RA101495, a subcutaneously-administered peptide inhibitor of complement component 5 (CS), for the treatment of paroxysmal nocturnal hemoglobinuria: phase 2 results

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BACKGROUND

• Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, clonal, hematopoietic stem cell disorder caused by a deficiency of glycosylphosphatidylinositol-anchored proteins (GPI-AP) on cell surfaces. Patients with acquired mutations in the glycosylphosphatidylinositol glycan class A gene lack functional complement regulatory proteins, resulting in abnormal accumulation of complement fragments on the surface of erythrocytes, and subsequent intravascular hemolysis by the membrane attack complex (MAC).

• RA101495 is a synthetic macrocyclic peptide that binds with high affinity to CS and prevents its cleavage into C5a and C5b, thereby preventing the assembly and cytolytic activity of MAC on GPI-AP-deficient erythrocytes. In a completed Phase 1 study in healthy volunteers, subcutaneously-administered RA101495 was safe and well-tolerated, and achieved rapid, complete, and sustained inhibition of complement activity.

AIMS

Studies RA101495-01.201 and RA101495-01.203 are international, multicenter, open-label, Phase 2 dose-finding studies designed to evaluate the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of RA101495 in patients with PNH.

METHODS

• Study RA101495-01.201 enrolled separate cohorts based on prior eculizumab treatment history.
  - The treatment naive cohort recruited 10 patients who had not previously received eculizumab.
  - The eculizumab switch cohort recruited 16 patients who had received treatment with eculizumab for at least 6 months prior to Screening.
• Study RA101495-01.203 recruited 3 patients who had received treatment with eculizumab for at least 6 months prior to Screening with evidence of inadequate response (LDH > 1.5xULN).
• All patients received an initial loading dose of 0.3 mg/kg of RA101495 administered subcutaneously (SC) at the Day 1 visit. Thereafter, patients self-administered once daily SC doses of 0.1 mg/kg or, upon dose escalation, 0.3 mg/kg for 12 weeks.
• The primary endpoint was the change in lactate dehydrogenase (LDH) from baseline to the mean of Week 6-12 values.
• Patients completing 12-weeks of dosing were eligible to enter a long-term extension study.

RESULTS

• RA101495 appears safe and well-tolerated with >700 patient weeks of exposure; no meningococcal infections or thromboembolic events; majority of adverse events unrelated to study drug; most common related adverse event was headache; 9 mild treatment-related adverse events, 6 of which were related to study drug; majority unrelated to study drug; most common related adverse event was headache; 9 mild treatment-naive patients successfully completed 12 weeks of dosing.
• The reduction in LDH levels after initiation of RA101495 was rapid and robust, and has been sustained in the long-term extension study for up to 48 weeks of dosing:

  - Rapid, robust, and sustained LDH reduction primary endpoint p<0.002

• The effect of RA101495 to reduce LDH was accompanied by consistent (95-98%) suppression of complement activity in an ex vivo antibody-sensitized sheep red blood cell (sRBC) direct hemolysis assay (below, left) and in the Weislab ELISA for alternative pathway activity (below, right).

• LDH reductions in treatment-naive patients were also associated with reductions in transfusion dependence (50% of transfusion-dependent naive patients achieved transfusion independence after starting RA101495) and improvements in quality of life (increase of 5.9 points in FACIT fatigue score) from Week 0 to Week 12.

RESULTS (CONTINUED)

• In patients switching from eculizumab to RA101495 (n=19), complete, sustained, and uninterrupted inhibition of complement activity was maintained in the sRBC hemolysis assay before, during, and after eculizumab washout (below, left).
• Despite adequate stoichiometric coverage of C5, a divergent LDH response was observed after switching based on prior transfusion-dependence on eculizumab (below, right).
• Breakthrough intravascular hemolysis leading to early withdrawal and reversion to eculizumab therapy was observed in 7/12 (58%) of transfusion-dependent switch patients but in only 1/17 (5%) of transfusion-independent switch patients.

CONCLUSIONS

RA101495, self-administered by low volume, daily, subcutaneous injection, appears safe and well-tolerated in patients with PNH. RA101495 rapidly and robustly reduces LDH to the levels seen in patients receiving eculizumab, and which are associated with improved long-term outcomes in PNH. These Phase 2 findings support a Phase 3 confirmatory trial and indicate that RA101495 may provide a more convenient and cost-effective treatment for PNH patients.