LATE-STAGE STANDOUTS

Spotlighting 196 agents, with profiles on 15 advances vying to be better, safer or cheaper than standard of care. **Marc Iskowitz** reports

Despite hand-wringing over the decrease in R&D productivity relative to the 1990s, it continues to be a fruitful period for pharma and biotech organizations. The concern nowadays is that a lot of the new, interesting products that get a regulatory OK don't find a very large market.

"Attention in the industry seems to have shifted from, 'Will we get this approved?' to 'How do we create a successful drug if we get it approved? How do we maximize its revenue potential?'" notes Dr. Ben Weintraub, director of research at *in*Thought Research, part of Symphony Health Solutions.

The writing is on the wall in cardiovascular disease, where the various ACE and ARB inhibitors have had a hard time competing, and in diabetes, where newer DPP-IV products have struggled to gain sales. Now, says Weintraub, case studies of somewhat lackluster performers are piling up in multiple sclerosis (See: Novartis' Gilenya) and in rheumatoid arthritis (See: J&J's Simponi and UCB's Cimzia).

The answer to ever more skeptical physicians, patients and payers? "When gearing up to go into competitive markets, companies must design trials to show which specific subsets of patients will benefit," Weintraub says.

They must also prove superior to standard of care. Even in hepatitis C therapy, where Merck's Victrelis and Vertex's Incivek boosted the response rate of injectable interferon from 40% to almost 80%, their sales are giving way as the field looks to Abbott's and Gilead's late-stage hep. C hopefuls, which promise to boost cure rates even further, while giving patients, for the first time, an FDA-sanctioned, all-oral regimen that doesn't require interferon.

In cancer, companies have gotten a lot better at finding the right niche for drugs. Take Roche's Herceptin, a mainstay of therapy for HER2+ breast cancer for over a decade. Now T-DM1, awaiting FDA approval, has the goal of "building a better Herceptin," says Kantar Health analyst Dr. Stephanie Hawthorne. Similarly, Bristol-Myers Squibb's Phase III agent BMS-936558 is an immuno-therapy like melanoma drug Yervoy, with seemingly better tolerability.

Both cancer contenders are profiled here, plus potential first-in-class products, ranging from Merck's anacetrapib and BMS/AstraZeneca's dapagliflozin—inhibitors of CETP and SGLT2, respectively, for treating atherosclerosis and diabetes—to AZ/Rigel's fostamatinib and Merck's odanacatib, blockers of SYK and CatK enzymes, respectively, for RA and osteoporosis. You'll also read about a biosimilar in development that could become a cheaper TNF inhibitor than Merck's Remicade, scheduled to go off patent in the US in 2015.

In addition to the cardiovascular, infectious disease, metabolic, rheumatology and oncology sectors, this report highlights neurology and orphan therapies, including Eli Lilly's solanezumab for Alzheimer's disease and Biogen Idec's long-acting clotting factors for hemophilia, as well as outlining late-stage agents in the respiratory and women's health areas, plus some in mid-stage, too.

Consistent with our methodology the last several years, 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 approval, plus a quick way to gauge the likelihood of an FDA OK called the *in*Thought Approvability Index (anything above 50% stands a good chance).

THERAPEUTIC CATEGORIES:

Cardiovascular

PRODUCTS GENERATING BUZZ

Anacetrapib Merck
Indication: Atherosclerosis (Phase III)
What the clinical trials found: Depending on dose, LDL-c fell by 16%-40% vs. placebo, and HDL-c rose by 44%-139%, depending on dose, in Phase IIb. There were no treatment-related serious adverse events.
***in*Thought Approvability Index and Comment:** 55%. Cardiologists remain excited about HDL-raising strategies. Anacetrapib is a molecular cousin of Pfizer's torcetrapib, ostensibly without the safety problems, and has a more profound impact on HDL-c and LDL-c than Roche's failed CETP inhibitor dalcetrapib. Estimated approval: Jan. 2017 (Source: Symphony Health Solutions)
Revenue forecast: $350 million in annual revenue in 2018, says Leerink Swann's Seamus Fernandez.
What the analysts are saying: CETP inhibitors represent a novel mechanism of action, but the jury is still out. Pfizer's torcetrapib increased risk of mortality and cardiovascular events. The dal-OUTCOMES trial was stopped because Roche's dalcetrapib was not reducing CV adverse events. Dalcetrapib increased HDL by 30% (and did not alter LDL). Anacetrapib, and Eli Lilly's evacetrapib, increase HDL by at least 100% and reduce LDL by 35%-45%. Physicians say that any new CETP inhibitor must also demonstrate significant plaque stabilization/regression and significant decreases in atherothrombotic disease to be seriously considered. —*Portia Gordon, VP, research & consulting, GfK HealthCare*

Eliquis (apixaban) Bristol-Myers Squibb/Pfizer
Indication: DVT/stroke prevention in non-valvular Afib (Prereg.)
What the clinical trials found: In Phase III, 21% reduction vs. warfarin in stroke or systemic embolism; 11% reduction in mortality; 31% reduction in major bleeding. Its overall mortality and safety are more impressive than BI's Pradaxa or J&J/Bayer's Xarelto.
***in*Thought Approvability Index and Comment:** 98%. Eliquis is a very similar drug to Pradaxa and Xarelto. Because of their very complicated development programs, there will be niches for all three of these drugs, but the clinical niche for Eliquis will be the largest. Twice delayed, a new PDUFA date is set for March. Estimated approval: March 2013 (Source: Symphony Health Solutions)
***in*Thought revenue forecast:** $5.1 billion in peak sales in 2021.
What the analysts are saying: Physicians still hold hope for this oral factor Xa inhibitor, whose NDA was resubmitted in September. Clinicians are impressed with trials establishing Eliquis superiority vs. warfarin and aspirin in preventing/reducing stroke or systemic embolism. Being third to market, Eliquis' superior safety profile will help to erode competitors' share, however, data must demonstrate superiority in stroke, bleeding and mortality in AF, and Eliquis must be competitively priced to attract payers. —*Portia Gordon, VP, research & consulting, GfK HealthCare*

OTHER KEY PRODUCTS IN THE PIPELINE

Lomitapide Aegerion
Hypercholesterolemia (Prereg.)

AMG 145 Amgen
Hypercholesterolemia (Ph.III)

Cangrelor AstraZeneca
Coronary artery disease (Ph.III)

Desmoteplase Bayer
Stroke (Ph.III)

BMY 13105/Bucindolol Bristol-Myers Squibb
Heart failure (Prereg.)

Edoxaban Daiichi Sankyo
VTE (Ph.III)

Avatrombopag Eisai
Idiopathic thrombocytopenic purpura (Ph.III)

Evacetrapib/LY 2484595 Eli Lilly
Atherosclerosis (Ph.III)

Ularitide EXR Therapeutics
Acute heart failure (Ph.III)

Nebivolol/valsartan Forest
Acute heart failure (Ph.III)

Stedicor Forest
Ventricular arrhythmias (Ph.III)

Kynamro (mipomersen) Genzyme/Isis
Hypercholesterolemia (Prereg.)

Darapladib GSK
Atherosclerosis (Ph.III)

Defibrotide Medison/Sigma-Tau
Veno-occlusive disorders (Ph.III)

Vorapaxar Merck
ACS (Ph.III)

MK-0653c Merck
Atorvastatin/ezetimibe Hypercholesterolemia (Prereg.)

Tredaptive (MK-0524A) Merck
Niacin controlled release/laropiprant Atherosclerosis (Ph. III)

LCZ696 Novartis
Heart failure (Ph.III)

Tafamidis meglumine Pfizer
Cardiomyopathies (Ph.III)

Betrixaban Portola
Thromboembolism (Ph. III)

Aspirin/omeprazole 325/40 Pozen
Cardio disorders (Ph.III)

Aleglitazar/RG1439 Roche
Cardio disorders/type 2 diab. (Ph.III)

Vapreotide BMY 41606 Salix
Esophageal varices (Prereg.)

Otamixaban Sanofi
ACS (Ph.II)

SAR236553/REGN727 Sanofi/Regeneron
Hypercholesterolemia (Ph.II)

Relaxin (serelaxin) Novartis
Indication: Acute heart failure (Phase III)
What the clinical trials found: Phase III data were mixed, showing the drug improves symptoms of shortness of breath (albeit mildly) and is safe.
***in*Thought Approvability Index:** 75%. Estimated approval: Jan. 2014 (Source: Symphony Health Solutions)
What the analysts are saying: Given the dearth of effective therapies available for heart failure patients, we think this drug is likely approvable on the current dataset…[and] could potentially cross the $1 billion/year threshold with effective marketing. —*Tim Anderson, MD, senior analyst, Bernstein Research*

Infectious Disease

PRODUCTS GENERATING BUZZ

ABT-450/r+-267+-333+ribavirin Abbott Labs
Indication: Hepatitis C virus (Phase III)
What the clinical trials found: This non-nucleotide, oral regimen achieved a 97.5% SVR12 in GT1, therapy-naïve patients and 93% SVR in null responders, in Phase IIb. Ribavarin and boosted ritonavir were required to achieve 90%+SVR. Safety appeared consistent with standard of care.
***in*Thought Approvability Index and Comment:** 66%. Even though GS-7977 (see below) is the frontrunner in the hep. C pipeline, there is more than enough room for several different regimens to be successful. Abbott's and others will find a clinical niche. Estimated approval: July 2015 (Source: Symphony Health Solutions)
***in*Thought revenue forecast:** $1.1 billion in peak annual sales by 2019.

Dolutegravir GlaxoSmithKline/Pfizer/Shionogi
Indication: HIV/AIDS (Phase III)
What the clinical trials found: 88% of patients taking integrase inhibitor dolutegravir plus GSK's Epzicom produced virological suppression at 48 weeks, vs. 81% of those taking Gilead's Atripla in Phase III. Positive safety results have been reported.
Revenue forecast: £857 million ($1.4 billion) in annual sales in 2016, says Bernstein's Tim Anderson.
What the analysts are saying: KOLs are especially intrigued by dolutegravir's once-daily dosing and attractive resistance profile. In trials, naïve patients who failed dolutegravir did not develop resistance to integrase or nucleoside reverse transcriptase inhibitors. So dolutegravir may be able to meet an unmet need for a sturdier integrase inhibitor with a higher barrier to resistance. A dolutegravir+Epzicom regimen demonstrated superior tolerability to Atripla in treatment-naïve patients, especially with respect to CNS side effects. If co-formulated, tolerability could also give dolutegravir/Epzicom a potential edge over Stribild, which features elvitegravir but is burdened by cobicistat's side-effect profile. *—Mimi Doi, PhD, JD, assoc. VP, GfK HealthCare*

Sofosbuvir/GS-7977 Gilead Sciences
Indication: Hepatitis C virus (Phase III)
What the clinical trials found: 100% with genotype 1 infection taking this nucleotide drug with Gilead's NS5A inhibitor GS-5885 achieved SVR4, in the Phase II ELECTRON study of 25 patients. The safety profile was acceptable.
***in*Thought Approvability Index and Comment:** 60%. '7977 is the most promising hep. C drug in development but has a lot to live up to to justify the nearly $11 billion Gilead paid for Pharmasset. Estimated approval: March 2015 (Source: Symphony Health Solutions)
***in*Thought revenue forecast:** $2.1 billion in peak annual sales by 2019.

OTHER KEY PRODUCTS IN THE PIPELINE

Motavizumab Abbott Labs
RSV (Ph.III)

Peramivir BioCryst
Influenza A virus H1N1 (Ph.III)

Asunaprevir+daclatasvir BMS
Hepatitis C (Ph.III)

BMS 914143 BMS
Hepatitis B/C (Ph.III)

Faldaprevir/BI 201335+BI 207127 Boehringer Ingelheim
Hepatitis C (Ph.III)

Oritavancin/LY 333328 Eli Lilly
Gram-positive infections (Ph.III)

Avibactam/ceftazidime Forest
Gram-negative infections (Ph.III)

GSK 2282512A GSK
Influenza virus vaccine (Prereg.)

GSK 2321138A GSK
Influenza virus vaccine (Prereg.)

Meningococcal vaccine GSK
Groups ACYW-135 conjugate (Ph.III)

MMR vaccine GSK
MMR (Ph.III)

NB 001 GSK
Herpes simplex virus (Ph.III)

Rifaximin GSK
Clostridium infections (Ph.III)

Varicella zoster vaccine GSK
Varicella zoster virus (Ph.III)

Bedaquiline/TMC207 J&J
Tuberculosis (Prereg.)

Simeprevir J&J
Hepatitis C (Ph.III)

Actoxumab/bezlotoxumab/ MK-3415A Merck
Clostridium infections (Ph.III)

Thymalfasin Merck
Hepatitis B (Ph.III)

V 503 Merck
HPV infection (Ph.III)

V 212 Merck
Herpes zoster (Ph.III)

V 419 Merck/Sanofi Pasteur
Hib-DTaP-hepatitis-B-poliovirus vaccine (Ph.III)

Delamanid/OPC 67683 Otsuka
Tuberculosis (Ph.III)

DTaP vaccine adult Sanofi
(Ph.III)

ChimeriVax Sanofi
Dengue fever vaccine (Ph.II)

DTaP-poliovirus vaccine Sanofi Pasteur *(Ph.III)*

Japanese encephalitis vaccine Sanofi Pasteur *(Ph.III)*

What the analysts are saying: GS-7977 thus far appears to successfully combine very high efficacy with a relatively clean side effect profile. Its oral administration is also seen as far superior to current therapies that are given as weekly injections. Currently, the drug is on track for a late 2014 approval, assuming no safety concerns emerge. Safety will be key given that this has so far been the biggest stumbling block for some of Gilead's competitors developing all-oral HCV treatments. *—Marite Talbergs, SVP, research and consulting, GfK HealthCare*

Metabolic

PRODUCTS GENERATING BUZZ

Dapagliflozin Bristol-Myers Squibb/AstraZeneca
Indication: Type 2 diabetes (Preregistration); T1D (Ph.II)
What the clinical trials found: Lowers blood glucose levels, improves blood pressure and promotes weight reduction. The FDA raised concerns about bladder, breast cancer and liver risk, as well as cardiovascular issues.
***in*Thought Approvability Index and Comment:** 54%. In January FDA told BMS/AZ to collect more safety data, and now J&J's canagliflozin or Lilly/BI's empagliflozin are vying to be the first FDA-approved SGLT2 inhibitor. ADA data were reassuring, and dapa' will have a good shot when it goes back before FDA. Estimated approval: Jan. 2014 (Source: Symphony Health Solutions)
***in*Thought revenue forecast:** $609 million in annual sales by 2019.
What the analysts are saying: Cardiovascular risk underlies the way the FDA is looking at diabetes drugs (See: Avandia). On the other hand, there's a real need to help patients control blood-glucose and to control cardio-related co-morbidities. Clinical trials indicate that SGLT2s provide such benefit, but safety must be demonstrated. Results for J&J's canagliflozin (awaiting approval) indicate superior efficacy to dapa' in lowering HbA1C, without the same side effects. Dapa' may have been the first to go before the FDA, but there need to be more definitive statements on superiority and safety before we see a shakeout. *—Dave Jacobson, SVP, Roper global diabetes group, GfK HealthCare*

Tresiba (insulin degludec) Novo Nordisk
Indication: Type 2 diabetes (Preregistration); T1D (Prereg.)
What the clinical trials found: Trials among patients with type 2 diabetes suggested a 43% reduction in nighttime hypoglycemia vs. Sanofi's Lantus (seen mostly in one trial), longer duration and more flexible dosing times. The FDA has flagged cardio issues.
***in*Thought Approvability Index and Comment:** 79%. Novo Nordisk wants to leapfrog long-acting insulin Lantus, which is set to come off patent. But November's FDA advisory panel meeting cast some doubt on its timely approval and commercial success. Estimated approval: Jan. 2013 (Source: Symphony Health Solutions)
***in*Thought revenue forecast:** $2.2 billion in annual sales in 2019.
What the analysts are saying: Tresiba—and sister product Ryzodeg, which includes a rapid-acting insulin—are designed for type 2s who need better post-prandial glucose control. [At press time, an FDA advisory panel voted 8-4 in favor of approval, but 12-0 that a large cardiovascular outcomes trial is needed to better define the potential cardiovascular signal seen in Phase III. Some also questioned its hypoglycemia benefit. *–Ed.*] While the cardio analysis can be done post marketing, US approval could be delayed (an October deadline already passed). Tresiba is also expected to initially cost more, and that could be an issue for existing insulin users—if Lantus is working for someone and there is a cost factor, why would the physician or patient switch? On the other hand, the cost may be offset by the potential of improved control of severe hypoglycemia, extended control over time and better compliance among new and existing insulin patients, if demonstrated. *—Dave Jacobson, SVP, Roper global diabetes group, GfK HealthCare*

OTHER KEY PRODUCTS IN THE PIPELINE

Bardoxolone methyl Abbott
Diabetic nephropathies (Ph.III)

Metreleptin Amylin
Lipodystrophy (Ph.III)

Lesinurad/RDEA-594 AstraZeneca
Gout (Ph.III)

Empagliflozin/BI 10773 BI/Lilly
Type 2 diabetes (Ph.III)

Insulin peglispro/LY2605541 BI/Lilly
Type 1/2 diabetes (Ph.III)

Linagliptin+pioglitazone BI/Lilly
Type 2 diabetes (Ph.III)

LY 2963016 (insulin glargine) BI/Lilly
Type 1/2 diabetes (Ph.III)

Metreleptin BMS/AZ
Lipodystrophy (Prereg.)

Arxxant/LY333531 Eli Lilly/Alcon
Diabetic macular edema (Prereg.)

Dulaglutide/LY2189265 Eli Lilly
Type 2 diabetes (Ph.III)

Syncria (albiglutide) GSK
Type 2 diabetes (Ph.III)

Canagliflozin J&J
Type 2 diabetes (Prereg.)

Afrezza MannKind
Type 1/2 diabetes (Ph.III)

Janacti/MK-0431C Merck
Type 2 diabetes (Ph.III)

MK-3102 Merck
Type 2 diabetes (Ph.III)

Galvus (vildagliptin) Novartis
Type 2 diabetes (Ph.III)

LCQ 908 Novartis
Hyperlipoproteinemia type I (Ph.III)

IDegLira Novo Nordisk
Type 2 diabetes (Ph.III)

Semaglutide Novo Nordisk
Type 2 diabetes (Ph.III)

Aleglitazar Roche
Type 2 diabetes (Ph.III)

Lixisenatide Sanofi
Type 2 diabetes (Prereg.)

Nesina (alogliptin) Takeda
Type 2 diabetes (Prereg.)

Mitiglinide Takeda
Type 2 diabetes (Prereg.)

TAK-875 Takeda
Type 2 diabetes (Ph.III)

Trelagliptin/SYR-472 Takeda
Type 2 diabetes (Ph.II)

Contrave Takeda/Orexigen
Obesity (Ph.III)

MABp1 XBiotech
Type 2 diabetes (Ph.II)

Beloranib Zafgen
Obesity (Ph.IIa)

Oncology

PRODUCTS GENERATING BUZZ

BMS-936558 Bristol-Myers Squibb
Indication: NSCLC/melanoma/RCC (Phase III)
What the clinical trials found: Overall response rates of 28% in melanoma, 18% in non-small cell lung cancer, and 27% in renal cell carcinoma in Phase I. The drug looks to be extremely well-tolerated, with low rates of immune-related adverse events.
***in*Thought Comment:** Use of this anti-PD-1 monoclonal antibody is gaining fans, given tumor shrinkage rates. While data are limited, response rates seen so far—15-30% in heavily refractory patients—suggest the anti-PD1 approach is viable. Estimated approval: 2015 (Source: Symphony Health Solutions)
Revenue forecast: $2.0 billion in 2020, says Leerink Swann's Seamus Fernandez.
What the analysts are saying: BMS-936558 is an immuno-therapy like melanoma drug Yervoy (ipilimumab, Bristol-Myers Squibb), only better tolerated. Also exciting is the potential to have a biomarker (response may be limited to patients who overexpress PD-L1). We expect excitement for trials and for patients to enroll rather quickly, especially given the paucity of effective options in second-line NSCLC and the novel MOA. Other PD-1 inhibitors are being developed by Teva and CureTech, GSK and Amplimmune, as well as Merck. *—Stephanie Hawthorne, PhD, director, Kantar Health*

T-DM1 Roche/Genentech
Indication: 2nd line metastatic HER2-pos. breast cancer (Prereg.)
What the clinical trials found: In Phase III, patients had a statistically significantly longer PFS (9.6 vs. 6.4 mos.) vs. GlaxoSmithKline's Tykerb plus Roche's Xeloda. Interim OS analysis suggested a 38% reduction in the risk of death. T-DM1 is also very well tolerated.
***in*Thought Approvability Index and Comment:** 81%. T-DM1 packages Herceptin (trastuzumab) with a chemotherapy, DM1 (emtansine), with the goal of targeting to breast cancer cells that express HER2. The road to approval has been long and hard (T-DM1 has been in development since 2001), but Genentech finally seems to be on track. Estimated approval: 1Q13 (Source: Symphony Health Solutions)
Revenue forecast: CHF 623 ($660 million) in annual revenue in 2016, says Bernstein's Tim Anderson.
What the analysts are saying: T-DM1 is well-positioned to displace Tykerb/Xeloda in previously-treated mBC patients. We expect T-DM1 to be quickly adopted as a new standard of care in second- and third-line mBC, and eventually for it to move into the first-line setting (it's currently being studied in the Phase III MARIANNE trial in this indication). Genentech and Roche have a strong reputation in the HER2+ mBC space, with Herceptin entrenched, Perjeta (pertuzumab) recently approved for use in combination with Herceptin/chemotherapy in first-line mBC, and T-DM1 now poised to enter. We expect a premium price over Herceptin. *—Stephanie Hawthorne, PhD, director, Kantar Health*

OTHER KEY PRODUCTS IN THE PIPELINE

Linifanib Abbott
Liver cancer (Ph. III)

Talimogene Amgen
Malignant melanoma (Ph.III)

Trebananib Amgen
Fallopian tube cancer (Ph.III)

Zibotentan/AZD4054 AstraZeneca
Prostate (Ph.III)

Alemtuzumab Bayer
CLL (Ph.III)

Brivanib BMS
Liver cancer (Ph.III)

Elotuzumab BMS
Multiple myeloma (Ph.III)

Necitumumab BMS
NSCL (Ph.III)

Afatinib Boehringer Ingelheim
Breast cancer (Ph.III)

Nintedanib Boehringer Ingelheim
NSCL (Ph.III)

Amrubicin Celgene
NSCL (Ph.III)

Azacitidine Celgene
AML (PH.III)

Pomalidomide Celgene
Multiple myeloma (Prereg.)

Denileukin diftitox Eisai
Bone metastases (Prereg.)

Lenvatinib Eisai
Thyroid cancer (Ph.III)

Farletuzumab Eisai
Ovarian cancer (Ph.III)

Astuprotimut-R/MAGE-A3 GSK
Malignant melanoma (Ph.III)

Dabrafenib GSK
Malignant melanoma (Prereg.)

Dabrafenib-trametinib GSK
Malignant melanoma (Ph.III)

Trametinib GSK
Breast cancer (Ph.III)

Enzastaurin Eli Lilly
B cell lymphoma (Ph.III)

Ramucirumab Eli Lilly
Gastric/breast/CRC (Ph.III)

Ibrutinib J&J
CLL (Ph.III)

Trabectedin J&J
Breast/ovarian cancer (Ph.III)

MK 7965 Merck
CLL (Ph.III)

MK 8109 Merck
Ovarian cancer (Ph.III)

MK 8669 Merck
Sarcoma (Pre-Reg)

BKM 120 Novartis
Breast cancer (Ph.III)

Dovitinib Novartis
Renal cancer (Ph.III)

Midostaurin Novartis
AML (Ph.III)

Mifamurtide Novartis
Osteosarcoma (Ph.III)

Panobinostat Novartis
Malignant melanoma (Ph.III)

Signifor Novartis
Carcinoid tumors (Ph.III)

Azacitidine Pfizer
AML (Ph.III)

Inotuzumab/PF 5208773 Pfizer
NHL (Ph.III)

GA 101/RG 7159 Roche
B cell lymphoma (Ph.III)

Onartuzumab Roche
NSCL (Ph.III)

Iniparib Sanofi
Breast cancer (Ph.III)

Ombrabulin Sanofi
Soft tissue sarcoma (Ph.III)

Rheumatology

PRODUCTS GENERATING BUZZ

Fostamatinib (R788) AstraZeneca + Rigel
Indication: Rheumatoid arthritis (Phase III)
What the clinical trials found: In Phase IIb, patients achieving ACR20 ranged from 37-66%, depending on dosage, at six months. There were minimal safety issues.
***in*Thought Approvability Index and Comment:** 55%. Fostamatinib, an oral RA drug, is the most advanced syk inhibitor, an alternative to JAK inhibitors like Pfizer's recently approved Xeljanz (tofacitinib). AZ/Rigel, and the developers of other syk and JAK inhibitors, could also gain an edge over Xeljanz if they can develop once-daily dosing. Estimated approval: Sept. 2014 (Source: Symphony Health Solutions)
***in*Thought revenue forecast:** $657 million in annual sales by 2019.

Infliximab biosimilar/CT-P13 Celltrion
Indication: Rheumatoid arthritis (Phase III)
What the clinical trials found: In Phase III, 73.4% of patients taking CT-P13 achieved an ACR20 score (20% improvement; the level considered minimally clinically important) at week 30, vs. 69.7% for J&J/Merck's Remicade (infliximab). Safety was comparable.
***in*Thought Comment:** Celltrion, which has been quite transparent about its biosimilar of Remicade, may be able to get it approved as a branded drug in the US. Rather than making it the first true biosimilar monoclonal antibody in the US, an approval would make CT-P13 the sixth TNF inhibitor drug in the market. Estimated approval: 2017 (Source: Symphony Health Solutions)
***in*Thought revenue forecast:** TNF biosimilars will generate $1.1 billion in peak annual sales by 2019, but how that's divided up among Celltrion and other players is the big unknown.
What the analysts are saying: In the US, responses from patients and physicians have been mixed. Some want lower prices and are looking forward to a biosimilar Remicade, and others are leery about its safety and efficacy. Its precise impact remains to be seen. However, analysts say Remicade sales are likely to decline in 2017, so the transition from Remicade, if it continues to work well, will be gradual. Also, price estimates for biosimilar Remicade range from 10-50% of Remicade's cost. If the savings are not as dramatic, will that provide sufficient motivation for doctors to prescribe and patients to try a biosimilar Remicade? *—Joanne French, VP, health practice, GfK HealthCare*

Odanacatib Merck
Indication: Osteoporosis (Phase III)
What the clinical trials found: In Phase IIb, odanacatib improved bone mineral density at a higher rate vs. placebo and was generally well tolerated. In July a Phase III trial was stopped early because of positive results and a favorable benefit-to-risk profile.
***in*Thought Approvability Index and Comment:** 60%. It's difficult to see how this drug can compete effectively against the bisphosphonates, which have been so successful and so inexpensive. A niche of patients who don't tolerate bisphosphonates well would be candidates, but that's already the niche Prolia (Amgen) fills, and Prolia revenues are not all that exciting. Lack of head-to-head data with bisphosphonates is surprisingly absent from the Merck program. Estimated approval: February 2014 (Source: Symphony Health Solutions)
***in*Thought revenue forecast:** $1.5 billion in annual sales in 2019.
What the analysts are saying: Odanacatib could succeed Merck's Fosamax, which had $3 billion in annual sales before its patent expired in 2008. Current options are limited: patients link the bisphosphonates to osteonecrosis of the jaw and atypical fractures, and most don't want injections. Odanacatib should do what previous therapies cannot—block the main culprit of existing bone tissue breakdown (the CatK enzyme) while allowing the osteoblast to form bone. Whether patients will be required to try generic Fosamax before odanacatib depends on final clinical trial results. *—Harris Kaplan, CEO, Healogix*

OTHER KEY PRODUCTS IN THE PIPELINE

Hydrocodone/paracetamol controlled release Abbott
Osteoarthritis (Prereg.)

Romosozumab Amgen
Osteoporosis (Ph. III)

Apremilast Celgene
Psoriasis (Ph. IIII)
Psoriatic arthritis (Ph. III)

LY2439821 (ixekizumab) Eli Lilly
Rheumatoid Arthritis (Ph. III)
Psoriasis (Ph. II)

Tabalumab (LY 2127399) Eli Lilly
Rheumatoid arthritis (Ph. III)
Lupus (Ph. III)

Baricitinib Eli Lilly/Incyte
Rheumatoid arthritis (Ph. III)

Traficet-EN (1605786) GSK
Crohn's disease (Ph. III)

Lodotra Horizon/SkyePharma
Rheumatoid arthritis (Prereg.)

IP 880 Iroko
Osteoarthritis (Ph. III)

IP 889 Iroko
Osteoarthritis (Ph. II)

Arcoxia (etoricoxib/MK 663) Merck
Rheumatoid arthritis (Ph. III)
Ankylosing spondylitis (Ph. III)

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

Naproxcinod NicOx
Osteoarthritis (Prereg.)

Calcitonin oral (SMC 021) Novartis
Osteoarthritis (Ph. III)

Secukinumab (AIN-457) Novartis
Psoriasis (Ph. III)
Psoriatic arthritis (Ph. III)
Rheumatoid arthritis (Ph. III)

Sarilumab (REGN-88) Regeneron
Rheumatoid arthritis (Ph. III)
Ankylosing spondylitis (Ph. III)

Actemra (tocilizumab) Roche
Rheumatoid arthritis, subcutaneous form (Ph. III)

Vedolizumab (MLN0002) Takeda
Ulcerative colitis (Ph. III)
Crohn's (Ph. III)

VX-509 Vertex
Rheumatoid arthritis (Ph. II)

Other

PRODUCTS GENERATING BUZZ

NEUROLOGY

Solanezumab Eli Lilly
Indication: Alzheimer's disease (Phase III)
What the clinical trials found: In Phase III, secondary analysis of pooled data in patients with mild Alzheimer's found a significant benefit in cognition (34% reduction in cognitive decline). This could not be confirmed in a second trial. Side effects include lethargy, rash and angina.
***in*Thought Comment:** It's very unlikely the FDA will approve sola' as-is. Lilly will have to do additional clinical trials, and those are inherently unpredictable. If Lilly doesn't have biomarkers supporting clinical effectiveness, we see sola' having a 50-50 shot, but it will take several years (Source: Symphony Health Solutions)
Revenue forecast: Our model assumes a 2017 launch for sola, with peak (2020) estimates of $2.5 billion. *—Catherine Arnold, analyst, Credit Suisse*
What the analysts are saying: Although the cognitive effect in mild patients was not confirmed, being able to show benefit to the patient in terms of daily living activities (as opposed to only showing reduction in proxy measures of improvement) is important to practitioners as it is understandable to patients and their caregivers. Given the millions of patients that are or will be afflicted with Alzheimer's, this may hold blockbuster potential. *—Marite Talbergs, SVP, research and consulting, GfK HealthCare*

ORPHAN DISEASE

Recombinant factor VIII Fc (rFVIIIFc)
Recombinant factor IX Fc (rFIXFc) Biogen Idec/Sobi
Indication: Hemophilia A (Phase III)
What the clinical trials found: In separate Phase III trials, rFVIIIFc and rFIXFc were effective in controlling and preventing bleeding, routine prophylaxis and perioperative management. The long-acting clotting factor products were generally well-tolerated.
***in*Thought Approvability Index and Comment:** 56%. The hemophilia drug-development space has gotten a lot more interesting, with many compelling products coming. The two Biogen drugs have generated really nice data and look like they will be quite successful. Estimated approval date: Dec. 2014 (Source: Symphony Health Solutions)
***in*Thought revenue forecasts:** rFVIIIFc: $825 million in 2018; rFIXFc: $419 million in 2018.
What the analysts are saying: Frequency of administration is a negative for existing agents and is thought to impact quality of life, so any decreases in required use will make these products more convenient. Hemophilia patients are often reluctant to switch therapies when something has been working, so uptake could be slow in established patients. But given that administration is a common complaint, it is logical to believe that some may clamor for a less-frequent treatment. *—Michael Garcia, SVP, research and consulting, GfK HealthCare*

OTHER KEY PRODUCTS IN THE PIPELINE

NEUROLOGY

Dexpramipexole Biogen Idec
ALS (Ph.III)

BG-12 Biogen Idec
Multiple sclerosis (Prereg.)

BIIB017 Biogen Idec
Multiple sclerosis (Ph.III)

Tasimelteon BMS
Insomnia (Ph.III)

Eslicarbazepine acetate Eisai
Partial epilepsies (Ph.III)

Perampanel Eisai
Tonic-clonic epilepsy (Ph.III)

Edivoxetine Eli Lilly
Major depressive disorder (Ph.III)

Cariprazine Forest
Bipolar disorder (Ph.III)

Levomilnacipran Forest
Major depressive disorder (Prereg.)

Preladenant/MK-3814 Merck
Parkinson's disease (Ph.III)

Suvorexant Merck
Insomnia (Prereg.)

Safinamide Pfizer
Parkinson's (Ph.III)

Tafamidis meglumine Pfizer
Amyloid polyneuropathy (Prereg.)

Bitopertin Roche
Schizophrenia (Ph.III)

Ocrelizumab Roche/Biogen
Multiple sclerosis (Ph.III)

ORPHAN DISEASES

BMN-110/GALNS BioMarin
Mucopolysaccharidosis (Ph.III)

Migalastat GSK
Fabry's disease (Ph.III)

Pasireotide Novartis
Acromegaly (Ph.III)

N8-GP/NN7088 Novo Nordisk
Hemophilia A (Ph.III)

N9-GP/NN7999 Novo Nordisk
Hemophilia B (Ph.III)

Turoctocog alfa Novo Nordisk
Hemophilia A (Prereg.)

Tafamidis meglumine Pfizer
Amyloid polyneuropathy (Prereg.)

Eliglustat Sanofi/Genzyme
Gaucher's disease (Ph.III)

Empagliflozin Sanofi/Genzyme
Gaucher's disease (Ph.II)

Arbaclofen Seaside Therapeutics
Fragile X syndrome (Ph.III)

Idebenone Takeda
Friedreich's ataxia (Ph.III)

Miglustat United Therapeutics
Niemann-Pick diseases (Prereg.)

RESPIRATORY

A 64077 Abbott
COPD (Ph.III)

300 IR Abbott/Stallergenes
Seasonal allergic rhinitis (Ph.III)

FX125L Boehringer Ingelheim
Inflammatory diseases (Ph.II)

Olodaterol/tiotropium bromide BI
COPD (Ph.III)

GSK-642444 GSK
COPD (Ph.III)

Mepolizumab GSK
Asthma (Ph.III)

Relvar/Breo GSK
COPD (Prereg.)

Seebri Breezhaler Novartis
COPD (Ph.III)

Lebrikizumab Roche
Asthma (Ph.III)

WOMEN'S HEALTH

Elagolix Abbott
Endometriosis (Ph.III)

Trebananib Amgen
Fallopian tube cancer (Ph.III)

Serada Depomed
Hot flashes (Prereg.)

Trabectedin J&J
Breast/ovarian cancer (Ph.III)

Vintafolide Merck
Ovarian cancer (Ph.III)

Corifollitropin alfa Merck
Female infertility (Ph.III)

V503 Merck
Cervical cancer prevention (Ph.III)

Conjugated estrogens/ bazedoxifene Ligand Pfizer
Vasomotor symptoms (Ph.III)