CLASS SEEKERS

These 16 agents, hand-picked from a total field of 164, are poised for approval, and possibly much more. **Marc Iskowitz** reports

Since the human genome was mapped in 2001, it's taken scientists another dozen or so years to really understand what those genes do and how they affect disease. Better understanding of genetic targets, plus pressure from the market to develop fully differentiated drugs, is leading to a new generation of breakthrough medicines.

But with all the talk of "drugging the genome," as analysts from Leerink Swann describe the ongoing efforts to develop therapies aimed at restoring normalcy among mutated genes and signaling pathways in cancer, it's possible to overlook two trends.

The first is what many drugmakers are doing to create alternate versions of, and to lower the cost of, existing drugs—in this case biologics.

"Who the players will be in the US, when we start to get biosimilars, is yet unclear, but every day seems to bring news of new biosimilars trials starting and different companies announcing they will play in this space," says Ben Weintraub, PhD, director of research at *in*Thought.

The coming year will be important in terms of quantifying the impact, he notes. The bellwether will be biosimilar versions of J&J's Remicade, launched in Europe by Celltrion and Hospira, and Eli Lilly's biosimilar insulin glargine, which is pending approval there and still in Phase III on these shores.

Secondly, Weintraub sees examples "of good drugs that are not really changing the standard of care because the unmet need is less than it has been in past." In other words, drug developers' success in therapeutic areas like oncology and autoimmune is setting the bar higher for new drugs–like Pfizer's RA pill Xeljanz, which he says lacks a compelling value proposition. "[Sanofi's] Lemtrada in the US will fall into that problem, too," predicts Weintraub. "It's a good drug, but it's hard to figure out how it fits into the current armamentarium."

With payers in the US, Europe and Japan increasingly scrutinous, difficulty defining a strong value proposition could spell trouble for any drug profiled here. However, many appear to be off to a good start.

The PD-1 inhibitors from BMS and Merck continue to yield early but oh-so-promising results in heavily pre-treated patients with skin, lung and kidney cancer. The PCSK9 inhibitors being developed by Sanofi and Amgen are emerging as an important new class for statin-refractory patients. And in immunology, IL-17 inhibitor secukinumab from Novartis looks poised to transform psoriasis treatment.

In addition to the autoimmune, cardiology, infectious disease, metabolic, neurology, and oncology sectors, the following pages highlight some of the most promising orphan therapies, including Biogen Idec's long-acting clotting factor for hemophilia A, as well as outlining late-stage agents in the respiratory and women's health areas, plus some in mid-stage.

Profiled agents are based on consultation with *in*Thought, Adis R&D Insight, GfK HealthCare and various other experts. Original analysis is updated to reflect the latest data sets (as of press time), and is complemented by revenue forecasts, lists of other key products and, where available, the estimated month of launch, plus a quick way to gauge the likelihood of an FDA OK called the Approvability Index (anything above 50% stands a good chance).

THERAPEUTIC CATEGORIES

Cardiology

PRODUCTS GENERATING BUZZ

Alirocumab/SAR236553 Sanofi/Regeneron

Indication: Hypercholesterolemia, hyperlipoproteinemia (Ph. III)
What the clinical trials found: A 47% reduction in LDL-C in a Phase III monotherapy study; 73% reduction when added to Lipitor in a Phase II trial. The percentage who reported treatment-emergent AEs was 78.4% ezetimibe, 69.2% alirocumab (ODYSSEY MONO).
***in*Thought Approvability Index and Comment:** 67%. This monoclonal antibody targets proprotein convertase subtilisin/kexin type 9 (PCSK9), for LDL-C reduction. This won't compete with statins, but a large number of people are statin-intolerant or refractory, so these drugs will help them. Estimated launch: 2016 (Source: Credit Suisse)
Credit Suisse revenue forecast: $865 million in global sales by 2020
What physicians are saying: [*At press time, new AHA/ACC treatment guidelines emphasized the benefit of statins while noting a lack of evidence that non-statin treatments reduce CV events. -Ed.*] A few cardiologists warn that cholesterol lowering, consistent at two weeks, begins to wane by four. Cleveland Clinic's Steven Nissen noted that a four-week dosing schedule may be more attractive than biweekly, "but the frequency is not a make-or-break consideration." —*Alex Bastian, VP, GfK Bridgehead*

Anacetrapib Merck

Indication: Atherosclerosis (Pre-reg.)
What the clinical trials found: Clearance time was estimated to be up to two years, data from Phase I and II studies of shorter duration indicate. A 138% increase in HDL-C and a 40% reduction in LDL-C (DEFINE) was seen.
***in*Thought Approvability Index and Comment:** 20%. This is pretty much the last man standing in the cholesterol ester transfer protein (CETP) inhibition category—the HDL-raising target that was so exciting a few years ago. In theory, the science is still sound. Many think other failures were class effects, and that this one is doomed, but there's no hard evidence of that. And if Phase III turns out to be OK, where others weren't, this will be a big success. Estimated launch: 2017 (Source: Symphony Health Solutions)
Credit Suisse revenue forecast: $2.4 billion in global sales by 2020
What the physicians are saying: Cardiologists said its tendency to stick around is a concern, but shouldn't prevent acceptance or approval. But Yale's Harlan Krumholz told *Forbes*, "A drug would have to be known to be incredibly safe before you would be willing to have it hang around in your body for years." —*Alex Bastian, VP, GfK Bridgehead*

Evolocumab/AMG-145 Amgen

Indication: Hypercholesterolemia, hyperlipoproteinemia (Ph. III)
What the clinical trials found: Reductions in LDL-C of up to 59% in pooled data from four 12-week Phase II studies involving populations with high cholesterol. AEs were seen more frequently with AMG-145 vs. placebo (57% vs. 49%), but it's considered safe and tolerable.
***in*Thought Approvability Index and Comment:** 25%. The second of two highly attractive development-stage compounds targeting PCSK9, AMG-145 is slightly behind the Sanofi/Regeneron product. Estimated launch: 2016 (Source: Credit Suisse)
Credit Suisse revenue forecast: $1 billion in global sales by 2020
What physicians are saying: "A 20% lowering of LDL cholesterol is clinically meaningful," said Nissen, who is conducting clinical trials of AMG-145 for which he gets research support. Brigham and Women's Hospital's Robert Giugliano added, "Statins...even at high doses do not always achieve the targeted level of LDL (bad) cholesterol in our high-risk patients. The LAPLACE-TIMI 57 study is very relevant in that the addition of AMG-145 to background therapy with statins resulted in significant reductions in LDL-C at all the doses tested." —*Alex Bastian, VP, GfK Bridgehead*

OTHER KEY PRODUCTS IN THE PIPELINE

Anivamersen-pegnivacogin Archemix
ACS (Ph. III)

Epanova AZ
Hypertriglyceridemia (Pre-reg.)

Avatrombopag Baxter
ITP (Ph. III)

Candesartan/nifedipine Bayer
Hypertension (Ph. III)

Metreleptin BMS
Lipodystrophy (Pre-reg.)

Gencaro (bucindolol) BMS
Heart failure (Pre-reg.)

Droxidopa Chelsea
Orthostatic hypotension (Pre-reg.)

Edoxaban Daiichi Sankyo
Venous thromboembolism (Ph. III)

Eritoran Eisai
Septic shock (Ph. III)

Evacetrapib Eli Lilly
Cardio disorders (Ph. III)

LY3015014 Eli Lilly
Hypercholesterolemia (Ph. III)

Tafamidis FoldRx
Cardiomyopathies (Ph. III)

Rinolazine Gilead
CAD (Ph. III)

Darapladib GSK
Atherosclerosis (Ph. III)

Eltrombopag GSK
ITP (Ph. III)

Desmoteplase Lundbeck
Stroke (Ph. III)

Vorapaxar/MK-5348 Merck
Pre-reg. Thrombosis

Ezetimibe/simvastatin MK-0653A Merck
ACS (Ph. III)

Relaxin (serelaxin) Novartis
Pre-reg. Heart failure

AHU 377/valasartan Novartis
Heart failure/hypertens. (Ph. III)

RN-316/PF04950615 Pfizer
Hypercholesterolemia (Ph. III)

Betrixaban Portola
Thromboembolism (Ph. III)

Terutroban Servier
Thromboembolism (Ph. III)

Defibrotide SOBI
Veno-occlusive dis. (Ph. III)

Perindopril XOMA
Hypertension (Ph. III)

Infectious Disease

PRODUCTS GENERATING BUZZ

ABT-450/r + -267 + -333 AbbVie

Indication: Hepatitis C (Ph. III)

What the clinical trials found: The INF- and RBV-free regimen ABT-450/r + -267 produced SVR12 rates of 95% in GT-1b treatment-naïve patients and 90% in null responders in Ph. IIb. SVR12 rates in those two cohorts hit 99% and 93%, respectively, among GT-1 patients taking the -333-containing regimen.

***in*Thought Comment:** This INF-free regimen combining non-nucleoside inhibitor NS5B (-333) with an NS5A inhibitor (-267) and protease inhibitor (-450) looks good perhaps for certain genotypes of HCV, and perhaps those refractory to Gilead's sofosbuvir (see below). Estimated launch: 2015 (Source: Symphony Health Solutions)

Credit Suisse revenue forecast: $1 billion in global annual sales by 2020

What the physicians are saying: Some potentially would like one regimen for all patients, but specialists might find more value in products for certain subtypes—an efficacious product in a subset of patients with easier dosing or containing fewer products overall. But AbbVie will be late to the game and have some work to do. —*Rishi Dalsania, consultant, GfK HealthCare*

Simeprevir Janssen

Indication: Hepatitis C (Pre-reg.)

What the clinical trials found: In GT-1a patients with the Q80K polymorphism (48% of those in two Phase III trials), SVR12 rates were 58% in the treatment group and 55% in the control group (statistically insignificant), vs. 84% in the segment without this polymorphism.

***in*Thought Approvability Index and Comment:** 90%. This small-molecule protease inhibitor (PI), specifically for GT-1 and -4 HCV infections, earned a unanimous vote from an FDA ad-com panel in October for GT-1 and should also get approved this year in an INF- and RBV-containing regimen. It's a small improvement over the existing PIs from Vertex and Merck, but could get a second life as part of an all-oral J&J regimen in 2014/15. Estimated launch: Jan. 2014 (Source: Symphony Health Solutions)

***in*Thought revenue forecast:** $637 million in global annual sales by 2016

What the physicians are saying: The Q80K matter, called out in October by the FDA ad-com panel, is an additional condition physicians would have to screen for, and could have a negative impact on perception. It will be interesting to see how they will approach this issue. —*Rishi Dalsania, consultant, GfK HealthCare*

Sofosbuvir Gilead

Indication: Hepatitis C virus (Pre-reg.)

What the clinical trials found: 95% of GT-2s achieved SVR12, 56% of GT-3s, in the Ph. III FISSION trial of treatment-naïve patients taking sofosbuvir + RBV; vs. 78% and 63%, respectively, in a group taking INF + RBV. No serious or severe cardiac AEs seen.

***in*Thought Approvability Index and Comment:** 90% (as part of an all-oral regimen in 2014). In October an FDA ad-com panel voted 15-0 in favor of approving this NS5B polymerase inhibitor without INF for GT-2 and -3 patients, and 15-0 for use along with INF (and RBV) in GT-1 and -4 infections. Its PDUFA date is Dec. 8, 2013, but the "real" approval will come when it's likely to get approved in an all-oral regimen with NS5A protein inhibitor ledipasvir. Estimated approval: Dec. 2013 (Source: Symphony Health Solutions)

***in*Thought revenue forecast:** $2.3 billion in global annual sales by 2016

What the physicians are saying: Sofosbuvir + RBV will likely be the first all-oral regimen to reach market, but for GT-2 and -3 at first—accounting for roughly 15% of the US HCV market. More anticipated is sofosbuvir + ledipasvir, a one-pill-a-day combo with which 95% of patients with the more common GT-1 achieved SVR12. It's also shown to be effective without ribavirin. Physicians want to get rid of RBV, because it's a burden from a pill standpoint and leads to anemia. —*Rishi Dalsania, consultant, GfK HealthCare*

OTHER KEY PRODUCTS IN THE PIPELINE

ABT-072 AbbVie
HCV (Ph. III)

Certolizumab AstraZeneca
Spondylitis (Pre-reg.)

Amikacin inhal. Bayer
Gram-neg. inf. (Ph. III)

Deleobuvir/BI 207127 Boehringer Ingelheim
Hep. C (Ph. III)

Faldaprevir/BI 201335 Boehringer Ingelheim
Hep. C (Ph. III)

Daclatasvir BMS
Virology (Ph. III)

Asunaprevir BMS
Virology (Ph. III)

Peginterferon lambda-1a BMS
Virology (Ph. III)

Ceftolozane/tazobactam Cubist
Gram-neg. inf./UTIs (Ph. III)

Cobicistat/darunavir Gilead
HIV/AIDS (Ph. III)

Ledipasvir/GS-5885 Gilead
HCV (Ph. III)

Zoster vaccine GSK
Herpes zoster (Ph. III)

Tivicay + Epzicom GSK
HIV infections (Pre-reg.)

GSK805 J&J
HCV (Ph. III)

TMC647055 J&J
HCV (Ph. III)

MK-3415A Merck
C. diff. inf. (Ph. III)

Vaniprevir/MK-7009 Merck
Hep. C (Ph. III)

V212 Merck
Herpes zoster (Ph. III)

V503 Merck
HPV vaccine (Ph. III)

MnB rLP2086 Pfizer
Meningitis B vacc. (Ph. III)

C. diff vaccine Sanofi
Prophylaxis (Ph. III)

Eravacycline Tetraphase
Infections (Ph. III)

Metabolic

PRODUCTS GENERATING BUZZ

LY 2963016 (insulin glargine biosimilar) Eli Lilly/Boehringer Ingelheim

Indication: Type 1/2 diabetes (Ph. III)

What the clinical trials found: Several studies were conducted using current insulin glargine as the comparator, including one Ph. III trial when administered with oral diabetic medications in patients with T2D, another when given in combination with mealtime insulin lispro (Humalog) in patients with T1D.

CS Approvability Index and *in*Thought Comment: 45%. This insulin glargine product was already filed in the EU as a true biosimilar of Sanofi's Lantus basal insulin. This will be a test case for biosimilars. The question is not approvability but how much of a discount they apply—our model has 30%—and how much can it disrupt the current branded drug.

Credit Suisse revenue forecast: $1.4 billion in annual sales by 2020

What the analysts are saying: The annual Roper Diabetes study of 2,000 patients suggests that Lantus will be hard to dislodge. If physicians and patients believe they've got something equivalent that's safe and effective, there seems to be opportunity. But the educational investment would need to be high. Lilly has the advantage of being a leader in the market. But most patients in our study are under the care of PCPs, who don't have a lot of time to invest in education. It's also unclear what will distinguish their product from Lantus. *—Mary McBride, president, GfK Roper Diabetes*

Dulaglutide Eli Lilly

Indication: Type 2 diabetes (Pre-reg.)

What the clinical trials found: Superior HbA1c reductions vs. placebo and vs. exenatide (AWARD-1), vs. metformin (AWARD-3) and vs. sitagliptin (AWARD-5); significant weight loss vs. sitagliptin, and similar weight loss to patients taking comparators in the other two trials. Mild-to-moderate nausea was the most common AE reported.

Credit Suisse Approvability Index and *in*Thought Comment: 50%. We already have a bunch of GLP-1s on the market, but it will be interesting to see how these formulations get used with insulin. Obviously the once-a-week version is similar to AZ/BMS's Bydureon and might have some advantages in terms of injectability and needle size. Estimated launch: 2014 (Source: Credit Suisse)

Credit Suisse revenue forecast: $806 million in global annual sales by 2020

What the analysts are saying: Since if you're on a GLP-1, our data show, you're more likely to see an endo—and endo's are a small proportion of prescribers—the chances of it being widely prescribed are more limited. (In our data, 5-6% of patients are on a GLP-1.) It's difficult to know how it will be priced. Lilly is still waiting for results from AWARD-6 (with Victoza as the comparator), so if they can show superiority, then with its once-weekly dosing, it would be in a good position. *—Mary McBride, president, GfK Roper Diabetes*

OTHER KEY PRODUCTS IN THE PIPELINE

SaxaDapa FDC AZ
Diabetes (Ph. III)

Empagliflozin BI/Lilly
Diabetes (Ph. III)

Albiglutide GSK
Diabetes (Ph. III)

Omarigliptin Merck
Diabetes (Ph. III)

Tresiba Novo Nordisk
T1/2 diabetes (Pre-reg.)

Ryzodeg Novo Nordisk
T1/2 diabetes (Pre-reg.)

NovoThirteen (rFXIII) Novo Nordisk
Congenital deficiency (Pre-reg.)

IDegLira Novo Nordisk
Diabetes (Pre-reg.)

FIAsp Novo Nordisk
Diabetes (Ph. III)

Semaglutide Novo Nordisk
Diabetes (Ph. III)

U300 Sanofi
Ph. III T1/2 diabetes (Ph. III)

Lyxumia Sanofi
Diabetes (Ph. III)

Contrave Takeda
Pre-reg. Obesity

TAK-875 Takeda
Diabetes (Ph. III)

DIAPep Teva
Diabetes (Ph. III)

Dapagliflozin BMS/AZ

Indication: Type 2 diabetes (Pre-reg.)

What the clinical trials found: New Ph. III data showed dapagliflozin added to metformin and sulfonylurea, at 24 weeks, reduced HbA1c -0.86% vs. -0.17% in the placebo group; reduction in mean body weight was -2.65 kg at week 24 vs. -0.58 kg in patients who received placebo. Rate of urinary tract infection: 6.4% for dapagliflozin vs. 6.4% for placebo.

CS Approvability Index and *in*Thought Comment: 50% (US). Two oral SGLT2 inhibitors from BMS and J&J were neck-and-neck in clinical development. BMS's was supposed to get approved first but got a CRL from the FDA in January 2012 requesting more data. Invokana (cangliflozin) was approved first, and its launch has been good. As far as we can tell, the clinical distinction between dapa' and cana' is minimal. It will be a question of how much an additional SGLT2 can expand the market and whether they can compete. The next PDUFA date is Jan. 11, 2014. Estimated approval: 2014 (Source: Credit Suisse)

Credit Suisse revenue forecast: $1.6 billion by 2020

What the analysts are saying: The new Ph. III data showing it to be effective as an add-on to metformin and sulfonylurea in terms of A1c reduction, combined with weight reduction and BP control, is advantageous. It looks like it's on the road to approval. If it reaches market, it's likely to be prescribed second- or third-line, competing with DPP-4s and GLP-1s. Kidney disease will not be a huge factor; not many T2D patients are reporting it. *—Mary McBride, president, GfK Roper Diabetes*

Neurology

PRODUCTS GENERATING BUZZ

Edivoxetine Eli Lilly

Indication: Major depressive disorder (Ph. III)

Credit Suisse Approvability Index and Comment: 60%. A small-molecule selective norepinephrine reuptake inhibitor for the oral treatment of depressive disorders and attention deficit hyperactivity disorder (ADHD). Estimated launch: 2015 (Source: Credit Suisse)

Credit Suisse revenue forecast: $918 million in annual global sales by 2020

What the analysts are saying: Edivoxetine has been perceived positively by physicians in general with predicted uptake expected to be high among treatment-resistant MDD patients. Due to the crowded anti-depressant market, this makes it more significant. More recent additions to treat-severe depression have included anti-psychotics, which are associated with a poor side-effect profile. Edivoxetine works as an SSRI, a class which is generally perceived more favorably by psychiatrists treating depression. There haven't been too many additions to the market of late, with the exception of Lundbeck's vortioxetine (which is also indicated for GAD). Edivoxetine could be a favorable choice. —*Thomas Russell, GfK HealthCare*

Lemtrada (alemtuzumab) Sanofi

Indication: MS (Pre-reg.)

What the clinical trials found: Ph.-III CARE-MS I and CARE-MS II trials—comparing Lemtrada with Merck/EMD Serono's Rebif—showed significant improvement over Rebif. In November, FDA reviewers objected to the design of these studies. It was generally well-tolerated except for some serious AEs: immune thrombocytopenia (ITP), thyroid disorders and some associated with INF.

***in*Thought Approvability Index and Comment:** 50% (MS). The drug did better than expected at November's FDA panel, based on the briefing documents. It has the advantage of being a drug where you take a course of treatment and then, in the best case, you're cured of MS. The bad thing is that it might give you a different autoimmune disease, like ITP. Lemtrada would have had a very bright outlook five years ago…not so much now because there are so many other good options. And the real Catch-22 is that it doesn't seem to work as well in people with advanced disease. Estimated launch: 2014 (Source: Symphony Health Solutions).

Credit Suisse revenue forecast: $1 billion in global annual sales by 2020

What the analysts are saying: Early reads were that efficacy is quite good. Side-effect issues will cause physicians and patients to think long and hard about whether the benefits outweigh potential risks. Our research shows 40% of doctors identify the drug unaided, 75-80% when given a list. They talk about efficacy, but almost as frequently about safety concerns. When asked what proportion of their patients they would consider to be good candidates for Lemtrada, they say about 10%. —*Paul Wojciak, research director, GfK HealthCare*

OTHER KEY PRODUCTS IN THE PIPELINE

Daclizumab AbbVie
Ph. III MS

Levodopa/carbidopa Intestinal gel AbbVie
Ph. III Parkinson's

Diprivan AZ
Ph. III Anesthetic

Naloxegol AZ
Ph. III Opioid-induced const.

Cariprazine Forest
Pre-reg. Schizophrenia/bipolar

Patrome (IPX066) GSK
Pre-reg. Parkinson's

Suvorexant Merck
Pre-reg. Insomnia

OPC-34712 Otsuka
Ph. III MDD/schiz./ADHD

Remoxy Pfizer
Pre-reg. Pain

ALO-02 Pfizer
Ph. III pain

Tanezumab Pfizer
Ph. III OA

Ocrelizumab/RG1594 Roche
Ph. III MS

Bitopertin/RG1678 Roche
Ph. III Psychotic disorders

Laquinimod Teva
Ph. III MS

Plegridy (PEG-interferon-β-1a) Biogen Idec

Indication: MS (Pre-reg.)

What the clinical trials found: New data analyses from year one of the two-year, Ph.-III ADVANCE study showed absence of measured disease activity (no relapse rate, disease progression or lesions) was significantly higher with Plegridy: 34% in a two-week dosing arm and 22% in a four-week dosing arm, vs. 15% in the placebo arm. Overall AE incidence was similar to placebo.

***in*Thought Approvability Index and Comment:** 80%. It may be just a long-acting form of Avonex, Biogen's other beta interferon (and in a subcutaneous form vs. Avonex's intramuscular injection). That said, it's better to have less-frequent dosing. We haven't seen Rebif or Betaseron come along with better formulations, so maybe this will get used quite a bit. This version also protects Biogen against biosimilars and gives them a distinct advantage over the other two rivals. Estimated launch: late 2014 (Source: Symphony Health Solutions)

***in*Thought revenue forecast:** $450 million in global annual sales by 2018

What the analysts are saying: The message Biogen is sending on Plegridy is that this will reduce the treatment burden for patients through fewer, less-painful injections, with the efficacy of Avonex, a drug doctors are very familiar with. Unaided, only 30% of neurologists are aware of Plegridy, but when given a list of products, awareness increases to 75-80%. Also, a large majority anticipate that, as a result of prescribing Plegridy, they will decrease use of Avonex. The other thing they're asking is how much more expensive this will be. —*Paul Wojciak, research director, GfK HealthCare*

Oncology

PRODUCTS GENERATING BUZZ

Nivolumab Bristol-Myers Squibb

Indication: NSCLC/melanoma/RCC (Ph. III)

What the clinical trials found: Durable response across all three tumors in the heavily pre-treated. Nivolumab + Yervoy melanoma combo trial showed 53% response rate—additive over each agent alone. Looks to be extremely well-tolerated.

***in*Thought Approvability Index and Comment:** 57%. The anti-PD1 compounds from BMS, which won fast-track designation in three tumor types, and Merck, which received the FDA's breakthrough designation for treating melanoma, are vying for pole position in what looks to be an important new approach to cancer care, immuno-oncology (I/O). If it turns out that Merck has it and BMS doesn't, that will prove whether breakthrough status makes a difference. Expected launch: for both compounds: Mid-2015 (Source: Symphony Health Solutions)

Leerink Swann revenue forecast: $7-17B US/$14-34B WW opportunity by 2025 for I/O, with 45% going to first-to-market BMS, 25% to Roche, 20% to Merck, 10% to AstraZeneca

What the analysts are saying: In melanoma, these drugs are replacing chemo; the real buzz is around long-term cure. We could boost it higher than Yervoy's 20% long-term cure rate. And I/Os, which skirt the resistance that often develops with targeted molecular therapeutics, may compete in BRAF-mutant populations with inhibitors of BRAF (Roche's Zelboraf, GSK's Tafinlar) and MEK (GSK's Mekinist). —*Stephanie Hawthorne, PhD, director, Kantar Health*

LDK 378 Novartis

Indication: NSCLC (Phase III)

What the clinical trials found: 60% ORR in a Phase I trial of patients with ALK+ NSCLC, including patients who had received crizotinib therapy (ORR of 59%) and patients who were crizotinib-naïve (ORR of 62%); 47 out of 78 patients showed partial responses.

***in*Thought Approvability Index and Comment:** 88%. This oral drug looks to be a viable back-up to Pfizer's Xalkori (crizotinib), the first ALK inhibitor but one which (like many molecular targeted drugs) encounters resistance. It could also compete to be a first-line choice. We're just scratching the surface with ALK inhibition. Given the resistance issue, we need more than two drugs in that class, which is no problem because Roche, Ariad and several others are lining up hopefuls. Expected launch: 2016 (Source: Credit Suisse)

Credit Suisse revenue forecast: $374 million in global annual sales by 2020

What the analysts are saying: The Phase-I data showing 50% ORR in Xalkori-naïve and 67% in the Xalkori-resistant reflect about the same level of benefit. LDK 378 may not be stronger than Xalkori, but it doesn't lose efficacy (i.e., remains effective) when used post-Xalkori, which will be important for its launch. The compound received breakthrough therapy designation, and Novartis aims to file it in early 2014. The Chugai/Roche ALK inhibitor had good data, but I don't hear as many people talking about that one. For oncologists who have patients with the ALK mutation, these will be important, but ALK is only 3% of lung cancer. —*Stephanie Hawthorne, PhD, director, Kantar Health*

OTHER KEY PRODUCTS IN THE PIPELINE

Elotuzumab AbbVie
Multiple myeloma (Ph.III)

T-VEC Amgen
Mal. melanoma (Ph.III)

Trebananib/AMG-386 Amgen
Ovarian (Ph.III)

AP 26113 Ariad
NSCLC (Ph.II)

Moxetumomab pasudotox AZ
Hairy cell leukemia (Ph.III)

MEDI4736 AZ
Solid tumors (Ph.I)

Nintedanib Boehringer Ingelheim
NSCLC (Ph.III)

Volasertib Boehringer Ingelheim
Various cancers (Ph.III)

BMS-936559 BMS
Solid tumors (Ph.I)

Elotuzumab BMS
Multiple myeloma (Ph.III)

Necitimumab Eli Lilly
NSCLC (Ph.III)

LY-2835219 Eli Lilly
Cancer (late-stage) (Ph.II)

Ramucirumab Eli Lilly
Gastric (Pre-reg.)

Idelalisib Gilead
NHL (Pre-reg.)

MAGE-3 GSK
Mel/NSCLC (Ph.III)

ARN-509 J&J
Prostate cancer (Ph.III)

Siltuximab J&J
Multicentric casteman's dis. (Pre-reg.)

Yondelis J&J
Sarcoma/ovarian (Ph.III)

MK3475 Merck
Mal. Melanoma (Ph.III)

Vintafolide Merck
Ovarian (Pre-reg.)

LBH589 Novartis
Multiple myeloma (Ph.III)

LDE225 Novartis
BCC (Ph.III)

LDK378 Novartis
NSCLC (Ph.III)

S-1 Otsuka
Gastric (Ph.III)

Dacomitinib Pfizer
NSCLC (Ph.III)

Palbociclib Pfizer
Breast (Ph.III)

Inotuzumab Pfizer
ALL (Ph.III)

Alectinib Roche
NSCLC (Ph.I/II)

Onartuzumab Roche
Gastric/NSCLC (Ph.III)

Cobimetinib combo Roche
Mel. (BRAF) (Ph.III)

MPDL-3280A Roche
NSCLC (Ph.II)

TAK-700 Takeda
Prostate (Ph.III)

MLN9708 Takeda
Mult. myeloma (Ph.III)

MLN8237 Takeda
Lymphoma (Ph.III)

StemEx Teva
Cancer (Ph.III)

Other

PRODUCTS GENERATING BUZZ

AUTOIMMUNE

Secukinumab Novartis

Indication: Ankylosing spondylitis/plaque psoriasis/psoriatic arthritis/RA (Phase III)

What the clinical trials found: In a Ph.-III trial of patients with moderate-to-severe plaque psoriasis, PASI 90 rate seen at week 52 was 65% and 33% in the secukinumab 300mg and Enbrel groups, respectively (statistically significant). AE incidence similar for both drugs.

***in*Thought Approvability Index and Comment:** 85%. This monoclonal antibody inhibits the IL-17A receptor, thought to be very important in immune response and, for reasons we don't completely understand, secukinumab is a game-changing drug in psoriasis that doesn't do much in RA and works about the same as other drugs in psioriatic arthritis. It seems to do the trick in psoriasis, where clinicians measure efficacy by seeing how many patients achieve a 50% clearance in the amount of rash on their body—PASI 50. J&J's Stelara raised the standard to PASI 75. But IL-17s are so good that they bypass that and require PASI 90. Scientists are starting to measure PASI 100, which in the world of drug development is as close to a cure as you can get. If someone had gotten up at a dermatology meeting five years ago and talked about PASI 100, they would have been laughed off the stage. Amgen and Lilly each have IL-17s that look to be just as good as Novartis's in psoriasis. This probably will get approved in psoriatic arthritis but not for RA, as it's not much better than the TNF inhibitors for that disease. Expected launch: 2014, psoriasis (Source: Credit Suisse)

Credit Suisse revenue forecast: $1.5 billion in annual global sales by 2020.

ORPHAN

Eloctate (recombinant factor VIII Fc) Biogen Idec/Sobi

Indication: Hemophilia A (Pre-registration)

***in*Thought Comment:** In partnership with Swedish Orphan Biovitrum AB (Sobi), Biogen Idec has two long-acting recombinant coagulation factors for the treatment of hemophilia A and B, Eloctate and Alprolix, respectively. Eloctate (rFVIIIFc) is poised to be approved next year. This continues to be a very active area, with several new drugs coming from Baxter and Sanofi, as well.

What the analysts are saying: Eloctate is currently under FDA review with potential approval in 1Q14 (PDUFA date in March 2014). Biogen Idec noted that it's planning for a mid-2014 commercial launch of Eloctate in the US (~90 days approval delay). Sobi has noted <1 year FDA delay for Eloctate would not impact its EU approval timeline. For Alprolix (rFIXFc) for hemophilia B, FDA approval is expected in 1Q14, as well. For Sobi territories (ex-US), Phase III pediatric data for Eloctate/Alprolix are on track for 1H14/2H14, respectively. —*Eun Yang, equity analyst, Jefferies*

OTHER KEY PRODUCTS IN THE PIPELINE

AUTOIMMUNE

Brodalumab/AMG-827 Amgen
Psoriasis (Ph.III)

Romosozumab/AMG-785 Amgen
Postmeno. Osteo. (Ph.III)

Brodalumab AZ
Psoriasis (Ph.III)

Lesinurad AZ
Gout (Ph.III)

Apremilast Celgene
Psoriatic arthritis (Pre-reg.)
Psoriasis (Ph.III)

Baricitinib Eli Lilly
RA (Ph.III)

Ixekizumab Eli Lilly
Psoriasis (Ph.III)

Tabalumab Eli Lilly
Lupus (Ph.III)

Sirukumab GSK/J&J
RA (Ph.III)

Vercirnon GSK
Crohhn's (Ph.III)

Tildrakizumab/MK-3222 Merck
Psoriasis (Ph.III)

AIN457 Novartis
Psoriasis (Ph.III)

Sarilumab Sanofi
RA (Ph.III)

Fedratinib Sanofi
Myelofibrosis (Ph.III)

Vedolizumab Takeda
Ulcerative colitis (Pre-reg.)

ORPHAN

Drisapersen GSK
DMD (Ph.III)

2696273 GSK
ADA-SCID (Ph.III)

Migalastat GSK
Fabry (Ph.III)

N8-GP Novo Nordisk
Hemophilia A (Ph.III)

N9-GP Novo Nordisk
Hemophilia B (Ph.III)

AFQ056 Novartis
Fragile X synd. (Ph.III)

Tafamidis meglumine Pfizer
TFAP (Pre-reg.)

Cerdelga Sanofi
Gaucher (Pre-reg.)

Lumacaftor Vertex
Cystic fibrosis (Ph.III)

RESPIRATORY

PT003 GFF AZ
COPD (Ph.III)

Mepolizumab GSK
Asthma (Ph.III)

Fluticasone furoate (685698) GSK
asthma (Ph.III)

Anoro Ellipta GSK
COPD (Pre-reg.)

MK-7243 Merck
Allergy (Pre-reg.)

MK-3641 Merck
Allergy (Pre-reg.)

Lebrikizumab/RG3637 Roche
Severe asthma (Ph.III)

Octreotide/RG3806 Roche
Acromegaly (Ph.III)

WOMEN'S HEALTH

Elagolix AbbVie
Endometriosis (Ph.III)

NOMAC/MK-8175A Merck
Contraception (Ph.III)

MK-8962 Merck
Fertility (Ph.III)

Viviant Pfizer
Osteo. (Pre-reg.)

Bazedoxifene-conjug estro. Pfizer
Vasomotor sympt. (Pre-reg.)