FDA snubs Sarepta's exon 53-targeting dystrophy drug

FDA's rebuff of Sarepta's new antisense drug leaves the Duchenne community perplexed.

Sarepta Therapeutics' agents for Duchenne muscular dystrophy (DMD) have polarized regulators since the [first-generation antisense drug](#) was approved in 2016. The US Food and Drug Administration (FDA) gave Exondys 51 (eteplirsen) a green light despite weak evidence of clinical efficacy and internal divisions. Now in August the US regulator handed the biotech a complete response letter (CRL) for Vyondys 53, its new antisense drug targeting exon 53, refusing to grant an accelerated approval. The decision came as a surprise to many, but especially to the company, prompting some observers to suggest that tensions between the agency and the company over its first product and lack of commencement of a post-marketing trial were still simmering.

Controversy over Sarepta's first agent, Exondys 51, erupted when the exon-skipping phosphorodiamidate morpholino oligonucleotide antisense drug received the go-ahead following intense pressure from the patient community. Critics contended that FDA leadership [ignored](#)

the advice from internal reviewers who felt the efficacy data were unconvincing, two of whom resigned over the approval. Moreover, the approval was conditional on the company agreeing to conduct a two-year post-approval trial to show Exondys 51's efficacy. But by August 2019, the company had yet to begin such a trial and in the meantime had profited from sales of [\\$300 million in 2018](#).

The pushback against the first agent's approval had been "nearly unanimous," says Caleb Alexander, chairperson of the FDA committee that rejected Exondys 51 and codirector of Johns Hopkins School of Public Health Center for Drug Safety and Effectiveness. Alexander was not involved with FDA's recent review—but plays down the notion that the CRL reflects any bad blood left over from 2016. And even when there could be overarching concerns affecting both products, he notes that FDA reviews are kept scrupulously independent. The company had expected an approval for its new drug and was "shocked," said Sarepta CEO Douglas Ingram, on a call organized by patient

Race for undruggable KRAS speeds up

German drugmaker Boehringer Ingelheim has entered clinical studies with its pan-KRAS inhibitor BI 1701963, going after one of the most commonly mutated oncogenes—until recently considered undruggable. Previously, in September, the Ingelheim, Germany-based pharma entered a \$720 million deal with Mumbai-based drugmaker Lupin to test its KRAS inhibitors with Lupin's MEK inhibitor in gastrointestinal and lung cancers. KRAS and its role as a proto-oncogene in driving tumors was identified 30 years ago, but most attempts to tackle KRAS failed because the molecule lacks distinct drug-binding pockets. Amgen was the first to develop an inhibitor of the KRAS G12C-mutated form, the most frequent KRAS mutation in non-small-cell lung cancer (NSCLC). The company's AMG 510 is the most clinically advanced KRAS inhibitor and in phase 1 testing in patients with KRAS G12C-mutant cancer. At the September European Society for Medical Oncology (ESMO) meeting in Barcelona, Spain, AMG 510 led to 7 partial responses and 6 cases of stable disease in 13 evaluable patients with NSCLC. At ESMO, Amgen also reported data from 12 evaluable patients with colorectal cancer: AMG 510 led to 1 partial response and 10 cases of stable disease. Other KRAS inhibitors are not far behind. Mirati Therapeutics expects data this quarter from a phase 1/2 trial testing MRTX849, and Johnson & Johnson is evaluating JNJ-74699157 (ARS-3248) in a phase 1 study. Like Amgen, both companies are enrolling patients with KRAS G12C-mutant cancer, as their small-molecule drugs are KRAS G12C inhibitors. As for Boehringer, its phase 1 trial will evaluate BI 1701963 as monotherapy and in combination with Mekinist (trametinib) in 140 patients. Boehringer's drug is distinct from its competitors in that it is a pan-KRAS inhibitor that targets both KRAS G12C and SOS1, a protein responsible for RAS activation. The study is recruiting patients with any KRAS mutation.

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Muscle wasting in Duchenne muscular dystrophy: muscle fibers (dark purple) are destroyed and replaced by fibrous tissue (light purple). Credit: Biophoto Associates / Science Photo Library

“In science, a no-deal Brexit would be like a severe drought for an orchard. You can't expect to have a harvest after watering it again next year. All the trees are already dead.” Nobel Laureate Andre Geim of Manchester University sums up Brexit's potential impact on science. (The Guardian, 8 October 2019)