RA101495, A SUBCUTANEOUSLY-ADMINISTERED PEPTIDE INHIBITOR OF COMPLEMENT COMPONENT 5 (C5), 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 phosphatidylinositol 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 C5 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.

15 amino-acid cyclic peptide inhibitor of C5

BD UltraSafe Plus designed for subcutaneous self-administration

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.

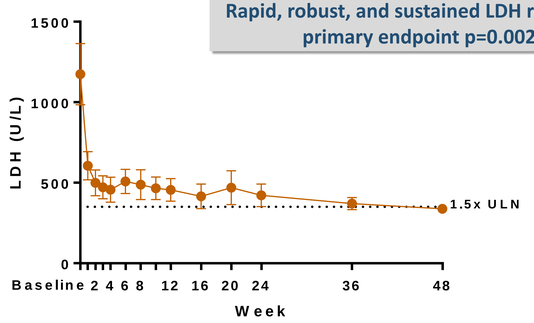
METHODS

- Study RA101495-01.201 enrolled separate cohorts based on prior eculizumab treatment history.
- The **treatment naïve 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 the Week 6-12 values.
- Patients completing 12-weeks of dosing were eligible to enter a long-term extension study.

RESULTS

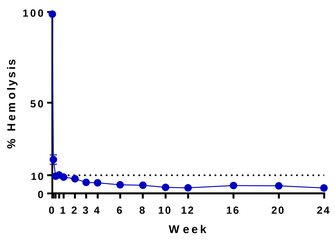
- RA101495 appears **safe and well-tolerated** with > 700 patient weeks of exposure; no meningococcal infections or thromboembolic events; majority of adverse events unrelated to study drug; most common related adverse event was headache; 9 mild (grade 1) injection site reactions out of > 5,000 injections; ~100% compliance.
- **In treatment naïve patients** (n=10), the pre-specified primary endpoint was met for **LDH reduction** from baseline to the mean of Weeks 6-12 (p=0.002).
- All 10 treatment-naïve 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

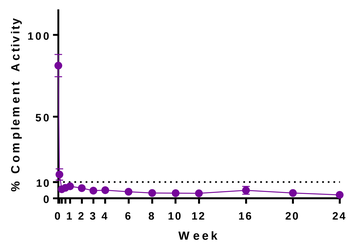


- The effect of RA101495 to reduce LDH was accompanied by **consistent** and **complete** (95-98%) **suppression of complement activity** in an ex-vivo antibody-sensitized sheep red blood cell (sRBC) direct hemolysis assay (below, left) and in the Weislab ELISA for alternative pathway activity (below,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

Rapid, complete, and sustained inhibition of classical pathway activity observed in sRBC assay



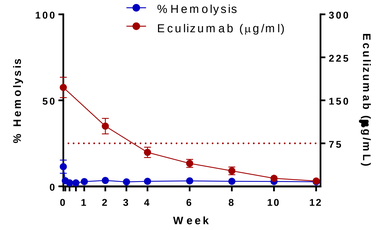
Rapid, complete, and sustained inhibition of alternative pathway activity observed in Weislab ELISA

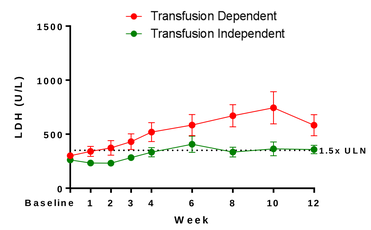


- LDH reductions in treatment-naïve patients were also associated with **reductions in transfusion dependence** (50% of transfusion-dependent naïve patients achieved transfusion independence after starting RA101495**)** and **improvements in quality of life** (increase of 5.9 points in FACIT fatigue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

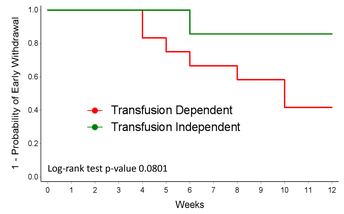
RESULTS (CONTINUED)

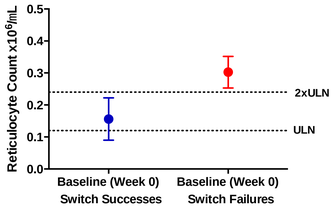
- **In patients switching from eculizumab to RA101495** (n=19), **complete**, **sustained**, and **uninterrupted** inhibition of complement activity was maintained in the sRBC hemolysis assay before, during, and after eculizumab washout (below, left).
- Despite adequate stoichiometric coverage of C5, a divergent LDH response was observed after switching according to **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 1/7 (14%) of transfusion-independent switch patients.





- Breakthrough hemolysis in switch patients coincided with the washout of eculizumab below therapeutic levels, occurring between Week 4 and Week 10 (below, left).
- Post-hoc analysis of the Phase 2 data also confirmed that an **absolute reticulocyte count < 2xULN** at the time of switching is an important additional predictor of switch success during washout (below, right).





Taken together, these data indicate that **pre-existing C3-mediated extravascular hemolysis on eculizumab** is the major risk factor for breakthrough intravascular hemolysis after switching to RA101495. Such patients can be readily identified and will be excluded from subsequent trials on the basis of transfusion-dependence and elevated reticulocytes.

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.