

CTFN Analysis: Antitrust Questions on UCB Acquisition of Ra Pharma Explored

By: Tyler Tulenko

Executive Summary

UCB's acquisition of Ra Pharmaceuticals could be reviewed under elevated drug overlap investigation standards apparently at work inside the FTC. The FTC seems to no longer look solely at mechanism of action but also at patient choice, when reviewing pharmaceutical overlaps. UCB and Ra both have a phase 3 drug indicated for myasthenia gravis (MG). Ra's zilucoplan and UCB's Rozanolixizumab have different mechanisms of action and are said to be complementary. Still, it remains unclear where Rozanolixizumab will fit into treatment protocols and whether it could compete with zilucoplan as the first choice for some refractory patients. CTFN analysts expect FTC scrutiny, but the specifics of the combination make a plausible theory of harm difficult to support. For this reason, CTFN analysts believe the deal could avoid a second request, though may see a pull-and-refile.

MG

Myasthenia gravis is an autoimmune condition in which the body's autoantibodies erroneously attack the body's acetylcholine receptors (AChRs), causing dysfunction in the receptors required to transmit nerve signals to muscles.

Generalized (or severe) myasthenia gravis describes the condition when the disease affects a broad range of muscle function. Symptoms include muscle weakness and loss of muscle control, which can lead to difficulty performing routine tasks such as breathing, swallowing, and speaking.

The first line therapy for MG is an acetylcholinesterase inhibitor, typically pyridostigmine (an off-patent medication). Such drugs slow the natural degradation of acetylcholine which leaves more of it to interact with the acetylcholine receptors that are under siege from the autoantibodies. For many patients taking one of these drugs alleviates symptoms.

For patients whose symptoms persist or worsen despite taking acetylcholinesterase inhibitors, immunosuppressive drugs are the next line of treatment as a complementary therapy.

There are several immunosuppressive options, including the most popular corticosteroid prednisone (an off-patent steroid). A steroid can suppress the autoantibodies attacking the acetylcholine receptors, while the acetylcholinesterase inhibitors increase the amount of acetylcholine.

Patients whose condition is unchanged after a corticosteroid and at least two other immunosuppressants, with persistent symptoms that limit functionality, are defined as having refractory MG. This patient population, the 10%-15% of patients whose disease proves resistant to the initial treatments, is where Ra's zilucoplan would compete.

TREATMENTS

For refractory MG, it is recommended patients are referred to a physician with expertise in managing the condition. Therapy options include surgery called a thymectomy, as well as plasmapheresis, intravenous immunoglobulin treatments, and medications with potential adverse side effects including cyclophosphamide (off-patent), rituximab (off-patent), and eculizumab – the branded drug Soliris, marketed by Alexion.

Nicholas Silvestri MD, Clinical Associate Professor of Neurology at the University of Buffalo and author of several recent articles on MG, explained to CTFN the current treatment paradigm for these patients: “There are many things to consider when deciding what treatment is best. The first consideration is age, if a patient is younger than 50 or has early MG, then often times a thymectomy is the best option.”

Dr. Silvestri continued: “For patients for whom a thymectomy is not an option, the best treatment depends on their antibody status. For patients that have antibodies to MuSK, rituximab is the best option since Soliris's mechanism of action would not work for those patients given the complement system is not activated. For gMG patients that have antibodies to acetylcholine receptor, Soliris works very well.”

When asked about cyclophosphamide, Dr. Silvestri replied: “I am well aware of the literature for cyclophosphamide treating MG patients. Despite this, I have never in my 12 years of practice seen it prescribed. It is a harsh medication with serious side effects. It was an option for serious refractory patients before Soliris was approved.”

ZILUCOPLAN

Ra’s zilucoplan, in phase 3 studies for generalized myasthenia gravis (gMG), has been gearing up for a fight against Soliris for this slice of the refractory patient population.

Soliris and zilucoplan are C5 inhibitors, which are needed for the body’s complement system to work. C5 inhibitors prevent the body’s immune system from causing the tissue damage that causes gMG patients’ most serious symptoms. The C5 inhibitor mechanism of action the drugs share is a powerful option for gMG patients that have acetylcholine receptor antibodies and do not respond to the first acetylcholinesterase inhibitor line of defense.

Soliris, costing \$500,000 per year per patient, had captured over 1,000 gMG patients per a company update in April, despite its high cost, because it is the only drug of its kind on the market which has proved effective.

If zilucoplan is approved, CTFN analysts expect competition between the two drugs on efficacy, patient convenience, and price.

When asked about this competitive dynamic, Dr. Silvestri explained, “Zilucoplan is subcutaneous while Soliris is intravenous, requiring time consuming infusions. For many patients, self-administered subcutaneous injections will be a big advantage for convenience. Still, some patients are unable to or prefer not to inject themselves, and for them Soliris will still be a great option. We do not yet know which drug is more efficacious, because zilucoplan is still in trials.”

Dr. Silvestri agreed the competitive dynamic between zilucoplan and Soliris could bring lower prices in a bid to win patients.

Ra outlined the competitive dynamic between the drugs in a [June investor presentation](#) where the two are compared.

ROZANOLIXIZUMAB

UCB's Rozanolixizumab is currently in phase 3 trials for MG.

Rozanolixizumab is a FcRn inhibitor which reduces serum immunoglobulin G (IgG) concentration, which means it reduces the level of antibodies that cause the dysfunction in the nerve-muscle junction.

UCB made a point of emphasizing Rozanolixizumab and zilucoplan are complementary in the merger announcement. The companies' narrative is that refractory patients (who cannot do a thymectomy and do not have MuSK) will use a C5 inhibitor as a baseline treatment, and then use Rozanolixizumab when symptoms flare.

If this narrative is determined to be true, CTFN analysts believe there should not be antitrust concerns. However, Dr. Silvestri told CTFN it is not yet obvious where Rozanolixizumab will fit into the patient treatment paradigm.

Dr. Silvestri did not appear to fully accept the companies' narrative: "You start a patient on one and see how it works. It is too early to tell which one will come first. We will have to wait for the results from the phase 3 trial, those results will dictate whether I first reach for an FcRn inhibitor or a C5 inhibitor."

CTFN analysts see a non-trivial probability Rozanolixizumab could either be similar in efficacy and safety with the C5 inhibitors and thus compete for patients, or could be considered a superior option and thus cannibalize the C5 inhibitors market share, unless introduced at a much higher price.

Dr. Silvestri emphasized the MG treatment space is rapidly changing: "We are so spoiled now to have these options and more coming down the pipeline. We are seeing a revolution in how MG is being treated."

PATIENT CHOICE

CTFN analysts believe the Spark Therapeutics/Roche precedent at the FTC shows the agency is looking at patient choice rather than solely at mechanism of action when evaluating pharmaceutical overlaps.

In the 2018 paper *Killer Acquisitions*, by Colleen Cunningham, Florian Ederer, and Song Ma, the three economists argued pharma companies were buying novel pipeline

treatments to inhibit development and thus prevent competition with their existing portfolio drugs.

The paper suggested the behavior was circumventing the FTC's traditional test of market definition relying on mechanism of action, and called for a new standard of overlap analysis in pharma merger reviews.

Arguably, the attention from the FTC on Roche's acquisition of Spark's development stage gene therapies for hemophilia – with Roche' present commercial success in the hemophilia market with Hemlibra – could be evidence of a shift in analysis at the FTC.

Still, in the case of UCB buying Ra, it is not yet clear where Rozanolixizumab will fit into the treatment paradigm, and therefore it would be difficult to articulate a similar catch-and-kill competitive harm.

If Rozanolixizumab ultimately fits into treatment protocols as a complementary, second line of defense for patients on a C5 inhibitor as the companies claim, there would not likely be price competition between it and the C5 inhibitors. If on the other hand, Rozanolixizumab competes with the C5 inhibitors as a first line medication for refractory patients that cannot have a thymectomy, it might be deemed to compete directly with Soliris and zilucoplan.

It appears too early to make a conclusive argument one way or the other. In the view of CTFN analysts, this lowers the risk of the transaction receiving deeper inquiry from the FTC or seeing the agency develop a theory of harm around UCB owning both zilucoplan and Rozanolixizumab.

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For inquiries, email info@ctfn.news or call +1 203 635 6555 or +44 (0) 203 514 5314

