APL-2, a complement C3 inhibitor, may potentially reduce both intravascular and extravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria

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BACKGROUND

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, potentially life-threatening disease characterized by complement-mediated hemolytic anemia.
- PNH arises from a somatic mutation resulting in impairment of an anchor protein responsible for the expression of numerous proteins at the cell surface of the red blood cells, including CD55 and CD59, two complement inhibitory proteins.
- Subsequent uncontrolled activation of the complement system leads to both intravascular hemolysis triggered by the membrane attack complex (MAC) and extravascular hemolysis, or cell opsonization, mediated by C3b accumulation at the cell surface.
- Due to the key position of C3 in the complement cascade, APL-2, a PEGylated cyclic peptide inhibitor of C3, may prevent both intravascular and extravascular hemolysis and could therefore be potential treatment for PNH.

AIM

To assess safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy of multiple doses of APL-2 given as monotherapy in patients with PNH.

STUDY DESIGN

- Cohort 1. Two subjects. APL-2: 180 mg/mL.
- Cohort 2: Three subjects. APL-2: 270 mg/mL.
- Daily subcutaneous injection of APL-2 for 4 weeks (Cohort 1) and up to a year (cohort 2).

ENTRY CRITERIA

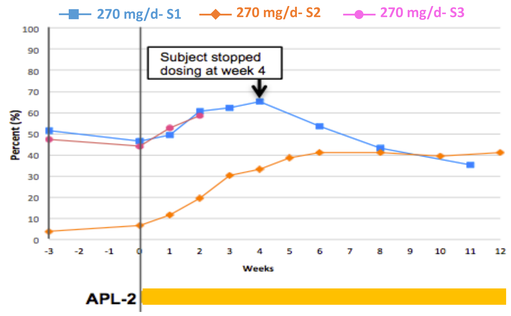
- Healthy male or female aged 18-55 years.
- Eculizumab-naïve subjects.
- Blood transfusion in the prior 12 months.
- Lactate dehydrogenase (LDH) levels ≥ 2 times the upper limit of normal (ULN).
- All subjects received vaccination against *N. Meningitides*, *S. pneumoniae* and *H. influenza* and commenced prophylactic oral antibiotics.

RESULTS

Cumulative Adverse Event Review

Verbatim/Preferred Term/SOC	AE Duration (Days)	Severity	Action taken treatment	Relationship to study drug	Outcome
Injection site erythema (5 reports)	2-3	Mild	None	Probably related	Recovered
Urinary Tract Infection	5	Moderate	Antibiotic - nitrofurantoin	Probably related	Recovered
Possible allergic reaction	4	Severe (SAE)	Temporary halt to dosing	Possibly related	Recovered
Nose Bleed	0	Mild	None	Not related	Recovered
Gum Bleed	0	Mild	None	Not related	Recovered
Injection site erythema 2 reports (upper quadrants)	1	Mild	None	Probably related	Recovered
URTI	22	Moderate	Antibiotics (after ~10 days of symptoms)	Not related	Recovered

A. PNH Type II + Type III cells



B. C3 deposition on type II + type III cells

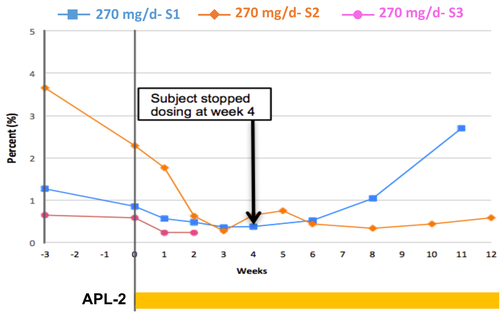
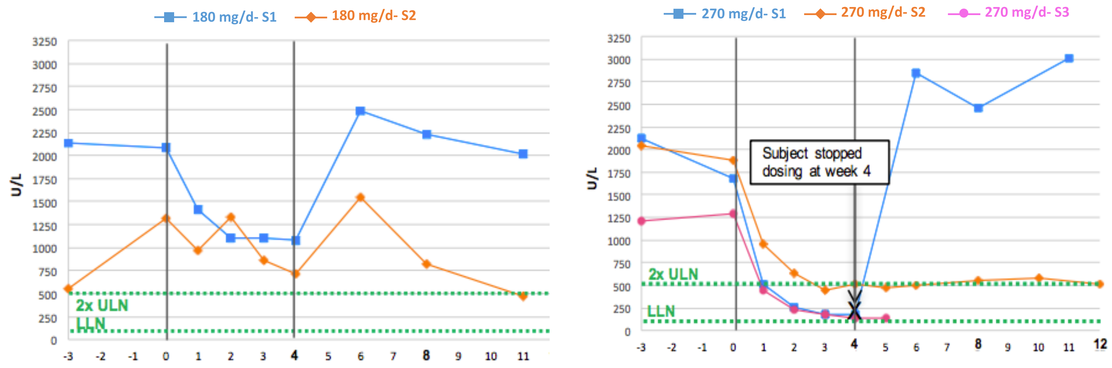


Figure 1. Clonal distribution of PNH RBCs and C3 deposition. (A) Percent of CD59 positive Type II and III cells over time. Type II and type III cells are derived from PNH stem cells, and carry, respectively, low or undetectable levels of CD55/CD59. Both type II and type III cells are susceptible to hemolysis. (B) Percent of C3 positive cells in the type I and III population. C3 fragment deposition on RBCs is a strong indicator of opsonization and extravascular hemolysis.

A. LDH levels



B. Hemoglobin levels

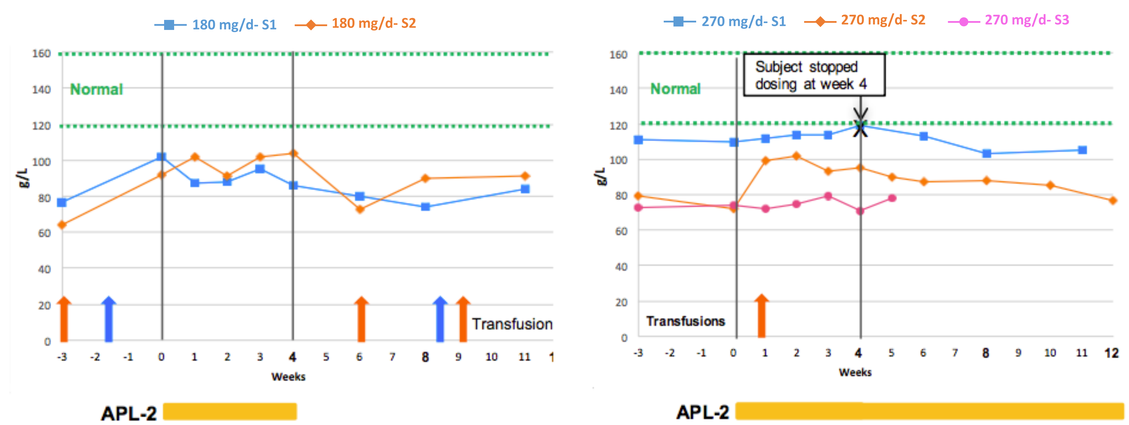


Figure 2: Biochemical indicators of hemolysis. (A) Levels of LDH, a marker of intravascular hemolysis. ULN: upper limit of normal; 2xULN is the higher level that has been associated with significantly increased risks of TE and mortality; LLN: lower limit of normal. (B) Hemoglobin levels. Normal level range is indicated by green dashed lines. Transfusion history (vertical arrow) includes whole blood/packed RBC transfusions performed prior to first dose at screening and all on-study transfusions. Dosing of APL-2 is indicated by horizontal yellow line. Cohort 1 (left panels) and cohort 2 (right panels). Subject (S1) in the second cohort withdrew consent for personal reasons; APL-2 was discontinued at 4 weeks.

CONCLUSIONS

- Daily subcutaneous injection of APL-2 is safe and well-tolerated at 180 and 270 mg/d.
- APL-2 in mono-therapy led to a sustained suppression of hemolysis with evidence of dose-response an increased proportion of PNH Type II and III RBCs, and a decreased C3 deposition.
- These data support the hypothesis that C3 inhibition may prevent both intravascular and extravascular hemolysis.
- APL-2 is the first C3 inhibitor tested in patients with PNH. APL-2 might help transfusion-dependent patients become transfusion-independent and might stabilize hemoglobin levels.