Mavrilimumab

Phase 2

Therapeutic Area

COVID-19-related acute respiratory distress syndrome (ARDS)

Giant cell arteritis (GCA) is a chronic inflammatory disease of medium-large arteries.

Mechanism of Action

Monoclonal antibody targets granulocyte macrophage colony-stimulating factor receptor alpha (GM-CSFR ⍰) and inhibits the signaling of granulocyte macrophage colony-stimulating factor (GM-CSF).

- GM-CSF is a key growth factor and cytokine that can govern the development and function of dendritic cells, monocytes, macrophages, and granulocytes (eg, neutrophils, basophils, and eosinophils).

US Prevalence

Historically, the annual number of pneumonia-associated ARDS cases in the U.S. has averaged over 300,000. In the past year, that number has spiked to more than 1,000,000 due to COVID-19. Over time, the company expects the incidence may revert to historical averages with occasional spikes. We estimate that there are approximately 75,000 to 150,000 patients with GCA in the United States.

Orphan Drug designation

Orphan Drug designation granted by the US Food and Drug Administration (FDA) for mavrilimumab for the treatment of giant cell arteritis.

KINIKSA

Rationale

GM-CSF is implicated in the mechanism of excessive and aberrant immune cell infiltration and activation in the lungs thought to contribute significantly to mortality in COVID-19. Robust literature evidence shows a consistent immunophenotype and pathology of ARDS across inflammatory/infectious etiologies (influx of neutrophils and upregulation of immature, pro-inflammatory macrophages).

- In April 2021, we announced data from the Phase 2 portion of the Phase 2/3 clinical trial of mavrilimumab in non-mechanically ventilated patients with severe COVID-19 pneumonia and hyperinflammation receiving local standard of care. Non-mechanically ventilated patients treated with mavrilimumab demonstrated a reduction in the risk of mechanical ventilation and death at Day 29 pooled across dose cohorts.

We believe that by blocking GM-CSF signaling, mavrilimumab may be able to reverse the course of GCA by upstream targeting of the cell types driving the inflammatory process, a mechanism that is different from currently available therapies.

- The GM-CSF signaling pathway has been shown to be upregulated in GCA biopsies versus control at both the messenger ribonucleic acid (mRNA) and protein level.
- Mavrilimumab reduced inflammatory molecules characteristic of GCA pathophysiology in an ex vivo GCA artery culture model.
- Mavrilimumab reduced arterial inflammation compared to control in an in vivo model of vasculitis.
- In previous Phase 2b trials in rheumatoid arthritis, mavrilimumab demonstrated rapid and prolonged reductions in interleukin-6 (IL-6) production, which is indicative of suppression of tissue inflammation upstream.

Status

COVID–19–related ARDS

In the Phase 2 portion of a Phase 2/3 trial of mavrilimumab in severe COVID-19, 116 non-mechanically ventilated patients were randomized in a 1:1:1 ratio to receive a single intravenous (IV) dose of mavrilimumab 10 mg/kg, 6 mg/kg or placebo. Data showed that patients treated with mavrilimumab demonstrated a reduction in the risk of mechanical ventilation and death at Day 29 pooled across dose levels. Clinical improvement was observed on top of steroids and/or antivirals. Mavrilimumab was well-tolerated and exhibited a favorable safety profile.

Kiniksa continues to enroll patients in the Phase 3 portion of the Phase 2/3 clinical trial of mavrilimumab in severe COVID-19 pneumonia and hyperinflammation.

GCA Status

We reported data from a randomized, double-blind, placebo-controlled Phase 2 clinical trial of mavrilimumab in GCA.

The Phase 2 trial randomized 70 patients 3:2 to mavrilimumab 150 mg (N=42) or placebo (N=28) biweekly injected subcutaneously, co-administered with a protocol-defined 26-week oral corticosteroid taper. Patients were stratified by new onset (n=35) or relapsing/refractory (n=35) disease.

The primary efficacy endpoint of time-to-first adjudicated GCA flare by Week 26 in all treated patients was statistically significant (Hazard Ratio = 0.38, p=0.0263). There was a 62% lower risk of flare in mavrilimumab recipients compared to placebo recipients.

The secondary efficacy endpoint of sustained remission at Week 26 in all treated patients was also statistically significant. The sustained remission rate was a 33.3 percentage points higher in mavrilimumab recipients (83.2%) compared to placebo recipients (49.9%) (p=0.0038). While the study was not powered for disease cohorts, there was a consistent trend of efficacy across the new onset and relapsing/refractory cohorts.

Mavrilimumab was well-tolerated; there were no drug-related serious adverse events, and the rates of drug-related treatment-emergent adverse events between mavrilimumab recipients and placebo recipients were similar.

A 12-week washout safety follow-up period is ongoing, and additional analyses of this Phase 2 trial are planned.

Kiniksa expects to provide next steps for mavrilimumab, including for giant cell arteritis (GCA), in the first half of 2021.

Unmet Need

Kiniksa believes there remains an urgent unmet need for patients who are hospitalized with COVID-19-related ARDS. These patients transition from an early phase of the disease characterized by high viral replication and load to a subsequent phase of aberrant inflammatory response that causes tissue damage and thrombosis, ARDS, and death. Uncontrolled viral replication increases the likelihood of variants that allow the virus to evade the protective effects of vaccines and virus-neutralizing cocktails; however, we believe that mavrilimumab blocks the body's counterproductive inflammatory reaction in a way that is agnostic to the coronavirus sequence. As such, Kiniksa believes mavrilimumab has the potential to remain effective despite the risk from emerging COVID-19 variants.

Corticosteroids are the mainstay for the treatment of GCA, but approximately 50% to 70% of patients are corticosteroid refractory or corticosteroid dependent. Long-term administration of corticosteroids carries significant morbidity, especially in an elderly population such as in those with GCA. The FDA recently approved an inhibitor of IL-6 activity as an adjunct to a corticosteroid taper for the treatment of GCA; however, IL-6 production is downstream of GM-CSF and does not address all of the underlying causes of inflammation.