FibroGen

MDS trial; Phase III study of anemia in Myelodysplastic Syndrome (MDS):

FibroGen has been conducting together with Astra Zeneca a global Phase-3 study to assess the efficacy and safety of Roxadustat for treatment of anemia in patients with lower risk Myelodysplastic Syndrome (MDS) with low red blood cell (RBC) transfusion burden (LTB). The study has been enrolling patients at approximately 70 global sites (Australia, Belgium, Germany, Israel, Italy, Russia, Korea, Spain, UK and USA). The first patient was randomized in April 2019. We hope that upon study completion we will be able to provide MDS patients with Roxadustat, an effective and safe, oral drug to treat anemia. Since this is a double-blind study, we do not know what the efficacy of Roxadustat is until all the data has been collected, and analyzed in an unblinded fashion. However, we are glad to report that we do not see any unusual or concerning safety signals up to date.

Our drug, Roxadustat is a potent and reversible orally bioavailable small-molecule inhibitor of HIF-PH enzymes. By inhibiting HIF-PH, roxadustat stimulates erythropoiesis via the HIF pathway in a manner consistent with the physiologic response to hypoxia. Its ability to stimulate erythropoiesis makes it a candidate for the treatment of anemia associated with many diseases such as MDS, chronic kidney disease (CKD) in nondialysis dependent chronic kidney disease (NDD-CKD) and dialysis-dependent chronic kidney disease (DD-CKD) patients, as well as non-myeloid malignancies under chemotherapy. We are also testing Roxadustat to treat anemia in patients who undergo chemotherapy due to different malignancies, such as lung-, pancreatic- and ovarian cancers. As of 07 September 2019, 13132 subjects (943 healthy subjects, 12120 CKD patients, 68 MDS patients, and 1 CIA patient) have received study drug in the roxadustat clinical program, of which an estimated > 7,000 subjects have received roxadustat.

The pharmacodynamics and efficacy of roxadustat can be summarized by the following:

Roxadustat produces more than dose proportional increases in endogenous plasma EPO levels, with peak increases at 8 to 12 hours post-dose.
Roxadustat increases hemoglobin (Hb) in a dose-dependent manner, regardless of baseline iron status or dependence on IV iron supplementation during treatment.
Roxadustat increases reticulocytes in healthy subjects and subjects with CKD.
Decreases in cholesterol were observed in healthy subjects and in subjects with NDD-CKD and DD-CKD treated with roxadustat.
No differences in pharmacology and efficacy were observed across different ethnicities.

Anemia is the most common clinical presentation in lower risk MDS, which results in prolonged transfusion requirements and risks related to RBC transfusion itself (Gupta, 1999), iron overload (Jabbour, 2008; Rose, 2001), and significant impairment of the quality of life (QoL) (Pinchon, 2009) in affected patients. The pathophysiology of anemia in MDS is complex, and involves ineffective erythropoiesis, dysregulated cytokine signaling, dysplastic features of hematopoietic progenitors and increased apoptosis of erythroid precursors, among other factors (Sekeres, 2007). The erythroid dysfunction in MDS often presents with fatigue and low Hb level. Anemia in MDS becomes more symptomatic with poorer clinical outcomes at lower Hb level (i.e., below 9 g/L) (Malcovati, 2011). As erythroid function continues to decline, RBC transfusion may become necessary as supportive treatment. Dependency on RBC transfusion has been associated with shorter life expectancy in patients with MDS (Malcovati, 2005).

The disease burden of anemia in MDS is high. Severe anemia interferes with patients' QoL and ability to work, and it negatively impacts the function other organ systems due to insufficient oxygen delivery (Cogle, 2015). When RBC transfusions become necessary to sustain bodily functions, not only are the frequent trips to the hospital burdensome to the patient, but the risk of transfusion-related infections can further threaten MDS patients. A fraction of MDS patients may also have a primary neutropenia due to bone marrow dysfunction or secondary neutropenia associated with medications for the treatment of MDS. Thus infection is the number one cause of death in MDS patients (Dayyani, 2010). Additional risks of transfusion include transfusion reactions (risk accumulates with exposure to more antigens through transfusions) and the iron overload from cumulative transfusions may lead to additional organ complications, particularly in heart, liver and endocrine organs (Dasararaju, 2015).

There is no FDA or EMA approved effective and safe pharmacologic treatment to treat anemia in lower risk MDS patients who are not suitable for lenalidomide or hypomethylating agents. ESAs are at times used off-label despite these agents not being approved by global health authorities for the treatment of MDS. With the recent addition of some new international sites in (Canada, France, Netherlands, Sweden, Denmark, Norway, Turkey, Poland, Serbia and India), we hope that we will be able to show the efficacy and safety of Roxadustat to treat anemia in MDS patients upon completion of this study. Please contact us, if you are interested in more details on the study itself or our published findings on Roxadustat in anemia patients. You can find the general information about this study on https://clinicaltrials.gov. You can also contact the Sponsor's medical study lead directly at kmodelska@fibrogen.com