FDA on Real-World Evidence: Let’s Keep Talking
By Bill Myers

The FDA has issued its long-awaited plan on real-world evidence, a document that many in the industry read as the beginning of a conversation.

The FDA doesn’t see real-world evidence as a substitute for clinical trials but as a possible augmentation to them, the document released last week, shows. It allows for the possibility of “hybrid” trials where data extracted from medical claims, electronic health records or lab or pharmacy databases could be used for “certain elements” of clinical trials.

Indeed, the agency has already accepted real-world data for some single-arm interventional trials, such as those that brought Amgen’s Blincyto (blinatumomab) to market as a treatment for Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia.

The agency “sees promise,” for instance, “in the opportunities created by pragmatic clinical trials, including broader inclusion/exclusion criteria and streamlined data collection,” noting in the framework that coming guidance “will explore pragmatic approaches to each stage of a clinical trials, including recruitment and enrollment of patients, strategies for facilitating interventions and approaches to assessing outcomes.”

But the FDA also makes clear that it has concerns about how data is gathered, whether it’s reliable and that there are some standard measures so that sponsors, sites see Real-World Evidence on page 4

FDA: New Approaches for Fatty Liver Clinical Trials
By Bill Myers

The FDA is encouraging fatty liver disease researchers to come up with new biomarkers for clinical trials to avoid invasive — and potentially dangerous — biopsies that drive away many would-be participants.

“The use of liver biopsies in clinical trials poses significant logistical challenges,” the agency says in new draft guidance. “Therefore, noninvasive biomarkers are needed (including imaging biomarkers) to supplant liver biopsy and provide a comparable or superior ability to accurately diagnose and assess” chronic inflammation or nonalcoholic steatohepatitis (NASH).

Nonalcoholic fatty liver disease can progress over years from fat in the liver to chronic fibrosis to cirrhosis. Only a fraction of NASH patients with liver fibrosis ever develop full-blown cirrhosis, but the FDA says there are no clear criteria to identify that slice of the population and last week’s draft guidance is an early move to help bring clarity to the regime.

It’s also an encouraging step, says Lindsay McNair, chief medical officer at WCG.

“Potential research participants may be understandably reluctant to enroll in studies which include multiple uncomfortable biopsy procedures, each involving procedural risks,” she tells CenterWatch. “We’re pleased to see the FDA again state the need for noninvasive methods to assess liver disease and to encourage sponsors to look for biomarker endpoints.”

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GSK Back in Cancer Business with $5.1 Billion Tesaro Merger

GlaxoSmithKline is getting back into the cancer business in a big way, with a proposed $5.1 billion takeover of Tesaro, maker of cancer gene therapy Zejula (niraparib).

Glaxo officials say they expect to close the deal — pending approval by the Federal Trade Commission — in the first quarter of 2019.

If given the nod, the move will give Glaxo rights to Zejula — approved for treatment of some forms of ovarian cancer and in trials for other types — and at least 14 other cancer drugs in the clinical trial pipeline.

This marks a dramatic return to oncology for Glaxo, which sold off most of its cancer assets to Novartis in 2014 for $16 billion. The sale followed the Phase III failure of Glaxo’s MAGE-A3 melanoma immunotherapy.

Glaxo CEO Emma Walmsley said the acquisition “will strengthen our pharmaceuticals business by accelerating the build of our oncology pipeline and commercial footprint.”

Earlier this year, Glaxo hired Hal Barron from Calico, a subsidiary of Alphabet (Google’s parent company), to run its R&D department. He said he was tasked with helping to rebuild the company’s oncology biz and take an aggressive approach to immunotherapy, broadly.

Drug Helps Cut Sickle Cell Burden

A daily pill used to fight cancer has been found effective in protecting children against malaria as well as the painful and sometimes deadly effects of sickle cell disease.

Researchers gave 606 African children, ages one to 10, daily doses of hydroxyurea, an antimetabolite approved to treat some forms of leukemia, for six months.

They found pain dropped by an average of 55 percent and patients suffered 38 percent fewer infections, required 67 percent fewer transfusions and were 70 percent less likely to die. They were also 51 percent less likely to develop malaria.

The Phase I/II, dose-escalation trial, dubbed REACH, was led by researchers from the University of Cincinnati and the Centre Hospitalier Monkole; it was conducted at sites in four countries — the Democratic Republic of Congo, Uganda, Kenya and Angola.

The findings were published in the in the New England Journal of Medicine and presented at last week’s annual meeting of the American Society of Hematology (ASH).

Successful Non-Hodgkin’s Lymphoma Clinical Trial

Novartis’ Kymriah has been approved to treat non-Hodgkin’s lymphoma — and the lead researcher behind the pivotal trial that led to its OK is showing his work.

Stephen J. Schuster, director of the Lymphoma Program at the University of Pennsylvania’s Abramson Cancer Center, presented findings from the so-called JULIET trial at last week’s annual meeting of the American Society of Hematology (ASH).

JULIET was a Phase II, single arm trial involving 27 sites in 10 countries that began in July 2015.

During the trial, researchers gave 115 patients with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL) Kymriah (tisagenlecleucel). Overall, 54 percent of patients responded to the treatments, and 40 percent went into complete remission.

The current treatment involves high-dose chemo and an autologous stem cell transplant. But only half of patients are candidates for this approach — and the three-year, event-free survival rate for those who qualify for chemo/stem cell treatment is just 20 percent.

Keytruda Aces Another Trial

Merck's blockbuster drug Keytruda, already forecast to reach $7 billion in sales this year alone, has passed another clinical test — this time for patients with late-stage head and neck cancers.

During a clinical trial (spanning 20 countries), researchers from the Institute of Cancer Research and the Royal Marsden NHS Foundation Trust gave 247 patients with platinum-chemo resistant head and neck cancers Keytruda (pembrolizumab) and another 248 chemotherapy or cetuximab, the two standards of care.
On average, the patients who took Keytruda survived 8.4 months compared to 6.9 months for those in the standard therapy group. But researchers say the most promising finding was that the cancers disappeared in 36 of the Keytruda patients — and they were still cancer-free three years after their treatments began.

The scientists said they'll seek regulatory approval to use Keytruda for advanced head and neck cancers but called for more research to help identify which patients could benefit most from it.

Late last month, Merck, which sponsored the trial, announced that it was raising the price of Keytruda by an average of 1.5 percent.

**New Owner, Clinical Trial Media**

Clinical Trial Media, a patient recruiting and retention firm, has a new boss.

Officials announced that Cara Brant, who began her career at Clinical Trial Media in 2001 as a project coordinator, is the new owner and CEO of the Jericho, NY-based company.

Brant, who had risen to become chief operating officer — Clinical Trial’s first female, c-suite executive — left the company in 2016. Terms of her acquisition of the company weren’t disclosed.

Brant said she’s “thrilled to be at the helm” and is looking “forward to bridging the gap between healthcare, advertising and technology.”

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**Compliance for Sponsors**

The SOP for Good Clinical Practice by Sponsors of Clinical Trials ensures safe, effective and successful clinical trials and is a comprehensive, customizable and easy-to-use SOP.

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**The CRC’s Guide to Coordinating Clinical Research**

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- Comprehensive review of the CRC role and responsibilities
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- Preparing for and closing a clinical study
- Strategies on patient recruitment, engagement and retention
- And much more!
Real-World Evidence
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and regulators alike can be sure they’re comparing like with like.

The move is important because it begins to home in on and define real-world evidence, which had threatened to become an empty buzzword, says James Bannon, WCG’s president of scientific and regulatory review.

“At the end of the day, real-world evidence is going to depend on the clinical trial situation, the reliability of the data and ... the FDA is now giving [the industry] a forum ... to identify whether there’s utility and acceptability of real-world data,” Bannon says.

“The FDA is now giving [the industry] a forum ... to identify whether there’s utility and acceptability of real-world data.”

—James Bannon, president of scientific and regulatory review, WCG

“I still think that it’s going to be a case-by-case discussion that will evolve over time. It will come back to the utility and relevance of the data at hand.”

Bannon is one of many who doubt that real-world evidence will ever replace or supplant traditional clinical trials. He sees real-world data as being particularly helpful for measuring safety (especially once a drug’s already on the market) but doesn’t believe it will be very helpful for measuring efficacy, especially of novel compounds.

“The opportunity to use real-world evidence for very specific instances is going to take shape over time,” he says, “but I think the fundamental question is, ‘Can I substitute real-world data for some portion of an expensive clinical trial, or maybe cut down the size of an expensive trial?’”

Fatty Liver Drugs
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Fibrosis is considered the strongest predictor of poor outcomes — including death — in fatty liver disease, so sponsors should probably start there, the FDA says.

Drugs intended to treat NASH should follow double-blind, placebo-controlled protocol designs. Because inflammation moves slowly, sponsors should focus on shorter-term endpoints, including either a combination of reducing inflammation and keeping fibrosis in check or slowing fibrosis and keeping a lid on inflammation.

The FDA tailored its recommendations to different trial phases.

For early Phase II trials, the agency says it recognizes that proof-of-concept trials are attractive to sponsors but stresses they have to provide “adequate rationale and justification” for their design, including enrollment criteria, duration of trials and choice of endpoints.

Researchers may not need baseline studies of damaged tissues, depending on the trial’s endpoints, but sponsors should make sure that “these early trials capture the same or similar patient populations as those planned for the Phase III development programs.”

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“Potential research participants may be understandably reluctant to enroll in studies which include multiple uncomfortable biopsy procedures, each involving procedural risks.”

—Lindsay McNair, chief medical officer, WCG

Sponsors should also test multiple dose levels in the early stages of a Phase II trial, the draft doc says.

They should shift gears and zero in on damaged tissue if they prove — late in Phase II trials — that a drug works on its target population. A drug can move on to Phase III trials if:

- It hits histological endpoints, such as reducing inflammation or improving liver fibrosis;
- Researchers document its effects and variability among patients — and dose response; and
- The Phase II trial has been given enough time, typically at least a year to 18 months (unless sponsors can “provide clear scientific justification” for a shortened study), to produce results.

Sponsors should also be prepared to design a biomarker strategy late in Phase II trials.

The draft guidance says sponsors should think carefully about inclusion and exclusion criteria for Phase III trials, noting that, in most cases, patients should have been diagnosed with NASH plus fibrosis no more than six months before they enroll in a trial.

Patients with high inflammation activity scores, high Model for End-Stage Liver Disease scores or a documented history of Gilbert’s syndrome can also be included, the FDA says.

The protocol should be clear about exclusion criteria and evidence of portal hypertension — and patients with liver enzyme levels more than five times the upper limit of normal should be excluded from Phase III trials. Ditto patients with other chronic liver diseases.

Celebrating

50

Years of Pioneering, Together.

It isn’t in our nature to seek the limelight or to sing our own praises. But when you turn 50, well, that’s something pretty special. We don’t want to celebrate alone though, because we know the real power comes from pioneering together. To all of those who share our passion for protecting people and are inspired by science and medical discovery, a heart felt thank you for joining us on our first 50 years of pioneering together!
### Drug & Device Pipeline News

For news on trial results, FDA approvals and drugs in development, Join the LinkedIn Drug Research Updates group!

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Moradi MD Research is a branch of Dr. Amir Moradi’s private practice. Its mission is to continue to advance the frontier of rejuvenation science through innovation and research. The goal of the team is to learn tirelessly and teach generously.

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Nephrology Research of Michigan conducts Phase II, III and IV clinical trials. The primary therapeutic areas include chronic kidney disease, hypertension, diabetes and anemia — and, for devices, migraine, hypercalcemia, obesity, gout and lupus.

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NOCFRC/VRG is part of AMR. AMR acknowledges the importance of multi-site coordination, allowing it to maximize economies of scale and consistency to exceed Sponsor goals ahead of schedule and under budget.

**Oklahoma Heart Hospital Research Foundation**

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(405) 608-4758  
bheightower@okheart.com

Founded in 1993 by a group of cardiologists, OHHRF has conducted 376 studies and has a regulatory turnaround time of five days. OHHRF has 350 active patients in the database, an 81% average percent of total patients randomized and 85% of studies meet enrollment goals.

**Pharmaceutical Research & Consulting, Inc.**

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ewarner@suburbanresearch.com

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