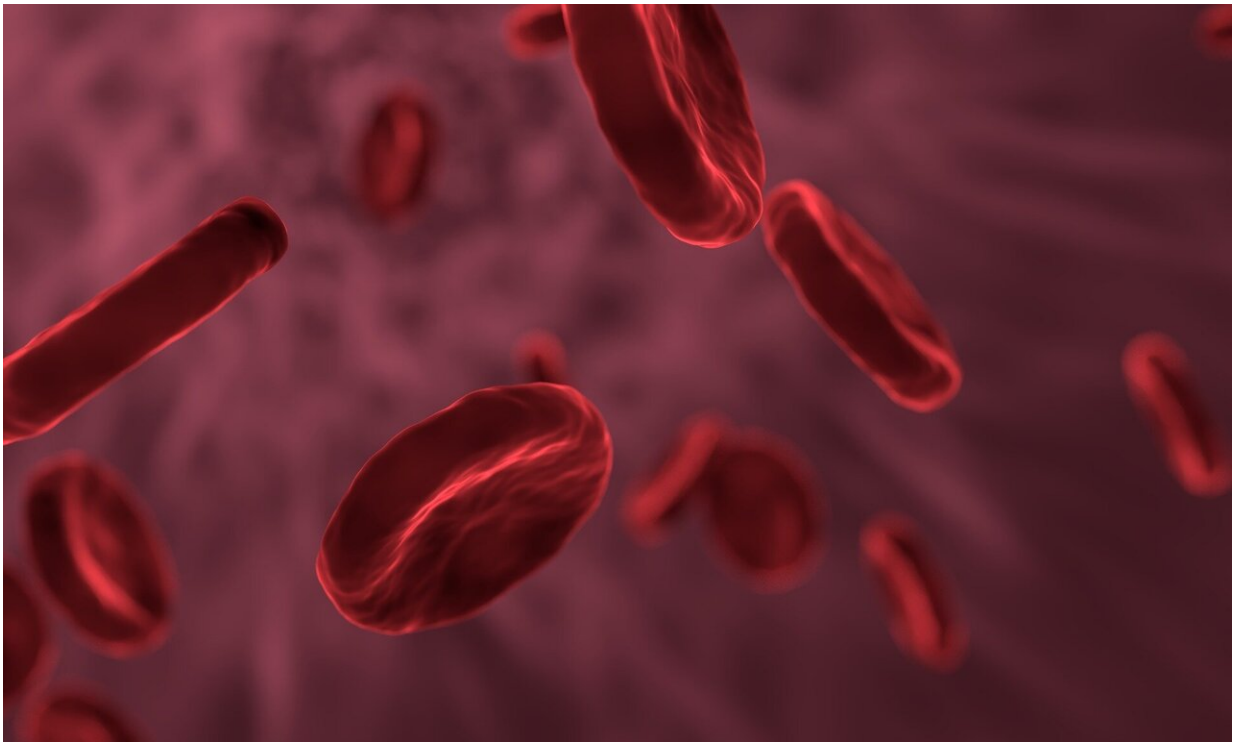
# Phase 3 clinical trial results lead to approval of oral drug for red blood cell disorder

April 14 2022



Credit: CC0 Public Domain

Researchers have published the results of a clinical trial that led the U.S. Food and Drug Administration to recently approve mitapivat for the treatment of adults with pyruvate kinase deficiency—a rare genetic condition that leads to the destruction of red blood cells, or hemolytic anemia. The primary results from the global, phase 3, randomized,

placebo-controlled ACTIVATE trial, which was conducted by an international team including investigators at Massachusetts General Hospital (MGH), are published in the *New England Journal of Medicine*.

"The lifelong anemia associated with pyruvate kinase deficiency results in chronic fatigue, reduced exercise tolerance, and a reduced ability to concentrate at work or school, which can make it a challenge to get through even a normal day," says lead author Hanny Al-Samkari, MD, a hematologist and clinical investigator at MGH and an assistant professor of Medicine at Harvard Medical School. "Moreover, most patients develop other potentially serious complications, like iron overload in the liver and/or heart (which can cause cancer or death), osteoporosis, gallbladder disease, blood clots, and other issues."

Pyruvate kinase deficiency is characterized by mutations in the PKLR gene that encodes the pyruvate kinase enzyme in red blood cells. This enzyme is critical for maintaining red blood cells' energy levels and, therefore, their normal life span. Mitapivat can activate and stabilize the mutated pyruvate kinase that's expressed in patients' red blood cells, thereby restoring the enzyme's activity.

"This is a 'disease modifying' therapy because it targets the underlying problem to improve or eliminate anemia and potentially prevent or reverse many of the other complications associated with pyruvate kinase deficiency," says Al-Samkari. "It is the first disease-modifying medication for pyruvate kinase deficiency, which up until now has been treated only with supportive measures like blood transfusion or removing a patient's spleen."

In the ACTIVATE trial designed and conducted by Al-Samkari and his colleagues, 80 patients were randomized to receive either mitapivat (5 mg twice daily, with potential escalation to 20 or 50 mg twice daily) or placebo for 24 weeks. The primary end point was a hemoglobin response

(an indicator of red blood cell levels) that was sustained at two or more scheduled assessments at weeks 16, 20, and 24.

Sixteen of the 40 patients (40%) who received mitapivat had a hemoglobin response, compared with none of the patients who received placebo. Patients who received mitapivat also had a greater response than those who received placebo with respect to secondary end points, which included other markers of red blood cell health. Patients treated with mitapivat also had a significant improvement in quality of life compared with patients receiving placebo as measured by disease-specific instruments.

The most common adverse events were nausea (in 18% of patients in the mitapivat group and 23% of patients in the placebo group) and headache (in 15% of patients in the mitapivat group and 33% of patients in the placebo group).

"The opportunity to develop a disease-modifying therapy for a disease like pyruvate kinase deficiency not only helps patients with this disease but also brings hope to patients with other similar disorders," says Al-Samkari. "Because energy is everything to red blood cells, this drug may help patients with more common anemias like sickle cell disease and thalassemia. We are looking at this right now in other clinical trials, and early studies have been very promising."

**More information:** Hanny Al-Samkari et al, Mitapivat versus Placebo for Pyruvate Kinase Deficiency, *New England Journal of Medicine* (2022). DOI: 10.1056/NEJMoa2116634

Provided by Massachusetts General Hospital