Inhibition of C3 With APL-2 Results in Normalization of Markers of Intravascular and Extravascular Hemolysis in Subjects with Paroxysmal Nocturnal Hemoglobinuria (PNH)

Raymond S.M. Wong, MRCP, FRCP; Humphrey W.H. Pullon, FRACP, FRCPA; Patrick Johnson, PhD; Pimjai Niparuck, MD; Tontanai Numbenjapon, MD; Jameela Sathar, MB, MRCP, MRCPath; Lisa Tan; Eric Tse, MBBS, PhD, FRCP, FRCPath; and Federico Grossi, MD, PhD

Background

- PNH is rare, acquired, potentially life-threatening hemolytic disease characterized by bone marrow failure and hemolysis due to complement-mediated hemolytic anemia and as increased risk of thrombosis.
- Uncontrolled complement activation leads to intravascular hemolysis (IVH) mediated by the activity of C5a, C5b-9, and membrane attack complex (MAC). Extravascular hemolysis (EVH) is mediated by accumulation of C3b, causing extravascular destruction of RBCs and reticuloendothelial activation.

Objective

The objective of this study was to assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of multiple doses of APL-2, administered by daily subcutaneous injection (SC), in subjects with PNH.

Materials and Methods

- Subjects were treated with APL-2 at doses of 4.25 mg/kg or 8.5 mg/kg for 85 days.
- Safety, tolerability, PK, PD, and efficacy were evaluated.

Results

- Changes in Hematologic and Blood Chemistry Parameters
  - Measurable improvements were observed in multiple parameters, including Hb, LDH, total bilirubin, and reticulocyte count.
  - Reductions in LDH were rapid following initiation of APL-2 therapy, with 95% of subjects achieving an LDH in the normal range by day 29.
  - Increases in Hb were sustained and durable as represented by a mean Hb of 12.2 g/dL at day 85.
  - Reductions in total bilirubin were rapid and sustained, with mean total bilirubin maintained within the normal range at all timepoints beyond day 29.

- Quality of Life Assessment
  - Fatigue as measured by the FACT-Fatigue instrument improved rapidly (within 2 weeks) after initiation of APL-2 therapy, and the mean (SD) change from baseline at day 29 was 6.4 (2.7).

- Treatment with APL-2 Has Been Safe and Well-Tolerated
  - No serious adverse reactions or thromboembolic events were observed.
  - One subject was withdrawn due to progression of aplastic anemia related to underlying PNH and one subject was withdrawn due to progression of an underlying malignancy.

Conclusion

- Treatment with APL-2 in complement-inhibitor-naïve PNH patients resulted in rapid and durable normalization of Hb, LDH, and total bilirubin.
- Previously transfusion dependent patients did not require any transfusions during maintenance treatment with APL-2.
- Clinically relevant improvement in FACT-Fatigue score was observed.
- APL-2 was safe and well tolerated.