What Does FDA’s ‘Breakthrough’ Pathway Mean for Neurology?

BY GINA SHAW

Over the past year, the US Food and Drug Administration (FDA) has granted “breakthrough” status to some 22 emerging therapies, a new designation created by the FDA Safety and Innovation Act of 2012. The “breakthrough” status joins three other expedited FDA designations for serious conditions: fast-track, accelerated-approval, and priority-review. [See “FDA Expedited Programs.”]

The newest designation allows that “preliminary clinical evidence [for a serious condition]...may demonstrate substantial improvement over available therapies on a clinically significant endpoint or endpoints,” wrote scientists with the FDA’s Center for Drug Evaluation and Research (CDER) in the Nov. 14 New England Journal of Medicine (NEJM). In addition to the benefits of fast-track designation (rolling review, possible priority review, frequent interaction with FDA sources), “breakthrough” drugs also receive “intensive guidance on an efficient drug development program, beginning as early as phase 1” and “organizational commitment involving FDA senior managers.”

Most of the drugs on the breakthrough list are oncology compounds, but three are designed to treat neurologic conditions: amifampridine phosphate for Lambert–Eaton myasthenic syndrome, imigranmab for sporadic inclusion-body myositis, and drisapersen for Duchenne muscular dystrophy (DMD), the most common and rapidly progressive of the muscular dystrophies.

WHAT CAN RESEARCHERS EXPECT?

What can researchers into these (and potentially other) serious, challenging neurologic conditions expect from this new designation?

It’s hard to say at this point. Before the NEJM article went to press, drisapersen’s developer, GlaxoSmithKline, announced that the drug had failed to meet its primary endpoint of a statistically significant difference in the six-minute timed walk test, a standard assessment of functional decline in Duchenne muscular dystrophy.

FDA, 23andMe

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There are already direct-to-consumer companies that have genetic counselors available, Goldman said. Even then, for many of these companies, it’s not a requirement to go through counselors to order the testing. “The rationale is that people should have a right to their own genetic information, that we shouldn’t be paternalistic — but a lot of it is highly sensitive medical information.”

These private companies, she said, don’t want a “gatekeeper because you’re not going to make money if there is a gatekeeper — and that’s a big concern.” Somehow there needs to be a balance between getting good meaningful information and “having the right to it.” One website called Counsyl, which provides genetic information mainly for autosomal, recessive genes that are used for prenatal screening, provides information to the consumer, but it has to be ordered through a medical center. That’s one option 23andMe might consider, Goldman told Neurology Today.

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LINK UP FOR MORE INFORMATION

- FDA warning letter to 23andMe: http://1.usa.gov/1c9xX9B
- 23andMe responds to the FDA: http://mediacenter.23andme.com
- Class-action lawsuit against 23andMe: http://bit.ly/1IEJZaD
- Previous coverage of 23andMe in Neurology Today: http://bit.ly/J2EEgZ
DMD. The 125 boys on the drug did no better on the timed walk than did the 61 on placebo; there was a similar lack of superiority for drisapersen found with secondary endpoints such as the 10-meter walk-run test, the four-stair climb, and the North Star Ambulatory Assessment.

Did the breakthrough designation benefit the drug’s developers in any way, even if only by helping it “fail faster?” Neurology Today sought comment from GSK researchers, but was unable to secure a response at press time.

The DMD community would certainly like to know, said Sharon Hesterlee, PhD, vice president of research at the Parent Project Muscular Dystrophy, an advocacy organization that funds research and provides support services to families with children with DMD. “Our understanding is that the breakthrough designation means better access to the FDA and a better turnaround time for getting questions answered, and potentially accelerated approval as well. We’d like to know if the designation improved GSK’s timeline on drisapersen and got them answers faster.”

Tantalizingly for DMD researchers, the FDA confirms that a surrogate endpoint — such as dystrophin production — could also be sufficient for the approval of a breakthrough drug.

Whether that was the case for GSK or not, the FDA confirms that the breakthrough designation has led to approval of at least one therapy based primarily on phase 2 data. In November, the FDA approved ibrutinib for the treatment of mantle cell lymphoma (MCL), eight months after it had received breakthrough designation for that indication. “The efficacy and safety profile of ibrutinib were primarily evaluated in 111 patients with previously treated MCL in a single-arm phase 2 clinical trial,” said Eric Pahon, a spokesperson for CDER in an e-mail interview with Neurology Today.

Tantalizingly for DMD researchers, the FDA also confirms that a surrogate endpoint — such as dystrophin production — could also be sufficient for the approval of a breakthrough drug. “As a drug designated as a breakthrough therapy may be eligible for the accelerated approval pathway, if the relevant criteria are met, it is possible that surrogate endpoints could be acceptable for approval of a breakthrough designated drug,” Pahon commented.

GSK hadn’t pulled the plug on drisapersen yet, said Dr. Hesterlee — they’re still analyzing data to see if there are subgroups of responders — but “it’s on life support.” [For more on the therapeutic approach used in the DMD drug, see “More on the Exon-Skipping Strategy”]

More on the Exon-Skipping Strategy

Do the recent FDA decisions and trial results mean the end for the exon-skipping technology as a therapeutic strategy for Duchenne muscular dystrophy (DMD)? Exon-skipping uses small bits of DNA called antisense nucleotides to mask or “skip” a malfunctioning exon on the dystrophin gene. It doesn’t aim to cure DMD — all 79 exons on the gene must function coherently to produce fully healthy levels of dystrophin protein. But if a damaged exon can be taken out of the equation, the rest of the cellular message can be read, and at least some dystrophin protein can be produced.

“Dystrophin is the scaffolding that holds the membrane of the muscles together. If you have none, or minimal, or it doesn’t work, you have Duchenne,” said Ann Tilton, MD, chief of the section of child neurology at Louisiana State University School of Medicine in New Orleans and a member of the Neurology Today editorial advisory board. “If you have an abnormal protein, but it partially works, you have a modified, less severe form of the disease. If you can make it a protein that works somewhat, you have the potential for someone to live much longer.” (Most boys with Duchenne die by the age of 25, usually as a result of lung and heart problems.)

Drisapersen aimed to “skip” exon 51, but it’s not the only drug out there targeting this exon. Sarepta’s eteplirsen also focuses on this exon, but uses a different chemistry.

—Gina Shaw

FDA Expedited Programs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fast-track designation</th>
<th>Breakthrough-therapy</th>
<th>Accelerated-approval pathway</th>
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<tr>
<td>Qualifying criteria</td>
<td>*A drug that is intended to treat a serious condition and for which nonclinical or clinical data demonstrate the potential to address an unmet medical need</td>
<td>A drug that is intended to treat a serious condition and that preliminary clinical evidence indicates may demonstrate substantial improvement over available therapies on a clinically significant end point or end points</td>
<td>A drug that treats a serious condition, generally provides a meaningful advantage over available therapies, and demonstrates an effect on a surrogate end point that is reasonably likely to predict clinical benefit or on a clinical end point that is reasonably likely to predict an effect on “irreversible morbidity or mortality” or other clinical benefit</td>
<td>**An application (original or efficacy supplement) for a drug that treats a serious condition and that approved would provide a significant improvement in safety or effectiveness</td>
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Features

| Opportunities for frequent interactions with FDA; possible eligibility for priority review, rolling review | All-fast-track designation features; intensive guidance on an efficient drug development program, beginning as early as phase 1, organizational commitment involving FDA senior managers | Approval based on an effect on a surrogate or intermediate clinical end point that is reasonably likely to predict a drug’s clinical benefit | Shorter period for review of marketing application (6 months, as compared with the 10-month standard review) |

*Certain antibacterial and antifungal drugs are eligible for fast-track designation by law even if they do not otherwise meet the qualifying criteria.

**Certain applications and supplements are eligible for priority-review designation by law even if they do not otherwise meet the qualifying criteria.

After 84 weeks, the investigators reported, the data showed a continued stabilization of walking ability on the six-minute timed walk among the treated boys. "After 84 weeks, patients in the 30 mg/kg and 50 mg/kg dose cohorts who were able to perform the 6-minute walking test (modified Intent-to-Treat* or mITT population, n=6) showed a statistically significant treatment benefit of 46.4 meters (p≤0.045) when compared to the placebo/delayed-treatment cohort (n=4)," according to a Sarepta release.

They also reported a statistically significant increase (p≤0.001) in dystrophin-positive fibers, to 47 percent of normal. But in a meeting with Sarepta officials, FDA regulators questioned the robustness of the six-minute walk test data and the correlation with dystrophin production resulting from the phase 2 study.

Since then, 96-week data was presented at the World Muscle Society Congress in October, and the results still look promising, said Dr. Hesterlee. "This is a really progressive disease, and the longer the data set shows stabilization, the better and better it looks."

Sarepta is now planning a larger phase 3 trial, assuming that the accelerated approval pathway may remain unavailable — although they haven’t given up hope for a speedier process. “We are now working with the FDA to come to an agreement on a confirmatory..."
study design, and addressing the feedback they provided us to see if a New Drug Application may be a possibility in the future based on phase 2B data,” said Sarepta spokesperson Jim Baker. He said that the new study, in a larger group of patients, will involve sites in the US and Canada and will likely include the six-minute timed walk as its primary endpoint, along with other endpoints including dystrophin levels.

The drug appears to be very safe, said Dr. Hesterlee, and given the stakes with DMD, she is surprised by the level of pushback from the FDA. “They’re not bending rules or making allowances. They’re not bending rules or making allowances.

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They are saying it’s not about safety; it’s about efficacy and that we have to be sure that it works. But the parents have kids who are dying. It’s a progressive pediatric disease that is fatal, and we feel like we’re not getting a lot of the flexibility that has been so touted.” •

**LINK UP FOR MORE INFORMATION:**
- FDA Safety and Innovation Act of 2012: [http://1.usa.gov/1gGb3bH](http://1.usa.gov/1gGb3bH)