Roche Sees "New Front in Critical Care Medicine" With CDx Deal Aimed at Septic Shock

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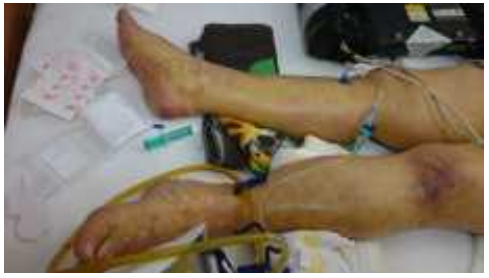

NEW YORK (360Dx) – In a first for its centralized and point-of-care business, Roche Diagnostics recently inked an agreement to collaborate in developing a biomarker-based companion diagnostic test for a septic shock treatment that biotech startup Inotrem is evaluating in clinical trials.

Roche Diagnostics' tie up with Inotrem is the first collaboration undertaken with a biotech startup by the company's centralized and point-of-care business, an indication of Roche's confidence in the therapeutic compound, Jean-Jacques Palombo, a senior vice president and lifecycle leader in Roche Diagnostics, said in an interview.

The companion diagnostic is being developed by Roche under an exclusive agreement.

Assuming the drug, which is in early clinical trials, is successful, the lead compound would likely be available on the market no sooner than 2023, according to Roche and Inotrem. According to Roche, the deal could open new pathways to diagnosing and treating septic shock.

The targeted therapy, Motrem (LR12), presents a new approach in the market for sepsis treatment and diagnosis that is attracting extensive attention from clinicians and *in vitro* diagnostics companies, mainly because of the high mortality associated with the condition. In addition to its function as an aid to Inotrem in the development of its new drug for septic shock, which is the final complication of sepsis, the biomarker test could eventually be especially useful for clinicians looking to identify patients who have the highest risk of death, Palombo added.

"Although sepsis starts with an infection, mortality comes from the body's response to that infection," Palombo said, adding, "The body overreacts and creates an amplification loop of sTREM1 proteins, which triggers an abnormal response that leads to organs such as the kidneys shutting down, and vessels as well as the heart not responding."

sTREM-1 is a marker of the activation of the TREM-1 immune amplification pathway, and high sTREM-1 plasma concentrations have been shown to be associated with a negative outcome in septic shock patients, Margarita Salcedo-Magguilli, chief development officer of Inotrem, said in an interview. TREM-1, or triggering receptor expressed on myeloid cells-1, is an immunoreceptor, and sTREM-1 is its soluble form.

Inotrem is currently conducting a Phase II clinical trial to demonstrate the benefit of Motrem, an inhibitor of the TREM-1 pathway.

Salcedo-Magguilli noted that although the companion diagnostic test has a few distinct applications within septic shock treatment and diagnosis, a common link is its ability to detect levels of sTREM-1.

Importantly, in clinical trials for development of the therapy to treat septic shock patients, the diagnostic test would identify subpopulations of patients who could benefit most from Motrem, because the pathway is highly activated in these patients, she noted. "That is the initial hypothesis, but we can also think about the companion diagnostic as a monitoring test because the treatment is expected to modulate the levels of soluble TREM," Salcedo-Magguilli said.

In addition to identifying suitable patient populations and monitoring their responses to Motrem, the companion diagnostic test also has potential as a standalone test that would tell clinicians when their patients are at most risk of dying, Palombo said.

If the companies are successful, use of the test as a clinical assay would be straightforward: A patient ruled in for sepsis would receive a blood test that determines his or her level of sTREM1. In commercial use, the test would be completed on a benchtop instrument, the Cobas e411, that's deployable across many geographies. In a clinical setting, "if you have the right blood or serum level of sTRIM1, you are eligible for the drug," he said.

The therapy would be administered as part of the standard of care for treating sepsis that includes surgery and prescription of antibiotics. Salcedo-Magguilli said that the drug is being designed to modulate a new response associated with infection and is independent of the type of pathogen leading to an infection.

The targeted therapy still has several phases of clinical trials before it could receive regulatory approval for marketing to patients.

Because of the companion diagnostics' multi-application potential, Roche intends to take a flexible approach to working with Inotrem in the joint project, Palombo noted. For that reason, the test will have a modular design, with modules tied to the varying requirements of the engagement.

Roche has already begun developing a prototype companion diagnostic. Its first milestone, according to Palombo, would be participation in a Phase IIb clinical trial involving the drug's development.

In a Phase I trial completed in 2016, the drug was "well tolerated" by healthy volunteers, Salcedo-Magguilli said. "We tested several ascending doses to ascertain the tolerance of the product around the pharmacologically active dose that we think is a good one," she added.

The firm has initiated a Phase IIa trial, expected to have roughly 300 patients, in which it is studying safety, pharmacodynamics, pharmacokinetics, and secondary endpoints in the target population. Once that's completed, the firm has plans to conduct a Phase IIb trial to test the drug's efficacy as an endpoint, and "see what the correlations with efficacy are in terms of levels of sTREM using, retrospectively, the prototype assay developed by Roche," she said. This phase of the trail would likely occur in 2019, the collaborators said.

"After that, we aim to build a Phase III trial [involving thousands of patients] to select patients in a prospective way, which would test and validate the companion diagnostic," Salcedo-Magguilli said.

She noted that the European Union's European Medicines Agency, which is responsible for the scientific evaluation, supervision, and safety monitoring of medicines in the EU, has granted access to its priority medicines scheme, which should accelerate development of the product. The purpose of the priority medicines scheme, which the EMA launched in 2016, is to bring treatments to patients more quickly by providing early and enhanced support to medicines that have the potential to address patients’ unmet needs.

Salcedo-Magguilli noted that Inotrem recently discovered that aside from its role in septic shock diagnosis and treatment, sTRIM has a major role in controlling inflammatory cell recruitment and activation after myocardial infarction, one of the main consequences of atherosclerosis. Motrem could, therefore, become a next-generation therapeutic approach in the management of acute myocardial infarction, and that has become part of the firm's clinical programs.

In the past, international groups have studied sTREM as a prognostic marker, but Inotrem has distinguished itself by showing that the marker is associated with the worst prognosis for septic shock patients, Salcedo-Magguilli noted.

Jean-Claude Gottraux, head of Roche Diagnostics centralized and point-of-care solutions, said in a statement that the collaboration with Inotrem represents a "great opportunity to participate to the opening of a new front in critical care medicine, particularly in an area known for its difficult and highly heterogeneous population."

Palombo noted that "developing a first-in-class drug and diagnostic in this kind of complicated disease is a risky business, but there is also a very high potential payoff for Roche and Inotrem, as well as patients, if we succeed."

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