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CITELINE COMMERCIAL

27 Apr 2020 |

Sanofi/Regeneron Refocus Kevzara COVID-19 Trial On Critical Patients, Showing Value Of A Proper Trial

by Jessica Merrill

A Phase III trial testing Kevzara in hospitalized COVID-19 patients will continue only with the high dose in more advanced critical patients after the low-dose was unsuccessful.

Sanofi and *Regeneron Pharmaceuticals Inc.*'s hope for positioning Kevzara (sarilumab) as a potential treatment for hospitalized COVID-19 patients was diminished based on the initial clinical trial results, showing the drug did not help less critically ill patients in the study. The Phase III trial will be amended to enroll only advanced "critical" patients treated with the higher 400 mg dose of Kevzara and to discontinue enrolling less advanced "severe" patients, the companies announced on 27 April.

Kevzara is an IL-6 inhibitor approved for rheumatoid arthritis. The companies hoped it could play a role in stopping the inflammatory response that causes acute respiratory distress syndrome (ARDS) in critically ill COVID-19 patients. (Also see "*Sanofi And Regeneron Initiate 400-Patient Coronavirus Trial With Kevzara*" - Scrip, 16 Mar, 2020.)

The news that Kevzara did not benefit less critically ill patients versus placebo is disappointing but also highlights the value of running controlled clinical trials even in a setting like COVID-19, where there has been a push to use some medicines despite a lack of clinical data.

"Even in a pandemic setting, it's both crucial and possible to obtain controlled data in adequately-sized trials to provide the evidence needed to inform optimal medical care," Regeneron president and chief scientific officer George Yancopoulus said in a statement.

"Emerging evidence with Kevzara and other repurposed drugs in the COVID-19 crisis highlight the challenges of making decisions about existing medicines for new viral threats using small,

uncontrolled studies," he added.

Regeneron initiated the study in March after a small 21-patient trial in China showed a potential benefit in patients treated with Roche's rival IL-6 inhibitor Actemra (tocilizumab) with rapidly reduced fever and improved oxygenation in severe patients. *Roche* has also initiated a Phase III trial studying Actemra in severe COVID-19 pneumonia, with results expected in the summer.

A randomized Phase II portion of the Kevzara study compared intravenously administered Kevzara at two doses, 400mg and 200 mg, versus placebo. The study assessed 457 hospitalized patients who were categorized as "severe" illness, "critical" illness or "multi-system organ dysfunction." Severe patients required oxygen supplementation without mechanical or high-flow oxygenation, while critical patients required mechanical ventilation or high-flow oxygenation or treatment in an intensive care unit.

Preliminary analysis of the Phase II portion of the trial demonstrated that Kevzara met the primary endpoint by rapidly lowering C-reactive protein (CRP), a key marker of inflammation. Baseline levels of IL-6 were elevated across all treatment arms, with higher levels observed in "critical" patients compared to "severe" patients.

But Kevzara had no notable benefit on clinical outcomes when combining the severe and critical groups versus placebo. There were negative trends for most outcomes in the severe group, however, while there were positive trends for all outcomes in the critical group. Regeneron and Sanofi further reviewed the discontinued "severe" group data, which revealed that clinical outcomes were balanced across the Kevzara and placebo treatment arms. Outcomes for the severe group were better than expected based on prior reports, regardless of treatment assignment.

The ongoing portion of the Phase III trial is continuing to enroll patients and currently includes more than 600 considered "critical." The companies remain blinded to the ongoing part of the trial and expect to report results in June. A second trial is running outside the US in approximately 400 COVID-19 patients.

During Sanofi's first quarter sales and earnings call on 24 April, CEO Paul Hudson said the company is stepping up production of Kevzara and would be in a good position to meet the demand for critical patients if the evidence supports that use.

"We stepped up as soon as we knew that this may or may not play a part," he said.