Biosimilars in Development Near End of Phase 3 Trials

Amgen's biosimilar candidate **ABP501** proved comparable to AbbVie's **adalimumab (Humira)** for patients with moderate to severe plaque psoriasis, based on results from a head-to-head phase 3 study. The study met its primary endpoint of improvement from baseline to Week 24. Amgen is also developing biosimilars of **cetuximab (Erbitux)** and **bevacizumab (Avastin).**

Amgen's own **etanercept (Enbrel)** is the target of biosimilar development. A 52-week study of **CHS0214,** by Coherus, demonstrated PASI-75 equivalence at Week 12 for the treatment of moderate to severe plaque psoriasis. The trial, which is still ongoing, is measuring mean percent change from baseline and the proportion of subjects achieving 75% improvement in PASI in patients given CHS0214 versus those given etanercept.

Novartis is waiting for FDA approval of a long-acting treatment for boosting white blood cell count, a biosimilar of Amgen's **pegfilgrastim (Neulasta).** This is Novartis's third biosimilar submission, with 10 more planned filings over the next three years. Novartis's previous filings also targeted Amgen drugs; the FDA is reviewing its application to market a copy of etanercept for rheumatoid arthritis and other autoimmune diseases, and Novartis's Sandoz subsidiary launched **Zarxio,** a **filgrastim (Neupogen)** biosimilar, in September. The company's other biosimilar prospects include Johnson & Johnson's **infliximab (Remicade)** and Genentech's **trastuzumab (Herceptin).**

HCV successes at AASLD

Oral combination medicines and regimens made headlines at the American Association for the Study of Liver Diseases (AASLD) 2015 Liver Meeting in San Francisco. Merck's once-daily **elbasvir/grazoprevir** tablet showed sustained virologic response 12 weeks after the completion of treatment (SVR12) in 95% of patients with chronic hepatitis C (HCV) who inject illegal drugs. Conducted in patients with HCV genotypes 1, 4, and 6, the C-EDGE CO-STAR study was of interest because limited research has been conducted in patients undergoing treatment for injection drug use.

Other AASLD presentations: In the ongoing TOPAZ-II study, 95% of adults with HCV genotypes 1a or 1b treated with AbbVie's **Viekira Pak** (ombitasvir, paritaprevir, ritonavir, dasabuvir) achieved SVR12 after 12 or 24 weeks of treatment. Participants in TOPAZ-II are being followed for 5 years post-treatment to evaluate the long-term impact of SVR12 on the progression of liver disease. ... In a systematic review of clinical trial data, patients with HIV and hepatitis C virus (HCV) co-infection, a once-daily regimen of **daclatasvir (Daklinza)** and **sofosbuvir (Harvoni)** achieved superior SVR12 compared with a regimen of sofosbuvir/ribavirin. The analysis was conducted by the Boston-based Health Economics and Outcomes Research Analysis Group and Bristol-Myers Squibb, maker of daclatasvir. Sofosbuvir is manufactured by Gilead.

Pleasing, puzzling CV data

Patients with type 2 diabetes and cardiovascular (CV) disease receiving the glucose-lowering agent **empagliflozin (Jardiance),** a sodium glucose cotransporter-2 (SGLT-2) inhibitor, were less likely than those taking placebo to die from CV causes, according to results of the large EMPA-REG OUTCOME study. The findings, published in the Nov. 26 issue of the *New England Journal of Medicine,* were hailed as landmark, as this is the first glucose-lowering drug to show superiority in a CV-outcomes trial. Investigators, however, admitted that they have yet to understand the outcome.

Setbacks in cancer trials

Bevacizumab combined with the chemotherapy agent **lomustine** for treating first recurrences of glioblastoma did not improve overall survival (OS), according to findings from the EORTC-26101 trial. OS was not statistically different between the two study arms, with a median OS of 9.1 months in the combination group versus 8.6 months in a control arm of patients receiving lomustine alone. Progression-free survival (PFS) data seemed more promising, however—4.17 months among patients receiving the combination treatment versus 1.54 months for the lomustine-alone group. 8.8% of patients in the combination-therapy arm had no progression at 1 year, compared with 1.9% of patients in the lomustine arm. Data were presented at the 20th Annual Scientific Meeting of the Society for Neuro-Oncology.

The introduction of tyrosine kinase inhibitors (TKIs) revolutionized the treatment of gastrointestinal stromal tumors (GIST), but secondary resistance remains an issue. New results from a group of patients who have been followed since 2004 show that those with high- or intermediate-risk GIST and who were given **imatinib (Gleevec)** after surgery had no gain in OS, but imatinib did appear to have long-term

Selected FDA approvals of biologics and other specialty drugs, Oct. 3, 2015–Dec. 31, 2015

New marketing approvals

Date (type)	Manufacturer	Drug (trade) name; administration	Indication	Notes
Oct. 16 (BLA)	Boehringer Ingelheim	idarucizumab (Praxbind); intravenous injection	Reversal of anticoagulation effects of dabigatran (Pradaxa) in patients needing emergency surgery or who have life-threatening or uncontrolled bleeding	First reversal agent for dabigatran received accelerated approval in a study of healthy volunteers. Continued approval may be contingent on results of an ongoing cohort case series study. WAC is $3,500.
Oct. 27 (BLA)	BioVex/Amgen	talimogene laherparepvec (Imlygic); intralesional injection	Local treatment of unresectable lesions in patients with recurrent melanoma	First FDA-approved oncolytic viral therapy is a genetically modified live herpes virus. Injected directly into melanoma lesions, it replicates and causes apoptosis. Average cost: $65,000.
Nov. 5 (NDA)	Gilead	elvitegravir/ cobicistat/ emtricitabine/ tenofovir (Genvoya); subcutaneous injection; oral tablet	HIV-1 in ARV-naive patients or to replace current therapy in patients whose HIV is suppressed; for patients age ≥12 years	Approval of 4-in-1 tablet based on four clinical trials of 3,171 patients randomized to Genvoya or another approved HIV treatment, depending on the trial. Genvoya reduced viral loads and was comparable to other treatments. Label carries black box warning about liver toxicity. Annual list price of $31,362 is in parity with its predecessor, Stribild.
Nov. 10 (NDA)	Genentech	cobimetinib (Cotellic); oral tablet	Unresectable or metastatic melanoma with BRAF V600E or V600K mutation, in combination with vemurafenib (Zelboraf)	Coadministration of cobimetinib (a MEK inhibitor) with vemurafenib (a BRAF inhibitor) is designed to counter effects of resistance to a single targeted treatment. In the coBRIM trial, PFS was 12.3 months in combination patients vs. 7.2 months in patients given vemurafenib alone.
Nov. 13 (NDA)	AstraZeneca	osimertinib (Tagrisso); oral tablet	Metastatic, EGFR T790M mutation-positive non–small-cell lung cancer	For use in patients with disease progression after treatment with an EGFR tyrosine-kinase inhibitor. FDA also approved a companion diagnostic to detect the T790M mutation. Approval based on surrogate ORR in AURA phase 2 open-label trials.
Nov. 20 (NDA)	Millenium/ Takeda	ixazomib (Ninlaro); oral capsule	In combination with lenalidomide (Revlimid) and dexamethasone in patients with MM who have received 1 prior therapy	Approval creates first all-oral regimen for MM with a proteasome inhibitor (PI). In the TOURMALINE-MM1 clinical trial of 722 patients, PFS in the study group was 5.9 months greater than in the lenalidomide/ dexamethasone/placebo group. $8,670-per-cycle cost is comparable to bortezomib (Velcade), an injected PI from the same maker.
Nov. 24 (BLA)	Eli Lilly	necitumumab (Portrazza); intravenous injection	In combination with gemcitabine and cisplatin for first-line use in patients with metastatic squamous non–small-cell lung cancer	In the SQUIRE trial, OS gain vs. chemo-alone arm (1.6 months) was statistically significant, though "marginal," according to one FDA advisor. An economic analysis at ASCO 2015 found that necitumumab must cost <$1,300 per 3-week cycle to be cost-effective. Its cost: $11,430 per month.
Dec. 16 (BLA)	Eli Lilly	insulin glargine (Basaglar); subcutaneous injection	Improve glycemic control in adults with types 1 and 2 diabetes and children with type 1 diabetes	Not technically a biosimilar because it was approved under the 505(b)2 pathway, Basaglar is the first approved follow-on to Sanofi's Lantus. The long-acting insulin analogue demonstrated similarity in two clinical trials enrolling 1,278 patients.

ARV=antiretroviral, BLA=biologics license application, EGFR=epidermal growth factor receptor, MM=multiple myeloma, NDA=new drug application, ORR=overall response rate, OS=overall survival, PFS=progression-free survival, 505(b)2=abbreviated new drug pathway.

Sources: ASCO, FDA, Fair Pricing Coalition, Fierce Biotech, Medscape, *New England Journal of Medicine, New York Times,* Physicians First Watch, theStreet.com, *Wall Street Journal,* and product labeling.

benefit for relapse-free survival. In patients given postsurgical imatinib, relapse-free survival was 84% at 3 years, compared with 66% in an observation group. At 5 years, the rates were 69% and 63% respectively.

Genmab has stopped its study comparing **ofatumumab (Arzerra)** with Genentech's **rituximab (Rituxan)** in the treatment of relapsed follicular non-Hodgkin's lymphoma (NHL). The decision followed an interim analysis conducted by an independent data monitoring committee. The analysis concluded that ofatumumab was unlikely to show superiority if the trial were to conclude as planned. The trial randomly assigned 516 patients with follicular NHL to receive either ofatumumab or rituximab by intravenous infusion in four weekly doses, with PFS being the primary outcome. Data from the study will be presented at a future scientific conference.

The troublesome state of oncology clinical trials

Although more than two thirds of the biologics pipeline is in oncology, conducting a clinical trial continues to be troublesome. Consider these:

- The National Cancer Institute estimates that up to 40% of oncology trials fail to achieve minimum enrollment. Covance estimates that more than 60% of phase 3 trials do not reach planned enrollment.
- Cancer patients who live on less than $50,000 a year take part in clinical trials at a rate one third lower than those who make more. The absence of low-income participants makes researchers' findings less representative of the general population.
- Various surveys suggest that 50% to 80% of patients do not have any information on potential clinical trials for their condition.
- Patients and providers often believe the default "standard of care" is better—or at least less risky—than a clinical trial.
- Patients are often selected on the basis of comorbidities. A Duke University study found that up to 40% of patients would not have received the trial drug if they were already receiving it for a comorbidity.
- Novel agents for cancer, such as **ibrutinib,** work by mechanisms distinct from chemotherapy and have shown efficacy regardless of prior regimens. But as additional drugs are approved, enrollment becomes more difficult. Studies often require participants to have either received or not received another approved drug.
- Biomarkers are increasingly a target in oncology, and some approved drugs are accompanied by a protocol to use a biomarker or a companion diagnostic to inform use. Payers can be expected to restrict access to costly targeted treatments, but simultaneously, makers of therapies with biomarkers can expect that eligible patients who test positive for a biomarker or mutation will be approved for coverage.
- Clinical trials are becoming more and more complex. For an average phase 3 trial, the number of endpoints and/or eligibility criteria has increased by at least 50% in the last 10 to 15 years.
- A study in the *Journal of the National Cancer Institute* found that 62% or recent phase 3 oncology trials failed to achieve results with statistical significance. Failed clinical trials are a huge cost to the drug sponsors, patients, and society as a whole.

—Katherine T. Adams

Sources: CovanceClinicalTrials.com; Duke Cancer Institute; Fred Hutchinson Cancer Research Center; *JAMA Oncology;* Gan HK et al, *J Natl Cancer Inst.* 2012;104:590–598.

Cholesterol-fighting booster

Adding **alirocumab (Praluent)** to standard-of-care therapy for low-density lipoprotein (LDL) cholesterol reduction is beneficial, according to a posthoc analysis of the six phase 3 ODYSSEY trials. An injection of alirocumab 75 mg lowered 74% of patients' LDL to a prespecified target within 8 weeks. The remaining 26% of patients achieved their goal by Week 24 when dosing was increased to 150 mg. Results were based on a pooled analysis of 1,291 patients with high CV risk or heterozygous familial hypercholesterolemia.

Have you heard?

Bioethics International, a not-for-profit organization focused on the ethics and governance of how medicines are researched, developed, and made accessible, published a study ranking large pharma companies by the transparency of their clinical trial results. On average, for each drug, only two thirds of clinical trials that supported new drug approvals in 2012 were disclosed, falling below legal and ethical standards. In addition, almost half of all FDA-reviewed drugs had at least one undisclosed phase 2 or 3 trial.

According to Bioethics International, three of 10 companies—GlaxoSmithKline, Johnson & Johnson, and Pfizer—publicly disclosed all clinical trial results for at least one of their reviewed drugs. The lowest-scoring company, Gilead, disclosed only 21% of trial results for **Stribild,** its HIV medication.

— Katherine T. Adams

All clinical studies mentioned in this article are phase 3 unless otherwise stated.