Apellis Summary

- Pioneers in the development of complement C3 inhibitors

- Wholly-owned, lead product candidate APL-2
  - Potent and selective C3 inhibitor

- Near-term clinical milestones in lead indications
  - Paroxysmal Nocturnal Hemoglobinuria (PNH): Start Phase 3: H1 2018, Monotherapy expansion, Switch-over Soliris → APL-2
  - Age-related Macular Degeneration (AMD) Phase 3: H2 2018
  - Auto-immune Hemolytic Anemia (AIHA) PoC: H1 2018
  - Complement-mediated Nephropathies (e.g. IgAN) PoC: H2 2018

- Broad, global IP protection

- Over 15 years of experience in drug development, complement and immunology
Complement System and APL-2
Roles of Complement

Complement inhibitors on the market

Classical Pathway

Lectin Pathway

Alternative Pathway

Inflammation

C3

Cell death, secretion, lysis, or proliferation

Cell removal, Antigen uptake by APCs

C5

Inflammation

C3a

C3b

C5a

C5b MAC

Amplification loop

Complement inhibitors on the market
APL-2 is a potent and selective C3 inhibitor

- APL-2
  - Long-acting version of APL-1
  - Subcutaneous for PNH
  - Intravitreal for GA

Lead candidate APL-2 targets C3 centrally in the complement cascade

Classical Pathway

Lectin Pathway

Alternative Pathway

Inflammation

Cell death, secretion, lysis, or proliferation

Cell removal, Antigen uptake by APCs

APL-2 targets C3 centrally in the complement cascade.
Evidence of safety of C3 inhibition

- A small population of individuals lack functional levels of C3 and C5*.
- These individuals are susceptible to infection by certain bacterial species.

**C5-deficient individuals**
Neisseria *meningitidis*

**C3-deficient individuals**
Neisseria *meningitidis*,
Streptococcus *pneumoniae*
Haemophilus *influenzae*

**INFECTION RISK MANAGEABLE WITH VACCINATION**

- **No cases of drug-related infections** following experiments involving >400 non-human primates.
  - Multiple compounds (APL-1, APL-2 and others).
  - Acute and chronic exposure.
  - Multiple routes of administration (subcutaneous, intravenous, intravitreal, nebulization).

- **Subcutaneous APL-2** → triple vaccination.
- **Intravitreal APL-2** → no vaccination.

Paroxysmal Nocturnal Hemoglobinuria
Meaningful unmet need in PNH

DISEASE

- ~4,700 patients in the US
- Severe anemia and thrombotic risk
- ~35% 5-year mortality if left untreated (main cause: thrombosis)

STANDARD OF CARE

- Soliris® only approved therapy
  - ~$583,000 / year / adult patient

UNMET NEED

- Soliris® does not fully control hemolysis
  - Majority of patients on Soliris® are anemic
  - 35-40% of patients on Soliris® are transfusion-dependent*

Underlying mechanism of PNH

- Absence or decrease of CD55: regulator of C3 convertase
  - Accumulation of C3b on cells

- Absence or decrease of CD59: regulator of MAC formation
  - Pore formation in cell membrane


**PIG-A gene mutation**
(uncontrolled activation of complement)

+ Clonal dominance
Intravascular vs extravascular hemolysis

**HEALTHY**

- No Complement-mediated hemolysis

**PNH Patients**

- C5/MAC-mediated Intravascular hemolysis
- C3b-mediated Extravascular hemolysis

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Complement-mediated intra- and extravascular hemolysis and inhibition by eculizumab

Classical Pathway

Lectin Pathway

Alternative Pathway

C3b on RBC

C3b on RBC

C5b, MAC

Amplification loop

C5

Eculizumab (C5, Alexion)

EXTRAVASCULAR HEMOLYSIS

INTRAVASCULAR HEMOLYSIS

Inflammation

C3a

C3b

C5a

C5b

Inflammation

INTRAVASCULAR HEMOLYSIS

- PROPRIETARY -
APL-2 blocks both intra- and extravascular hemolysis

Reduced anemia and transfusion dependency

Inflammation

C3

C3b

C3a

C5a

C5b

MAC

C5

Eculizumab (C5, Alexion)

INTRAVASCULAR HEMOLYSIS

EXTRAVASCULAR HEMOLYSIS

APL-2

Classical Pathway

Alternative Pathway

Lectin Pathway
Paroxysmal Nocturnal Hemoglobinuria
APL-2 (subcutaneous)
Two studies to show that APL-2 is safe & efficacious as
add-on to Soliris as well as monotherapy

► Paddock (New Zealand): APL-2 Monotherapy
  ▪ Subjects with PNH have never exposed to Soliris
  ▪ LDH ≥ 2xULN and at least one transfusion in previous year
  ▪ Endpoints: LDH, Hb, Reticulocyte counts
  ▪ High dose cohort n=3
  ▪ Expansion of Paddock planned (n=20)

► PharOah (United States): APL-2 add-on to Soliris
  ▪ Hb < 10 g/dL or at least one transfusion in previous year
  ▪ Endpoints: Hb, Transfusion Dependency, LDH, Reticulocyte counts
  ▪ High dose cohort n=6
  ▪ Soliris weaning planned
Paddock study (APL-2 monotherapy)
APL-2 monotherapy - 270 mg/d – Subject 1 of 3

NOTES

- Subject stopped dosing after week 4 due to personal reasons

APL-2 subq 270 mg / day
NOTES

- APL-2 dose increased to 360 mg/d at Week 24
  - LDH increase (unexpected)
  - Hb increase (expected)

- Subject diagnosed with metastatic ovarian carcinoma at Week 33 and stopped dosing at Week 34 (data available up to week 32)

- Tumor lysis may have contributed to elevated LDH

- GI bleeding due to cancer metastases may have contributed to low Hb
NOTES

- APL-2 subcutaneous pump infusion instead of injection initiated at Week 20
- Iron supplementation in Month 1
Pharoah study (Add-on to eculizumab)
APL-2 add-on to Soliris® improves hemoglobin and reduces LDH levels in PNH patients (n=6)

Soliris IV:
- 900 mg / 2 weeks (n=1)
- 900 mg / 1 week (n=3)
- 1,200 mg / 2 weeks (n=2)

APL-2 subq:
- 270 mg / day
Reticulocyte count (APL-2 270 g/day)
Conclusion

- APL-2 is the first C3 inhibitor tested in patients with PNH.

- APL-2 in mono-therapy or as add-on to standard-of-care.
  - Has been well tolerated at pharmacologically active doses.
  - Might help transfusion-dependent patients become transfusion-independent.
  - Might normalize Hb in patients with PNH.

- Phase 3 clinical trials in preparation.