If I fail to get adequate glucose control, I add Byetta. If I fail to get adequate fasting control, I add insulin—for most of the year, it's been Lantus, now it's either Lantus or Levemir. And that works for the most part. So I've been very happy with that kind of scheme. And I haven't really needed to do anything else, whereas other people—you know, the package insert says you can use Byetta in the presence of sulfonylureas and that's one of the places that they did the AMIGO studies. I personally stop the SFUs every time I start Byetta; I don't see any compelling reason to continue to give a drug that has weight gain and hypoglycemia associated with it when I can use a therapy that doesn't do those things. I wouldn't see any compelling reason to keep the SFUs on the market once the DPP4s are available.

KC: There has been so much use of monotherapy in the past, even when the patients are failing in getting to goal. Do you think that's going to change?

JS: I hope it changes. I think that one of the things that's going to drive that a little bit is the availability of DPP4s combined with metformin. Using DPP4s plus metformin, you won't be putting in a component that has weight gain, you won't be putting in a component that has hypoglycemia, and you will be treating both defects of the disease. Hopefully that idea will get traction.

KC: What about all the cross talk about metabolic syndrome? What's your view on that? This was a hot topic because of all the cardiology at the meeting.

JS: I think it's a semantic issue and arguing whether this is a syndrome or not is a silly waste of time. What we need to do is treat all of the risk factors! My philosophy on type 2 diabetes, aside from glycemic therapy, is that every patient should take a statin and aspirin. That would go far in treating the "syndrome." If you want to call some of it metabolic syndrome because certain features are occurring together, that's fine, but I think these discussions of semantics are a waste of time!

KC: Let's talk about the continuous monitoring developments. You know, this was the first meeting where there have been real continuous monitoring products out there, even without reimbursement. Where you see that market going?

JS: Well, you know, I was one of the first people to do blood glucose monitoring in the '70s when everybody else was doing urine glucose monitoring! The first time I presented data from my experience was at a meeting of what was then called the Florida Diabetes Association. It was in January of 1977 at a meeting in Tampa. And they had a panel of experts there—remember this was 1977—I was a young guy then. So I went up there and they had all these doctors critiquing the young people like me. So I presented our blood glucose data and there was a panel of experts there—three guys—and the first said to me, "Young man, you know that if you allow patients to do this, what's going to happen is, they're going to pay too much attention to their blood sugar. They're going to try too hard. We're going to have cars crashing all over the place with people who are hypoglycemic and you're going to kill an awful lot of people." And the other two guys on the panel said, "Well, it doesn't matter because patients won't do this anyway because it involves sticking their finger and they're not going to like that." And so they wouldn't do it. They thought of me as just a crazy young man. But that's how they thought about it: the patients would not, could not, and should not do this. And yet, blood glucose monitoring, as you know, has taken off. There is no doubt about the fact that we absolutely couldn't manage diabetes today without it. But in the beginning it was looked at as highly suspicious.

KC: Times have really changed dramatically in diabetes care.

JS: Right. After people began blood testing the arguments got to be not over whether patients would not, could not, or should not do blood glucose monitoring, but rather over what were the differences between the various methods and what should the rules be; the whole level of discussion changed. So I think the more players that are in a market like the continuous market, the more likely you get that kind of noise around it that can lead to success; I think that's where we are right now with continuous. We are at the threshold of trying to get the whole climate to change to something vastly different and that's going to cause a lot of shakiness. But I do think that it's just going to change the whole way we deal with diabetes. It will modernize it completely.

KC: You know, we understand a randomized controlled trial has just been backed by Diabetes UK to test urine; it's monitoring urine versus blood glucose monitoring in type 2 patients on oral drugs ..

JS: Why would anybody care? It's totally bizarre that they would do this. I mean there are people who might say "Well, there is no proof, in terms of evidence-based medicine, that blood glucose makes a difference," but they're deluding themselves. And all the studies would be useless if people didn't *know* their blood sugar. It's an integral component of the total method of dealing with diabetes, you can't do without it. And it is insane for them to be so purist, insisting on the urine testing.

KC: Anyways, back to continuous – how about continuous in type 2?:

JS: You know why continuous is really going to win in type 2? We're going to go from now, where it's three and five days to seven days or 14 days so that we have a longer duration. We're going to eventually have one calibration for each sensor you put it in, and then the factory calibration. When we have factory calibration that can last for a week or so, it will be a whole lot easier to put on a Dex Com sensor and leave it in place than it is to stick your fingers. More importantly, somebody with type 2 diabetes that's been measuring one sugar a week will now have access to continuous glucose monitoring and they'll be able to look at the impact of what they eat and what it does to their blood sugar. And they'll be able to look at their blood sugars and see, wow, this really is still too high and I have to take something else. And we're going to end up with people who will routinely be walking around with A1cs in the 6s instead of

routinely walking around in the 8s and 9s. And that's going to really change the face of diabetes. Remember Dr. Rizza's speech. I think it's essential we move to continuous and I say the sooner we get there, the better.

KC: Do you think that endocrinologists will start renting them and using the continuous monitors part-time in their type 2?

JS: I think in the end, everybody will use it all the time because the patients will love it. With just sticking that thing in place and then being able to look at it without having to stick their finger anymore and knowing what they are continuously, and seeing what food does to blood glucose—everybody will want to do it all the time; nobody's going to give it up. It's time to look ahead and understand that we *can't* buy them off the shelves until factory-calibrated things that last a week or more. But that's only a couple of years away. And in the meantime, there'll be a vast uptake of continuous monitors. Imagine when you can have a $35 monitor in place and it lasts a week and you don't have to stick your finger. That just changes life completely. I also think the continuous monitors will come up with better readings better methods for assessing variability.

KC: One more question: We wondered if you had any thoughts any of the early/ basic science that was shown at the meeting?

JS: I didn't find enough intriguing to begin with, but there is clearly lots of potential for next year's ADA …..

KC: We can't wait to see you there! Thank you so much again for your time, insights, and commitment.