Metabolic

The prevalence of diabetes and obesity is still high, despite many piecemeal attempts at treating these co-morbidities. Among drug makers' latest efforts: pills that address both at once. **Noah Pines** talks to analysts, marketers and doctors about the upside potential, and the pitfalls

Diabetes and obesity are two of the most well-known and highly publicized chronic metabolic conditions facing developed countries today. The two, which often occur concomitantly in patients, also pose an attractive area for drug makers—insulins, other injectables and pills generated over $29 billion in US sales last year, a 12% increase over 2011, according to data from Source Healthcare Analytics.

Yet, despite the abundance of existing medication classes for these rapidly expanding problems, there still remains substantial opportunity for better options. Obesity rates remain stubbornly high. A couple of drugs for the condition were recently approved—Vivus' Qsymia and Arena's Belviq—and both are in launch mode. (More on those later.)

Likewise, in type 2 diabetes (T2d), many patients ultimately don't achieve HbA1c control for a variety of reasons, including non-compliance. Companies are combining different mechanisms of action to offer more versatile treatment regimens.

Takeda is set to launch Nesina and two combination pills after securing FDA approval for its DPP-4-inhibitor-based family of products in January. One of Nesina's brethren, Oseni, integrates the active ingredient in Nesina with pioglitazone, making it the first DPP-4 + TZD combo pill.

In the pre-launch arena, drug makers' attempts at helping physicians get metabolic co-morbidities under control includes a couple of oral t2d drugs expected to go in front of the FDA over the next 12 months. The first is Johnson & Johnson's Invokana (canagliflozin). In clinical trials, it has shown good (but not great) A1c lowering, decent hypoglycemia rates and some weight loss benefit. That last trait is important, since obesity is so common among patients with T2d.

"Weight loss sells when you are dealing with type 2 diabetes," says Robert Busch, MD, an endocrinologist in private practice in Albany, NY. That is, it could be the hook that gets patients to adhere to these drugs on an ongoing basis.

Moreover, it's a benefit most patients don't get with the leading diabetes pill, Merck's DPP-4, Januvia. "DPP-4s are weight neutral," says Busch. "Januvia has the benefits of a sulfonylurea without hypoglycemia—that is what sells it."

Busch sees a future where companies that already market a DPP-4 and also have an SGLT-2 under their roof—like AstraZeneca and Bristol-Myers Squibb, which market Onglyza and have the SGLT-2 Forxiga in development—may be able to combine them "and have a 'super A1c' pill for T2d." In this way, adds Busch, "[Canagliflozin] is particularly a threat to Januvia." In fact, data show Invokana beats Januvia in A1c-lowering.

And Invokana, if approved, could be added to other drug regimens, like GLP-1s, creating a regimen of two drugs for diabetes and weight loss with complementary mechanisms of action. The urinary glucose excretion induced by SGLT-2s has been associated with weight reduction, while GLP-1s (like Amylin's Byetta or Bydureon, and Novo Nordisk's Victoza) have weight-loss benefits though their initial indication is for diabetes.

The second late-stage SGLT-2, Forxiga (dapagliflozin), was rejected by FDA last year, after an advisory committee voted against the agent citing concerns about cancer risk and efficacy (it was approved in the EU, but rejected by NICE).

But "SGLT-2s are not going to be as easy to market as the DPP-4s," says Joachim Osther, who launched the first-in-class GLP-1 Byetta and its successor, Bydureon, when he was a brand director at Amylin. "The beauty of the DPP-4 is…what bonus A1c [control] that you get; there is zero cost in terms of the side-effect profile."

Not so with SGLT-2 drugs. "The safety profile is indisputably

TOP 50 METABOLIC PRODUCTS, 2012

Diabetes and other metabolic category leaders, ranked by US sales, and their media spend

Rank	Product	Manufacturer	US sales $ (millions)*	Vs. prior 12 mos.	TRx (millions)*	Vs. prior 12 mos.	US DTC media $ (000s)**	Vs. prior 12 mos.	US journal media $ (000s)**	Vs. prior 12 mos.
1	**NovoLog**	Novo Nordisk	$3,083.5	32.9%	6.2	15.8%	$0.0††††	N/A	$838.6	-39.3%
2	**Lantus**	Sanofi	$3,075.2	20.4%	8.7	-5.9%	$0.0	-100.0%	$1,485.8	-81.6%
3	**Januvia**	Merck	$3,051.1	23.5%	8.5	12.8%	$38,637.0	42.0%	$12.2	-97.4%
4	**Lantus SoloStar**	Sanofi	$2,786.8	44.6%	7.9	27.9%	$4,049.9	N/A	$978.5	-75.0%
5	**Humalog**	Eli Lilly	$2,073.0	13.4%	5.2	0.3%	$894.4††	100.0%	$348.0	-93.3%
6	**Actos**	Takeda	$2,025.3	-47.2%	4.8	-56.3%	$22.6	-94.0%	$0.0	N/A
7	**Levemir**	Novo Nordisk	$1,457.6	38.4%	3.8	19.3%	$0.0†††	N/A	$1,386.9	-63.3%
8	**Metformin HCL**	Generic	$1,382.7	-30.2%	12.1	9.5%	$0.0	N/A	$31.3	N/A
9	**Victoza†**	Novo Nordisk	$1,188.2	61.4%	2.2	41.1%	$10,982.7	-42.0%	$5,099.7	13.4%
10	**Janumet**	Merck	$1,178.4	23.3%	3.6	11.9%	$0.0	N/A	$635.9	11.6%
11	**Synthroid**	Abbott	$1,000.0	6.5%	23.8	-3.0%	$0.0	N/A	$0.0	N/A
12	**Levothyroxine sodium**	Generic	$873.0	11.2%	79.7	6.2%	$0.0	N/A	$0.0	N/A
13	**NovoLog mix 70/30**	Novo Nordisk	$841.4	23.8%	1.7	6.4%	$0.0	N/A	$70.4	N/A
14	**Pioglitazone HCl**	Generic	$624.7	N/A	2.0	N/A	$0.0	N/A	$90.3	N/A
15	**Onglyza**	AstraZeneca/BMS	$598.1	41.7%	1.9	24.4%	$1,963.0	-91.0%	$1,129.6	-34.6%
16	**Byetta**	Amylin	$597.0	-11.2%	1.3	-18.0%	$0.0	N/A	$3,068.8	60.8%
17	**Humalog mix 75-25**	Eli Lilly	$411.8	3.6%	0.9	-7.9%	$0.0	N/A	$0.0	N/A
18	**Metformin HCL ER**	Generic	$400.1	31.2%	12.1	9.5%	$0.0	N/A	$0.0	N/A
19	**Glimepride**	Generic	$387.6	57.4%	12.2	5.1%	$0.0	N/A	$0.0	N/A
20	**Humulin R**	Eli Lilly	$352.4	45.7%	1.0	-9.7%	$0.0	N/A	$0.0	N/A
21	**Novolin 70-30**	Novo Nordisk	$347.6	13.8%	0.9	2.0%	$0.0	N/A	$0.0	N/A
22	**ACTOplus Met**	Takeda	$319.5	-42.1%	0.8	-52.0%	$0.0	N/A	$0.0	N/A
23	**Humulin 70-30**	Eli Lilly	$302.3	7.7%	1.5	-13.9%	$0.0	N/A	$0.0	N/A
24	**Prandin**	Novo Nordisk	$288.3	9.2%	0.7	-9.3%	$0.0	N/A	$0.0	N/A
25	**Humulin N**	Eli Lilly	$284.6	5.5%	1.7	-16.9%	$0.0	N/A	$0.0	N/A
26	**Novolin N**	Novo Nordisk	$281.6	16.7%	0.7	18.6%	$0.0	N/A	$0.0	N/A
27	**Kombiglyze XR**	AstraZeneca/BMS	$261.7	171.8%	1.0	133.6%	$0.0†††††	N/A	$1,477.7	-7.1%
28	**Phentermine HCL**	Generic	$236.7	1.8%	7.3	-0.8%	$0.0	N/A	$0.0	N/A
29	**Glyburide**	Generic	$224.3	-20.1%	7.7	-6.3%	$0.0	N/A	$0.0	N/A
30	**Novolin R**	Novo Nordisk	$194.6	5.6%	0.4	6.7%	$0.0	N/A	$0.0	N/A
31	**Tradjenta**	Lilly/BI	$188.5	584.1%	0.6	498.9%	$0.0	N/A	$3,779.1	36.7%
32	**Glumetza**	Santarus/Depomed	$184.4	85.0%	0.4	33.4%	$0.0	N/A	$27.4	N/A
33	**Bydureon**	Amylin	$138.4	N/A	0.3	N/A	$0.0	N/A	$2,430.2	N/A
34	**Levoxyl**	King	$134.1	-7.2%	5.0	-19.3%	$0.0	N/A	$0.0	N/A
35	**Glipizide ER**	Generic	$118.6	-3.6%	4.4	-5.8%	$0.0	N/A	$0.0	N/A
36	**Pioglitazone-metformin**	Generic	$116.6	N/A	0.3	N/A	$0.0	N/A	$0.0	N/A
37	**Apidra**	Sanofi	$111.1	44.8%	0.4	52.3%	$0.0	N/A	$0.0	N/A
38	**Glipizide XL**	Generic	$100.2	4.4%	2.9	1.9%	$0.0	N/A	$0.0	N/A
39	**SymlinPen 120**	Amylin	$91.1	-3.7%	0.1	-18.6%	$0.0	N/A	$0.0	N/A
40	**Nateglinide**	Generic	$85.3	-5.1%	0.5	1.6%	$0.0	N/A	$0.0	N/A
41	**Liothyronine sodium**	Generic	$84.4	16.5%	1.7	14.7%	$0.0	N/A	$0.0	N/A
42	**Glyburide-metformin HCL**	Generic	$77.9	-16.1%	3.3	-11.1%	$0.0	N/A	$0.0	N/A
43	**Humalog mix 50-50**	Eli Lilly	$66.7	6.0%	0.1	-6.5%	$0.0	N/A	$0.0	N/A
44	**Glipizide**	Generic	$63.1	0.8%	9.5	2.6%	$0.0	N/A	$0.0	N/A
45	**Janumet XR**	Merck	$50.4	N/A	0.2	N/A	$0.0	N/A	$1,258.3	N/A
46	**Fortamet**	Andrx	$48.2	-45.8%	0.1	-71.3%	$0.0	N/A	$0.0	N/A
47	**Methimazole**	Generic	$37.6	-17.1%	1.8	5.3%	$0.0	N/A	$0.0	N/A
48	**Duetact**	Takeda	$34.5	-14.5%	0.1	-31.7%	$0.0	N/A	$0.0	N/A
49	**Apidra SoloStar**	Sanofi	$34.5	-43.4%	0.1	-46.0%	$0.0	N/A	$0.0	N/A
50	**Armour Thyroid**	Forest	$34.4	19.9%	3.8	21.1%	$0.0	N/A	$0.0	N/A

*Manufacturer benchmark sales (MBS) and TRx for full-year 2012
**DTC/journal spend between 10/11-9/12 inclusive. Sources: Sales/TRx, Source Healthcare Analytics; DTC media spend, Nielsen; journals, Kantar Media. TRx count includes retail only.
†Sales for 3-pak, 2-pak ††Media spend for Humalog family, $3.3 million
†††Media spend for Levemir family, $13.9 million
††††Media spend for NovoLog family, $2.3 million
†††††Media spend for Kombiglyze/Onglyza, $677,439

CLINICAL CORNER

2012 ushered in a new era in weight-loss drugs, with the FDA's reversal on treatments such as Vivus Pharmaceutical's Qsymia and Arena's Belviq, but a potential competitor's recent success may shake up the clinical trial space.

Neil Weisman

Orexigen, which hopes to enter the weight-loss category with its experimental drug Contrave, has introduced an approach to clinical trials that's shrunk its ramp-up time by over a year. The secret: treat trials like product launches and start with a multi-pronged, consumer-friendly pitch.

By foregoing the slow-burn recruitment flow that typically begins with approaching a research organization and expands to include third-party recruitment when numbers lag, Orexigen did it all at once, shaving 14 months from what was expected to be a two-year process. The goal was 9,000 patients and the company garnered 100,000 responses.

"There's a good chance if they took two years to run and operate this study that [Orexigen] wouldn't have made it to the finish line," Neil Weisman, EVP of marketing firm Blue Chip, tells *MM&M*. Instead, Blue Chip came in at the start to help shape the messaging from both clinical and patient perspectives. This meant treating recruitment like a launch, with materials that resonated with the way patients perceive themselves—typical for advertising, but novel for clinical trials.

For example, Weisman said the patients they targeted didn't like the terms "very overweight" and "obese," and only a quarter of the patients who met the Contrave profile considered themselves "very overweight." So marketing materials eschewed those loaded terms.

The media mix included paid search, social media, television, traditional print media and direct marketing. Weisman said direct marketing proved to be the most effective recruiting tool. The website (thelightstudy.com) featured sales-like language. (Companies should ensure that any campaign language is compliant with FDA regulations for recruiting study subjects—*Ed.*)

When running metabolic-related clinical studies, recruiting volunteers is often easier in the community setting, says Robert Busch, MD, an endocrinologist in private practice in Albany, NY, who is a principal investigator on trials for such companies in the metabolic space as Eli Lilly, AbbVie and Bristol-Myers Squibb.

Busch says his practice mines data from its EHR, calling patients who qualify for trials, as opposed to, say, study centers that advertise. "In the community setting," says Busch, "you use a central [investigational review board], so you can get studies off the ground quickly."

Once recruited, subjects are often eager to participate again, especially in trials designed to test a drug vs. an active placebo, where their medications are paid for. Says Busch, "These patients get very good care in their clinical trials, so they are requesting, 'Do you have any other trials that I can be in after the study?'" *—Deborah Weinstein, with additional reporting by Noah Pines*

worse than the DPP-4s, so it is hard to think this is the first drug you'd rush out to use," says the Bernstein Research analyst Tim Anderson, MD. Yeast infections should keep certain patients off of these therapies.

Then again, says Osther, "Everyone knows this is a PCP-driven marketplace…and for them, having another oral option is a very positive thing." The question is, will the upside—some weight loss and A1c-lowering—resonate all that much?

"[The new class] is innovative to enough of a point where it is clinically relevant…but we have it barely making blockbuster status," adds Leon Henderson, MD, an analyst with *in*Thought Research, part of Symphony Health Solutions. At press time, *in*Thought had forecast Invokana, which would be the first in its class, to reach 2019 worldwide revenue of about a billion dollars.

Insulins are starting to be reinvented, as well, although it could be a while before the FDA approves an ultra long-acting formulation. Degludec from Novo Nordisk, now dubbed Tresiba, was to be a competitor to Sanofi's top product Lantus, a basal insulin. At press time, Novo announced that the shot won't be approved until it submits more data from a new trial, potentially delaying its arrival on these shores until at least 2015, possibly later. That goes for all formulations of degludec; Novo had been developing it with a rapid-acting insulin, dubbed Ryzodeg, and a Tresiba + Victoza fixed-dose combination.

The FDA asked Novo for the fresh data to flesh out a cardiovascular safety signal. The delay means less competition for Lantus in the US (degludec already cemented a thumbs-up in the EU and Japan), higher sales and more time to test its own ultra.

Now, back to the anti-obesity category. Joining Roche's Xenical/Alli on the obesity drug market, Arena's Belviq is just getting out of the gate this spring. And Vivus' Qsymia, which debuted last year, is not on a mega-blockbuster trajectory, due to the headwinds of past experience (See: Abbott's Meridia and Roche's Acomplia, both of which were withdrawn from the market, after approval, due to safety concerns), legal liability and a tough payer environment. It's a tightly controlled launch through a limited number of mail-order pharmacies. For the fourth quarter of last year, Qsymia sales were only $2 million.

"People are very cautious," says Henderson. "Regulators, physicians and patients have been burned in the past with obesity agents and the adversities that have caused all to be withdrawn from the market. People are being quite cautious in that respect."

Given the history of weight-loss products, Vivus is playing it slow, taking an educational approach and building trust with physicians who treat co-morbidities—cardiologists, endocrinologists and internists who see a lot of diabetes. "They are marketing it as a drug for people with metabolic syndrome," says Busch. "They are marketing it to the caregivers who treat the consequences of obesity."

Says *in*Thought's Henderson, "[Vivus] seems to be navigating the reimbursement challenges perhaps better than expected, which is why we may see some acceleration in usage as time goes on. Doctors need to follow patients in specific ways. Third party payers are approving it at rate higher than initially anticipated."

Busch says about 30% of his patients are covered due to the co-morbidities of hypertension, diabetes and obesity.

"If the patient is asking about it, then I prescribe it," says Busch. "I don't want to entice the patient with the weight loss—'You can lose 9-12% of your weight'—and then they find out it's not covered." ■