Treatment with APL-2 in patients who remain anemic despite treatment with Soliris® leads to increases in hemoglobin, transfusion avoidance and broad control of hemolysis

Carlos de Castro, MD*, Ilene Weitz, MD, Pascal Deschatelets, PhD, Cedric Francois, MD, PhD, Jaroslav Maciejewski, MD, PhD*, Ellya Roman, MD, Vivek Sharma, MD, Lisa Tan†, Federico Grossi, MD, PhD*

1Duke University School of Medicine, Durham, NC, USA, 2Neck-USC School of Medicine, Los Angeles, CA, USA, 3Apellis Pharmaceuticals, Waltham, MA, USA, 4Fauci Cancer Institute, Translational Hematology and Oncology Research, Cleveland, OH, USA, 5Lakes Research, Miami Lakes, FL, USA, 6University of Louisville, Louisville, KY, USA, 7Lisa Tan Pharma Consulting, Cambridge, UK, 8Apellis Pharmaceuticals, Waltham, MA

Background

- APL-2 is a pegylated cyclic peptide that binds to C3, exerting broad inhibition of the complement cascade, preventing both IVH and EVH and helping the body restore normal complement activity (Figure 3).

- The only approved treatment for PNH is Soliris® (eculizumab) as a CS inhibitor which only treats IVH.

- Up to 75% of patients treated with Soliris® continue to experience ongoing anemia and its associated symptoms.

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Aim, Methods, Eligibility

Aim

Assess the response to SC APL-2 as an add-on to standard-of-care in patients with PNH who continue to be anemic despite treatment with eculizumab (Soliris®).

Methods

Study CP-0154, an open-label study conducted in the USA, designed to assess safety, tolerability, pharmacokinetics and pharmacodynamics of APL-2 administered daily by SC injections as an add-on to standard of care (Soliris®).

Key Eligibility Criteria

- PNH (WBC clone >10%) and persistent anemia
- On treatment with Soliris® (IV) for 3 months prior to screening
- Hb < 10 g/dL at screening OR have received ≥3 units of RBCs by transfusion or ≥1 transfusion within 12 months prior to screening
- Platelet count >50,000/μL
- Absolute neutrophil count >500 x10⁹ /L
- Platelet count >30,000/μL
- ≥1 transfusion within 12 months prior to screening
- Hb < 10 g/dL at screening OR have received ≥3 units of RBCs by transfusion or ≥1 transfusion within 12 months prior to screening
- Platelet count >50,000/μL
- Absolute neutrophil count >500 x10⁹ /L
- Platelet count >30,000/μL

Eligibility

Six subjects entered the cohort and 2 were withdrawn after approximately 8 months; 1 due to significant co-morbidities and 1 who became pregnant during the study.

Study CP-0514, an open-label study conducted in the USA, designed to assess safety, tolerability, pharmacokinetics and pharmacodynamics of APL-2 administered daily by SC injections as an add-on to standard of care (Soliris®).

Key Eligibility Criteria

- PNH (WBC clone >10%) and persistent anemia
- On treatment with Soliris® (IV) for 3 months prior to screening
- Hb < 10 g/dL at screening OR have received ≥3 units of RBCs by transfusion or ≥1 transfusion within 12 months prior to screening
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- Platelet count >30,000/μL

Conclusions

- All 4 subjects responded rapidly after initiating APL-2 therapy, with a mean Hb of 11.4 g/dL at day 1 and 12.1 g/dL at day 29.

- The decrease in ARC and total bilirubin was durable, as represented by a mean ARC of 99.3 ± 10.5, and mean bilirubin of 0.53 mg/dL on Day 561, respectively.

- The effects observed when APL-2 was co-administered with Soliris® were maintained when subjects were switched and treated with APL-2 monotherapy.

- Treatment with APL-2 prevents extravascular and intravascular hemolysis.

References


Table 1. Key Baseline Characteristics of 4 Ongoing Patients

| Subject | Age (y) | BMI | ECU | SGC | WBC | Hb | Bili | ARC | Months on Soliris® | Months on APL-2
|---------|---------|-----|-----|-----|-----|-----|-----|-----|------------------|------------------|
| Patient 1 | 45 | 25.2 | 1.20 | 0.4 | 9.6 | 129 | 1.8 | 96.3 | 12 | 12
| Patient 2 | 35 | 22.8 | 1.15 | 0.4 | 9.6 | 129 | 1.8 | 96.3 | 12 | 12
| Patient 3 | 47 | 27.8 | 1.15 | 0.4 | 9.6 | 129 | 1.8 | 96.3 | 12 | 12
| Patient 4 | 48 | 25.1 | 1.20 | 0.4 | 9.6 | 129 | 1.8 | 96.3 | 12 | 12

Baseline

- Transfusion independence
- Decreases in serum total bilirubin
- Increases in hemoglobin

Gradual Soliris® Dose Discontinuation

- APL-2 was dosed to label-approved dose of 900 mg bi-weekly between months 6 and 12 of APL-2 therapy.

Soliris® was discontinued between months 14 and 22 of APL-2 therapy and subjects continue to be maintained with APL-2 monotherapy.

The decrease in ARC and total bilirubin was durable, as represented by a mean ARC of 99.3 ± 10.5, and mean bilirubin of 0.53 mg/dL on Day 561, respectively.

Conclusions

- All 4 subjects responded rapidly after initiating APL-2 therapy, with a mean Hb of 11.4 g/dL at day 1 and 12.1 g/dL at day 29.

- The effects observed when APL-2 was co-administered with Soliris® were maintained when subjects were switched and treated with APL-2 monotherapy.

- Treatment with APL-2 prevents extravascular and intravascular hemolysis.

Table 2. Summary of Key Parameters Before and After Treatment with APL-2

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<thead>
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<th>Parameter</th>
<th>Pre-Treatment</th>
<th>Post-Treatment</th>
<th>Change</th>
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<tr>
<td>Hemoglobin (g/dL)</td>
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<td>11.4</td>
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<td>Transfusions, units/year</td>
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<td>10</td>
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<tr>
<td>C3 deposition (ng/mL)</td>
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<tr>
<td>C5 deposition (ng/mL)</td>
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<tr>
<td>Patient days (days)</td>
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Table 3. Safety of APL-2

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<th>Grade 3</th>
<th>Total</th>
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<td>Flu-like symptoms</td>
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<td>0</td>
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</tr>
<tr>
<td>Fatigue</td>
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<td>1</td>
<td>0</td>
<td>3</td>
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Figure 1. Decrease in Serum Total Bilirubin in Response to APL-2

Figure 2. Increase in Hemoglobin (Hb) in Response to APL-2

Figure 3. Decrease in Serum Total Bilirubin in Response to APL-2

Figure 4. C3d Deposition on Pooled Type II (CD59-diminished) and Type III (CD59-negative) Red Blood Cells

Figure 5. C3 and C5 Deposition on Pooled Type II (CD59-diminished) and Type III (CD59-negative) Red Blood Cells

Figure 6. Decrease in Serum Total Bilirubin in Response to APL-2

Figure 7. C3 deposition on Type II (CD59-diminished) and Type III (CD59-negative) Red Blood Cells

Figure 8. Key Neurological Symptoms on Day 561