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POSTER ABSTRACTS

102.IRON HOMEOSTASIS AND BIOLOGY

Single Ascending Doses of REGN7999, a Monoclonal Antibody Inhibitor of TMPRSS6, Increase Serum Hepcidin and Cause Deep, Sustained Reductions in Serum Iron in Healthy Human Volunteers

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Background: Iron overload (IOL) develops in dyserythropoieses such as beta-thalassemia and myelodysplastic syndromes due both to red blood cell transfusions as well as inappropriate regulation of the hormone hepcidin, a key regulator of iron homeostasis. Hepcidin, produced in the liver, sequesters iron mainly in enterocytes and macrophages. In the setting of hepcidin down-regulation, toxic levels of labile iron can accumulate in organs such as the heart, liver, bone marrow, pancreas, and pituitary gland. The current standard-of-care for the treatment of IOL is iron chelation. Chelation solubilizes iron for renal excretion, but is associated with toxicities and limited patient satisfaction, severely limiting adoption and efficacy in certain disorders of IOL. There is a high unmet need for novel therapies which can safely reduce, and even prevent, toxic iron accumulation in organs in patients with IOL. Transmembrane serine protease 6 (TMPRSS6) is a membrane-bound serine protease whose expression is highly restricted to hepatocytes, where its only known role is inhibiting hepcidin transcription by cleaving the hemojuvelin co-receptor and thus reducing the bone morphogenetic protein (BMP) signaling pathway driving hepcidin production.
Aims: REGN7999, an investigational monoclonal antibody targeting TMPRSS6, is being developed for the treatment of IOL. We have conducted a phase 1, first-in-human, placebo-controlled, single ascending dose study in healthy volunteers (NCT05481333) to explore the safety, tolerability, pharmacokinetics, and pharmacologic effects associated with REGN7999 administration.
Methods: Healthy participants at a single center were randomized 6:2 to receive R7999 or placebo in 5 ascending IV and 3 ascending SC cohorts. Key inclusion criteria included hemoglobin, hematocrit, serum iron, and transferrin saturation at or above the lower limit of normal for age and sex. Female participants were required to be non-menstruating. The primary objective of the study was to identify the safety and tolerability of single doses of REGN7999. Key secondary and exploratory objectives included characterizing the drug concentration profile of REGN7999, and evaluating the effects of REGN7999 on serum biomarkers of iron homeostasis. Data reported uses the cutoff date of June 13, 2023.
Results: In all cohorts, a total of 64 subjects were exposed. REGN7999 was well-tolerated, with no serious adverse events reported, and no participants developed anemia. Single doses of REGN7999 (ranging from 10 to 900 mg) resulted in acute 2-fold to 12-fold increases in serum hepcidin among all the REGN7999 dose cohorts, as well as acute 50-70% reductions from baseline in serum iron with the longest sustained effects (up to 7 weeks) in the highest IV and SC dose cohorts.
Conclusion: Single doses of REGN7999 are well tolerated by healthy volunteers and lead to sustained reductions in serum iron with no associated safety concerns. These findings support continued development of REGN7999 for the treatment of IOL.

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