Welcome to Apellis at the Apella R&D Day 2018
Welcome & Today’s Objectives

Cedric Francois, MD, PhD,
Founder and Chief Executive Officer,
Apellis Pharmaceuticals
Forward Looking Statements

Statements in this presentation about future expectations, plans and prospects, as well as any other statements regarding matters that are not historical facts, may constitute “forward-looking statements” within the meaning of The Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to, statements relating to the implications of preliminary clinical data and planned or future clinical trials and the timing thereof. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “will,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: whether preliminary or interim results from a clinical trial will be predictive of the final results of the trial; whether results obtained in preclinical studies and clinical trials such as the results referenced in this presentation will be indicative of results that will be generated in future clinical trials; whether APL-2 will successfully advance through the clinical trial process on a timely basis, or at all, and receive approval from the United States Food and Drug Administration or equivalent foreign regulatory agencies; whether, if Apellis’ products receive approval, they will be successfully distributed and marketed; and other factors discussed in the “Risk Factors” section of Apellis’ Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on April 30, 2018, and the risks described in other filings that Apellis may make with the Securities and Exchange Commission. Any forward-looking statements contained in this press release speak only as of the date hereof, and Apellis specifically disclaims any obligation to update any forward-looking statement, whether as a result of new information, future events or otherwise.
## 2018 R&D Day Agenda

<table>
<thead>
<tr>
<th><strong>Introduction</strong></th>
<th><strong>Geographic Atrophy (GA)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>2:00 pm - 2:15 pm</td>
<td>Welcome and Today’s Objectives</td>
</tr>
<tr>
<td>2:15 pm - 2:30 pm</td>
<td>GA: Disease Burden, Health Care Resource Use and Progression</td>
</tr>
<tr>
<td>2:30 pm - 2:35 pm</td>
<td>GA: Patient Perspective</td>
</tr>
<tr>
<td>2:35 pm - 2:50 pm</td>
<td>APL-2 in GA: Phase II FILLY Trial 18-Month Results</td>
</tr>
<tr>
<td>2:50 pm - 3:05 pm</td>
<td>APL-2 in GA: Phase III Program</td>
</tr>
<tr>
<td>3:05 pm - 3:25 pm</td>
<td>Geographic Atrophy Q&amp;A</td>
</tr>
<tr>
<td>3:25 pm - 3:35 pm</td>
<td>10 Minute Break</td>
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</tbody>
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<table>
<thead>
<tr>
<th><strong>Paroxysmal Nocturnal Hemoglobinuria (PNH)</strong></th>
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<tbody>
<tr>
<td>3:35 pm - 3:50 pm</td>
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<tr>
<td>3:50 pm - 3:55 pm</td>
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<tr>
<td>3:55 pm - 4:10 pm</td>
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<tr>
<td>4:10 pm - 4:30 pm</td>
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<thead>
<tr>
<th><strong>Early Stage Pipeline</strong></th>
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<tbody>
<tr>
<td>4:30 pm - 4:45 pm</td>
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<tr>
<th><strong>Closing Remarks</strong></th>
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</thead>
<tbody>
<tr>
<td>4:45 pm – 5:00 pm</td>
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</tbody>
</table>

### Cocktail Reception
5:00 pm – 6:00 pm
The Complement System
Complement central to innate immunity

**Innate**
“Shock and Awe”

**Adaptive**
“Self vs Non-Self”
Rise of Adaptive Immunity

VERTEBRATA

RAG genes

50 families
Cell death, secretion, lysis, or proliferation

Inflammation

Cell removal

C3

C3a

C3b

C5

C5a

C5b

MAC

Approved Complement Inhibitors

Activation Pathways

Classical Pathway

Lectin Pathway

Alternative Pathway

Cinryze

Benainat

Ruconest

Soliris®

C3a

C3b

C5a

C5b

Inflammation

Cell death, secretion, lysis, or proliferation
Complement Immunotherapy
Key Milestones for 2018

**GA:**
Phase 2: 18 month safety & efficacy data

**PNH:**
Phase 1b: monotherapy expansion (interim)
Phase 1b: Soliris weaning in add-on study

**AIHA:**
Phase 2: POC monotherapy data

**CDN:**
Phase 2: POC monotherapy data

**PNH:**
Start of Phase 3 program

**GA:**
Start of Phase 3 program
Apellis 2018 R&D Day

GEOGRAPHIC ATROPHY (GA)
Geographic Atrophy: Disease Burden, Health Care Resource Use and Progression

Usha Chakravarthy, MD, PhD,
Professor of Ophthalmology and Consultant Ophthalmic Surgeon, Queen’s University of Belfast
GA is a cause of similar levels of visual morbidity as CNV

- Real-world data confirm that GA is a progressive disease and is associated with high levels of visual impairment, with impacts on mobility and independence.
- Proportion of eyes progressing to blindness is greater than that recorded in previous clinical studies.
- GA and CNV are manifestations of the same disorder with specific temporal relationships.
Early and late age-related macular degeneration
Introduction

- Geographic atrophy (GA) is an advanced manifestation of age-related macular degeneration (AMD) characterised by progressive and irreversible loss of the retinal pigment epithelium (RPE), photoreceptors and underlying choriocapillaris\textsuperscript{1,2}

- Patients experience visual function abnormalities, such as difficulty with reading and seeing in low-light conditions

- Major cause of legal blindness: \textasciitilde26\% in UK, \textasciitilde20\% in North America

- No approved treatment available\textsuperscript{2}

Prevalence and Incidence of GA

- GA affects >5 million people worldwide\textsuperscript{10}
- Variable prevalence reported in the different studies\textsuperscript{10,11}
  - Particularly when photographic grading has not been used
- GA prevalence
  - Quadruples per decade increase in age ≥50 years\textsuperscript{11}
- A meta-analysis estimated annual incidence of GA at 1.6 cases per 1000, equivalent to 160,000 new cases per year\textsuperscript{18}

---

**Background**

- GA affects >5 million people worldwide\textsuperscript{10}
- Variable prevalence reported in the different studies\textsuperscript{10,11}
  - Particularly when photographic grading has not been used
- GA prevalence
  - Quadruples per decade increase in age ≥50 years\textsuperscript{11}
- A meta-analysis estimated annual incidence of GA at 1.6 cases per 1000, equivalent to 160,000 new cases per year\textsuperscript{18}


AMD, age-related macular degeneration; GA, geographic atrophy; nAMD, neovascular age-related macular degeneration.
Rapid progression over 18M to multifocal GA
GA is responsible for sight loss in patients with wet AMD despite treatment with anti VEGF

98% of wet AMD patients developed GA, despite the treatment with anti-VEGF therapy when followed for 7 years as showed by the Seven-UP study

Rationale for UK EMR study

- Recent evidence suggesting that GA is the default pathway in AMD
- Increasing awareness that early forms of GA may be more common than previously recognised
- The extent of visual impact of GA may have been underestimated
  - The frequency of severe visual impairment/blindness arising from GA
  - The severity of visual impairment and consequent handicap due to GA
# The UK EMR AMD Study

## Study Design
- Retrospective analysis of a clinical dataset
- Study plan and aims defined prior to data cut
- EMR contains prospectively defined data fields (similar to electronic case report forms used in clinical trials rather than a retrospective chart review)

## Data Source
- Medisoft EMR

## Site Selection
- 10 NHS retina clinics contributed to the study

## Period Covered
- Data cut made in Feb 2016 (period covered Oct 2000–Feb 2016)
- Periods of EMR usage varied by centre as not all centres implemented EMR at the same time

AMD, age-related macular degeneration; EMR, electronic medical record; NHS, National Health Service. UK EMR GA study Chakravarthy et al Ophthalmology
Study Population – GA Cohorts

Anonymised data from 83,425 patients (diagnosis of any AMD) 10 UK retinal centres between 2000 and 2016

Cases with at least 1 eye with a clinical record of GA recorded at any visit N = 11,240 (13.5%)

Main Exclusions:
- Age at index <50 years
- CNV in both eyes at index date
- Study eye with <30 days’ follow-up
- No information for the fellow eye in the EMR system, or fellow eye is not classifiable
- Missing VA data ±90 days of index date

Disease definition

Eligible GA cohort - 4769 (5.7%)

GA:GA
1901 (39.9%)
Both study and fellow eye with GA

GA:CNV
1696 (35.6%)
Study eye with GA; fellow eye with CNV

GA:Early AMD
1172 (24.6%)
Study eye with GA; fellow eye with Early/Intermediate AMD

AMD, age-related macular degeneration; CNV, choroidal neovascularisation; EMR, electronic medical record; GA, geographic atrophy; VA, visual acuity.
Outcome Measures: Bilateral GA Cohort

**GA:GA Cohort**

<table>
<thead>
<tr>
<th>Populations Analysed</th>
<th>GA:GA ALL 1901</th>
<th>Did not meet definition of UK blindness at baseline* 1693</th>
<th>Eligible to drive at baseline† (UK standard) 523</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Progression to CNV</td>
<td></td>
<td>• Progression to blindness • Loss of ≥10 letters of VA • Loss of ≥15 letters of VA</td>
<td>• Progression to loss of eligibility to drive</td>
</tr>
</tbody>
</table>

* Blindness definition (UK): VA measurement of <20 ETDRS letters or Snellen 3/60 in the better-seeing eye.† Driving eligibility standard (UK): VA measurement in better-seeing eye of >70 letters or Snellen 6/12. CNV, choroidal neovascularisation; ETDRS, Early Treatment Diabetic Retinopathy Study; GA, geographic atrophy; VA, visual acuity.
Progression to CNV and VA Loss: Bilateral GA Cohort

<table>
<thead>
<tr>
<th>Study sample eligible for analyses (N)</th>
<th>1901</th>
<th>1693</th>
<th>1693</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) time to outcome (years)</td>
<td>1.1 (0.3–2.0)</td>
<td>3.3 (1.5–6.2)</td>
<td>2.4 (1.1–5.0)</td>
</tr>
</tbody>
</table>

CNV, choroidal neovascularisation; GA, geographic atrophy; IQR, interquartile range; VA, visual acuity.
Change in Mean VA from Baseline in Better-Seeing and Worse-Seeing Eyes Over Time: Bilateral GA Cohort

For each time point, patients had to have VA measurement at index and at the specific time point of 12, 24 or 60 months post index. For the better-seeing eye, the sample comprised 726, 414 and 80 patients for the 12, 24 and 60 time points, respectively. For the worse-seeing eye, the sample comprised 724, 413 and 80 patients for the 12, 24 and 60 time points, respectively.

ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity.

<table>
<thead>
<tr>
<th>Eye</th>
<th>Mean letter difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 Months</td>
</tr>
<tr>
<td>Better-seeing eye</td>
<td></td>
</tr>
<tr>
<td>-5.7</td>
<td>(4.6-6.9)</td>
</tr>
<tr>
<td>Worse-seeing eye</td>
<td></td>
</tr>
<tr>
<td>-2.0</td>
<td>(0.7-3.3)</td>
</tr>
</tbody>
</table>

For each time point, patients had to have VA measurement at index and at the specific time point of 12, 24 or 60 months post index. For the better-seeing eye, the sample comprised 726, 414 and 80 patients for the 12, 24 and 60 time points, respectively. For the worse-seeing eye, the sample comprised 724, 413 and 80 patients for the 12, 24 and 60 time points, respectively. ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity.
Progression of Vision To Blindness and VA Worse Than 20/40 in Better Eye: Bilateral GA Cohort*

One fifth of patients became eligible for blind registration

Two thirds of patients progressed to vision loss that rendered them ineligible to drive within 2 years

Study sample eligible for analyses (N) | 1693 | 523
---|---|---
Median (IQR) time to outcome (years) | 6.2 (3.3–8.5) | 1.6 (0.7–2.7)

* Results shown previously in All GA Cohorts section; included here for completeness. GA, geographic atrophy; IQR, interquartile range; VA, visual acuity.
Progression of GA
Distance VA may not change until GA covers fovea

<table>
<thead>
<tr>
<th>Baseline 20/63</th>
<th>2.3 years 20/63</th>
<th>4.0 years 20/63</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Baseline Image" /></td>
<td><img src="image2" alt="2.3 years Image" /></td>
<td><img src="image3" alt="4.0 years Image" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline 20/63</th>
<th>2.2 years 20/63</th>
<th>4.3 years 20/200</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image4" alt="Baseline Image" /></td>
<td><img src="image5" alt="2.2 years Image" /></td>
<td><img src="image6" alt="4.3 years Image" /></td>
</tr>
</tbody>
</table>

Courtesy of Frank Holz
Good distance VA does not mean that reading ability is maintained
### Self-reported visual function in patients with GA: change over time

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Year 1</th>
<th>Baseline</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reading</strong>*</td>
<td>71%</td>
<td>85%</td>
<td>74%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Hazy</strong></td>
<td>41%</td>
<td>43%</td>
<td>50%</td>
<td>45%</td>
</tr>
<tr>
<td><strong>Faces</strong>*</td>
<td>65%</td>
<td>78%</td>
<td>58%</td>
<td>84%</td>
</tr>
<tr>
<td><strong>Finding sign</strong></td>
<td>57%</td>
<td>71%</td>
<td>74%</td>
<td>86%</td>
</tr>
<tr>
<td><strong>Dim environment</strong></td>
<td>85%</td>
<td>91%</td>
<td>81%</td>
<td>95%</td>
</tr>
</tbody>
</table>

*Significant difference at p=0.05 level for both Year 1 and Year 2 comparisons

Sunness et al. IOVS e-abstract 2011;52:91
Key Takeaways

**GA is a cause of similar levels of visual morbidity as CNV**

- Real-world data confirm that GA is a progressive disease and is associated with high levels of visual impairment, with impacts on mobility and independence
- Proportion of eyes progressing to blindness is greater than that recorded in previous clinical studies
- GA and CNV are manifestations of the same disorder with specific temporal relationships
Geographic Atrophy: Patient Perspective

ROBERT SCHONFELD
APL-2 in GA: Phase II FILLY Trial
18-Month Results

Jeff Heier, MD
Co-President and Medical Director,
Ophthalmic Consultants of Boston
Key Takeaways

• APL-2 reduced the progression of GA secondary to AMD in the largest Phase 2 GA trial (n=246)

• Results correlated to treatment frequency with increasing effect size over time

• Further confidence in results from intra-patient control

• Upon discontinuation of APL-2, treatment effect declines
The Complement Pathway and Geographic Atrophy

![Diagram showing the complement pathways and their effects on inflammation and cellular processes.]

- **Lectin Pathway**
- **Classical Pathway**
- **Alternative Pathway**

**APL-2** influences the complement pathway, affecting:
- **C3**
- **C3a**
- **C3b**
- **C5**
- **C5a**
- **C5b**
- **MAC**

**Inflammation**
- Reduced

**Cell removal, Antigen uptake by APCs**
- Reduced

**Cell death, secretion, lysis, or proliferation**
- Reduced
FILLY - Phase 2 study of APL-2 in Geographic Atrophy

Sham Injections  
\( n = 81 \)

APL-2 injections every other month  
\( n = 79 \)

APL-2 injections every month  
\( n = 86 \)

- Sham Injections  
  APL-2 0 mg

- APL-2 injections every other month
  APL-2 0 mg
  APL-2 15 mg

- APL-2 injections every month
  APL-2 15 mg
Primary efficacy endpoint is the primary registration endpoint
Change in geographic atrophy (GA) lesion size from baseline to month 12.

Primary safety endpoint
Number and severity of local and systemic treatment emergent adverse events (TEAEs).
### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sham injections N=81</th>
<th>APL-2 every other month N=79</th>
<th>APL-2 monthly N=86</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bilateral GA, n (%)</strong></td>
<td>72 (90.0%)</td>
<td>64 (82.1%)</td>
<td>71 (85.5%)</td>
</tr>
<tr>
<td><strong>History of CNV in Fellow Eye, n (%)</strong></td>
<td>29 (35.8%)</td>
<td>28 (35.4%)</td>
<td>36 (41.9%)</td>
</tr>
<tr>
<td><strong>GA lesion size, mean, mm$^2$ (SD)</strong></td>
<td>8.2 (4.1)</td>
<td>8.9 (4.5)</td>
<td>8.0 (3.8)</td>
</tr>
<tr>
<td><strong>BCVA score, mean letters (SD)</strong></td>
<td>59.8 (17.2)</td>
<td>58.4 (16.0)</td>
<td>59.8 (15.7)</td>
</tr>
<tr>
<td><strong>BCVA score (Snellen equivalent)</strong></td>
<td>20/63</td>
<td>20/80</td>
<td>20/63</td>
</tr>
<tr>
<td><strong>LL-BCVA score, mean letters (SD)</strong></td>
<td>33.6 (17.8)</td>
<td>31.4 (17.1)</td>
<td>36.3 (16.6)</td>
</tr>
</tbody>
</table>

Groups were well balanced as to age, gender and race
APL-2 slows GA growth at 12 months (square root)

Modified Intent to Treat population (mITT), Observed, Mixed Effect Model

APL-2 every other month

APL-2 monthly

sham injections

Change from baseline in square root GA lesion growth (mm)

- 2 months: 0.25
- 6 months: 0.28
- 12 months: 0.35

20% lesion growth difference, p=0.067 vs Sham

29% lesion growth difference, p=0.008 vs Sham
Lesion growth by six-month periods (square root) – 12 months

**Sham injections**

- 0-6 months
- 6-12 months

**APL-2 injections every other month**

- 0-6 months
- 6-12 months

**APL-2 injections every month**

- 0-6 months
- 6-12 months

33% lesion growth difference vs sham p=0.01

47% lesion growth difference vs sham p < 0.001

Data from subjects with a measurable GA lesion size at both Months 6 & 12
FILLY sham group behaved consistently with recent publication

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sham</th>
<th>Lampalizumab, 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled (n=58)</td>
<td>q4w (n=596)</td>
<td>q6w (n603)</td>
</tr>
<tr>
<td>Change from baseline in square root GA area at 48 wk, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted mean (SE)</td>
<td>0.342 (0.007)</td>
<td>0.349 (0.007)</td>
</tr>
<tr>
<td>Difference in means (vs sham pooled)</td>
<td>0.006</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Holz, F.G., et al., Efficacy and Safety of Lampalizumab for Geographic Atrophy Due to Age-Related Macular Degeneration: Chroma and Spectri Phase 3 Randomized Clinical Trials. JAMA Ophthalmol, 2018
After cessation of treatment at 12 months, GA growth resumes but treatment effect is maintained through 18 months (square root).

<table>
<thead>
<tr>
<th>Time</th>
<th>Sham</th>
<th>APL-2 every other month</th>
<th>APL-2 monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>6 months</td>
<td>0.3</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>12 months</td>
<td>0.4</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>18 months</td>
<td>0.5</td>
<td>0.6</td>
<td>0.5</td>
</tr>
</tbody>
</table>

16% lesion growth difference, p=0.097 vs Sham
20% lesion growth difference, p=0.044 vs Sham

Modified Intent to Treat population (mITT), Observed, Mixed-Effect Model
Lesion growth by six-month periods (square root) – 18 months

Sham injections

APL-2 injections every other month

APL-2 injections every month

Data from subjects with a measurable GA lesion size at Months 6 & 12 & 18

9% lesion growth difference vs sham p >0.5

12% lesion growth difference vs sham p = 0.47
GA growth comparison: fellow eye vs study eye post hoc analysis

Sham Injections
n= 72

APL-2 injections every other month
n= 63

10% Difference
p > 0.1

APL-2 injections every month
n= 69

23% Difference
p = 0.083

Includes patients from the Bilateral GA Population
## New onset exudation – 18 months

<table>
<thead>
<tr>
<th></th>
<th>APL-2 Monthly</th>
<th>APL-2 EOM</th>
<th>Sham Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>n = 86</td>
<td>n = 79</td>
<td>n = 81</td>
</tr>
<tr>
<td>Subjects with wAMD in Study eye (%)</td>
<td>18 (20.9%)</td>
<td>7 (8.9%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>With History of CNV in Fellow Eye</td>
<td>n = 36</td>
<td>n = 28</td>
<td>n = 29</td>
</tr>
<tr>
<td>Subjects with wAMD in Study eye (%)</td>
<td>13 (36.1%)</td>
<td>5 (17.9%)</td>
<td>0</td>
</tr>
<tr>
<td>No CNV History in Fellow Eye</td>
<td>n = 50</td>
<td>n = 51</td>
<td>n = 52</td>
</tr>
<tr>
<td>Subjects with wAMD in Study eye (%)</td>
<td>5 (10.0%)</td>
<td>2 (3.9%)</td>
<td>1 (1.9%)</td>
</tr>
</tbody>
</table>
New onset exudation

• Subjects that developed exudation had minor loss of vision and were treated with anti-VEGF
• 6 patients developed wet AMD in the 12-18 month non-treatment period (5/6 had fellow eye wet AMD)

Subject 2 (monthly): Exudative AMD (Month 11)

Illustrative OCT scan of an exudative AMD with intraretinal fluid and RPE detachment
Key Takeaways

• APL-2 reduced the progression of GA secondary to AMD in the largest Phase 2 GA trial (n=246)

• Results correlated to treatment frequency with increasing effect size over time

• Further confidence in results from intra-patient control

• Upon discontinuation of APL-2, treatment effect declines
Apellis

APL-2 in GA: Phase III Program

Jason S. Slakter, MD
Clinical Professor of Ophthalmology, NYU School of Medicine
Director Digital Angiography Reading Center
Key Takeaways

- Apellis on track to start 2 Global Phase 3 studies H2 2018
- Same study population as FILLY Phase 2 trial
- Primary endpoint is the change in the total area of GA lesions measured by FAF at Month 12
- Addition of secondary endpoints to evaluate changes in visual function
# Phase 3 Study Overview

## 2 Global Studies

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with Geographic Atrophy secondary to AMD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st Endpoint</strong></td>
<td>Change in total area of GA lesion(s) based on FAF at Month 12</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Double Masked, Randomized 2:1:2:1</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>15 mg/0.1 mL Intravitreal Injection vs. Sham Injection</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>600 Subjects from approx. 100 multinational sites per study</td>
</tr>
</tbody>
</table>

Each study will have the following design:

- **Screening** - R:2:1:2:1
- **2 years**
  - APL-2 Monthly N = 200
  - APL-2 EOM N = 200
  - Sham Monthly N = 100
  - Sham EOM N = 100
No changes in Inclusion/Exclusion criteria from Filly Phase 2

• Key inclusion criteria - Study eye:
  – BCVA > 24 letters by ETDRS (20/320 Snellen equivalent)
  – The GA lesion must:
    a. Total GA: $\geq 2.5$ and $\leq 17.5$ mm$^2$
    b. If GA is multifocal, at least one focal lesion must be $\geq 1.25$ mm$^2$ (0.5 DA)
    c. Presence of any pattern of hyperautofluorescence in the junctional zone of GA. Absence of hyperautofluorescence (i.e. pattern = none) is exclusionary

• Neovascular AMD in fellow eye is **not exclusionary**
Key Endpoints

• Primary:
  – Change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm²) based on Fundus Autofluorescence (FAF)

• Secondary:
  – Best-corrected visual acuity (BCVA), low luminance BCVA, low luminance deficit in the study eye
  – Reading speed (study eye), as assessed by Minnesota Reading or Radner Reading (MNRead) Charts (in select sites)
  – Microperimetry
  – National Eye Institute Visual Functioning Questionnaire 25-Item Version (NEI VFQ-25) distance activity subscale score
  – Functional Reading Independence Index (FRI) composite score in the study eye
Key Phase 3 Improvements

• Double masked
• Increase frequency of imaging timepoints
• Inclusion of two vision function assessments:
  – Reading speed
  – Microperimetry
• Inclusion of two patient reported outcomes:
  – National Eye Institute Visual Functional Questionnaire (NEI VFQ-25)
  – Functional Reading Independent (FRI) Index
• Subjects that develop exudative AMD will continue to receive APL-2 in combination with anti-VEGF
Patients with GA may have good best-corrected visual acuity owing to central fovea preservation, but very poor function because of scotoma surround the fovea.

**Reading speed:**
- GA patients reported reading as the most important visual function activity perceives to decline over time.
- Objective measurement of a patient’s ability to read continuous text.

**Microperimetry:**
- Objective measurement of retinal sensitivity to different light stimulus.
Patient-Reported Outcome

- **NEI-VFQ 25**
  - Questionnaire designed to assess the influence of visual impairment on vision-related daily activities

- **Functional Reading Independence (FRI) Index**
  - Evaluates the level of independence patients have in performing activities that require reading, such as writing a check or reading a prescription

### VFQ-25 in Patients with AMD

<table>
<thead>
<tr>
<th>NEI VFQ-25 Subscale</th>
<th>AMD Group [Mean (SD)]</th>
<th>P</th>
<th>Reference Group [Mean (SD)]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Vision</td>
<td>53.0 (20.0)</td>
<td>&lt;0.001</td>
<td>83.0 (15.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difficulty with distance tasks</td>
<td>56.0 (29.0)</td>
<td>&lt;0.001</td>
<td>93.0 (11.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difficulty with near tasks</td>
<td>54.0 (27.0)</td>
<td>&lt;0.001</td>
<td>92.0 (13.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vision</td>
<td>77.0 (27.0)</td>
<td>0.011</td>
<td>97.0 (10.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Color Vision</td>
<td>85.0 (25.0)</td>
<td>&lt;0.001</td>
<td>98.0 (8.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


Management of New Onset Exudation

- In case of suspected new onset exudation, multiple imaging modalities will be used to confirm diagnosis.
- Patients will continue to receive treatment with APL-2 in addition to anti-VEGF therapy.
Key Takeaways

• Apellis on track to start 2 Global Phase 3 studies H2 2018

• Same study population as FILLY Phase 2 trial

• Primary endpoint is the change in the total area of GA lesions measured by FAF at Month 12

• Addition of secondary endpoints to evaluate changes in visual function
Geographic Atrophy

Q & A
Apellis

10 MINUTE BREAK
APL-2 IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)
APL-2 in PNH: Unmet Need & PADDOCK Trial Update

Peter Hillmen, MD, PhD,
Professor of Experimental Haematology,
University of Leeds
APL-2 in PNH: Unmet Need - Key Takeaways

- Eculizumab prevents intravascular hemolysis in PNH
- All patients receiving eculizumab have C3-loading on their PNH rbc leading to extravascular hemolysis
- Hemoglobin is universally reduced in PNH patients receiving eculizumab compared to a normal population
- 36% patients on eculizumab continue to require transfusions but many more have mild to moderate symptoms
PNH – Triad of Clinical Features

**Hemoglobinuria**
- Intravascular hemolysis
  - disabling symptoms
  - abdominal pain
  - dysphagia
  - erectile failure
  - severe lethargy

**Budd-Chiari syndrome**
- Thrombosis
  - liver, cerebral
  - 50% of patients
  - 33% of patients is fatal

**Aplastic anaemia**
- Bone Marrow Failure
  - often precedes PNH
  - selects for PNH clone
Central inhibition of complement

Lectin Pathway

Classical Pathway

Alternative Pathway

APL-2

C3

C3a → Inflammation

C3b

C5

C5a → Inflammation

C5b MAC

Cell removal, Antigen uptake by APCs

Cell death, secretion, lysis, or proliferation
Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare, life-threatening blood disease

PNH characterized by uncontrolled hemolysis

- Intravascular hemolysis: Red blood cell rupture in the circulation
- Extravascular hemolysis: Red blood cell destruction by macrophages in spleen and liver

- ~4,700 patients in US.
- 35% 5-year mortality if untreated (thrombosis, severe anemia).
- Alexion’s Soliris® (eculizumab) is only approved therapy.
- Treats only intravascular hemolysis.
- Approximate cost $500,000 annually.
~70% of eculizumab-treated patients remain anemic due to extravascular hemolysis

Hemoglobin (g/dL) in 141 random PNH Patients on Soliris®

- Severely Anemic: 26%
- Normal Hb: 29%
- Anemic: 45%
- < 10 g/dL
- 10 g/dL
- 12 g/dL
- > 12 g/dL

Source: Data measured from 141 PNH patients courtesy of Dr. Pete Hillmen and Dr. Anita Hill in Apellis sponsored research collaboration.
141 patients were identified for inclusion by the above criteria; 70 males and 71 females.

Median hemoglobin level for all patients = 109g/l.

72% had a mean hemoglobin below 120g/l despite treatment with eculizumab.

All patients had C3 on their red cells → some degree of extravascular hemolysis is always seen.

During the latest 12 months:
- 51 (36%) patients had at least one transfusion,
- 23 (16%) requiring 3 or more transfusions.
Transfusions in patients with PNH receiving eculizumab (n=141; all hemolytic)
Hemoglobin levels in patients with PNH receiving eculizumab (n=141; all hemolytic)

Normal individuals
Hemoglobin levels in patients with PNH receiving eculizumab (n=141; all hemolytic)

Normal individuals

PNH patients on eculizumab

>4 g/dL
Increased absolute reticulocyte counts in almost all patients with PNH receiving eculizumab (n=141; all hemolytic)
Increased absolute reticulocyte counts in almost all patients with PNH receiving eculizumab (n=141; all hemolytic)
LDH levels are slightly raised in patients with PNH receiving eculizumab (n=141; all hemolytic)
C3 red cell loading in PNH

PNH patient not on eculizumab

PNH patient on eculizumab
%C3-loaded PNH red cells in patients with PNH receiving eculizumab (n=141; all hemolytic)
APL-2 in PNH: Unmet Need - Key Takeaways

• Eculizumab prevents intravascular hemolysis in PNH

• All patients receiving eculizumab have C3-loading on their PNH rbc leading to extravascular hemolysis

• Hemoglobin is universally reduced in PNH patients receiving eculizumab compared to a normal population

• 36% patients on eculizumab continue to require transfusions but many more have mild to moderate symptoms
APL-2 In PNH: Paddock Update

Peter Hillmen, MD, PhD,
Professor of Experimental Haematology,
University of Leeds
APL-2 in PNH: PADDOCK - Key Takeaways

• Hemoglobin increases are clinically meaningful and different compared to C5 inhibitors

• “Normalization” of hemoglobin, reticulocyte count and bilirubin rarely seen with C5 inhibition

• APL-2 is well tolerated – two lead-in transfusions (not on pharmacology). Safety profile of APL-2 to date is very good

• Potential for meaningful superiority vs. C5 inhibitors
**PADDOCK Study Design: APL-2 monotherapy in eculizumab-naïve PNH**

### Key eligibility criteria:

- Diagnosis of PNH (WBC clone > 10%)
- LDH > 2X ULN
- Last transfusion within 12 months prior to screening
- Platelet count of > 30,000/mm³ and Absolute neutrophil count > 500 x10⁹/L

### Study design – Open label MAD

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Screen</th>
<th>Treat 28 days</th>
<th>Observe</th>
<th>Continue treatment for 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>180 mg sc APL-2</td>
<td>N=2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>270 mg sc APL-2</td>
<td>N=20</td>
<td></td>
<td></td>
<td>N=20</td>
</tr>
</tbody>
</table>

* Cohort 2 expanded to include up to 20 subjects
PADDOCK (interim): APL-2 shows potential to reach normal LDH levels as monotherapy in eculizumab naïve PNH patients – 270 mg/day

LDH (mean±SE)

Weeks

Week | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16
---|---|---|---|---|---|---|---|---|---
n | n=13 | n=13 | n=10 | n=8 | n=5 | n=5 | Not | n=4
Multiple of ULN | 9.54x | 1.76x | 0.80x | 0.66x | 0.79x | 0.95x | 0.94x | 

Excludes results from one of the original three patients, who had underlying metastatic ovarian cancer with a chronic low gastrointestinal bleed, unknown at the time of screening.

ALXN-1210 data taken from Alexion’s presentation of topline results of a Phase 3 clinical trial on March 15, 2018. Apellis has not conducted a head-to-head comparison of APL-2 and ALNX-1210. There may be differences between trial designs and subject characteristics of the Paddock APL-2 trial and the Phase 3 trial of ALXN-1210.
PADDOCK (interim): Preliminary results with APL-2 are encouraging in comparison to ALXN-1210 (data not from a head to head study)

Excludes results from one of the original three patients, who had underlying metastatic ovarian cancer with a chronic low gastrointestinal bleed, unknown at the time of screening.
At last measure; excludes one patient who had underlying metastatic ovarian cancer with a chronic low gastrointestinal bleed, unknown at the time of screening, which resulted in artificially low Hb and high LDH levels that were determined to be unrelated to PNH.

2/13 patients had transfusions, one at day 2 and a non-compliant patient at day 14; it is believed that neither patient had yet reached sufficient exposure to APL-2 for hematological benefit.
PADDOCK (interim): other measures of anemia meaningfully improved with APL-2 including reticulocytes and bilirubin

### Reticulocytes (mean±SE)

- **Weeks:** 0, 2, 4, 6, 8, 10, 12, 14, 16
- **n:**
  - 0: n=13
  - 2: n=13
  - 4: n=11
  - 6: n=8
  - 8: n=5
  - 10: n=5
  - 12: n=4
- **Normal range:** 10^9/L
- **Values:**
  - Week 0: 196
  - Week 2: 117
  - Week 4: 93
  - Week 6: 79
  - Week 8: 102
  - Week 10: 90
  - Week 12: 96
  - Week 14: 92

### Total Bilirubin (mean±SE)

- **Weeks:** 0, 2, 4, 6, 8, 10, 12, 14, 16
- **n:**
  - 0: n=13
  - 2: n=13
  - 4: n=11
  - 6: n=8
  - 8: n=5
  - 10: n=5
  - 12: n=4
  - 14: n=4
- **Normal range:** umol/L
- **Values:**
  - Week 0: 35
  - Week 2: 11
  - Week 4: 10
  - Week 6: 10
  - Week 8: 12
  - Week 10: 12
  - Week 12: 14
  - Week 14: Not Taken
  - Week 16: 13
APL-2 in PNH: PADDOCK - Key Takeaways

• Hemoglobin increases are clinically meaningful and different compared to C5 inhibitors

• “Normalization” of hemoglobin, reticulocyte count and bilirubin rarely seen with C5 inhibition

• APL-2 is well tolerated – two lead-in transfusions (not on pharmacology). Safety profile of APL-2 to date is very good

• Potential for meaningful superiority vs. C5 inhibitors
Paroxysmal Nocturnal Hemoglobinuria (PNH): Patient Perspective

BARRY KATSOOF

President, Canadian Association of PNH Patients
APL-2 in PNH: PHAROAH Trial Update

Anita Hill, MBChB (Hons), MRCP, FRCPA, PhD
Consultant Haematologist and Lead Clinician
for the National PNH Service, UK
APL-2 in PNH: PHAROAH - Key Takeaways

4 Patients Ongoing

- Hemoglobin stable & transfusion independent

Soliris Dose Reduction

- Successful dose reduction to approved 900mg/EOW in all high dose patients (100%)
- All hematologically unchanged (Hb, LDH stable)
- No transfusions required post-Soliris dose reduction

Soliris withdrawal -> APL-2 Monotherapy

- APL-2 increase from 270mg -> 360 mg/day
- 3/4 successfully withdrawn from Soliris (1×270 mg, 2×360 mg)
- 1 patient TBD:
  - Two unsuccessful attempts (1×270mg, 1×360mg)
  - Patient morbidly obese (BMI 46)
  - IRB approval for dose increase to 440mg
**PHAROAH**

**Key eligibility criteria:**

- Diagnosis of PNH (WBC clone > 10%)
- On treatment with eculizumab for at least 3 months
- Hb < 10 g/dL at screening OR have received at least one transfusion with 12 months prior to screening
- Platelet count of > 30,000/mm³ and ANC > 500 x 10⁹/L

**Study design – Open label MAD**

<table>
<thead>
<tr>
<th>180 mg APL-2</th>
<th>Screen</th>
<th>Treat 28 days</th>
<th>Observe</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>270 mg APL-2</th>
<th>Screen</th>
<th>Treat 28 days</th>
<th>Continue treatment for 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=6</td>
<td></td>
<td></td>
<td>N=6 entered (4 ongoing)</td>
</tr>
</tbody>
</table>
### PHAROAH - Baseline characteristics

6 Subjects enrolled by October 2016
- 35 combined transfusions in the 12 months before APL-2
- 5 out of 6 receiving higher than approved Soliris dose

<table>
<thead>
<tr>
<th></th>
<th>M/F</th>
<th>Age</th>
<th>BMI</th>
<th>Soliris dose</th>
<th>PRBC Transfusions in last 52 weeks</th>
<th>Hb NR (12-15)</th>
<th>LDH NR (110-209)</th>
<th>Bilirubin NR (0.2-1.2)</th>
<th>Reticulocytes NR 39-123</th>
<th>Months on Study</th>
<th>Ongoing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>F</td>
<td>50</td>
<td>35.2</td>
<td>1200 mg</td>
<td>x2w</td>
<td>8.4</td>
<td>1.8</td>
<td>199</td>
<td>362</td>
<td>22</td>
<td>Y</td>
</tr>
<tr>
<td>Patient 2</td>
<td>F</td>
<td>52</td>
<td>22.8</td>
<td>900 mg</td>
<td>x2w</td>
<td>9.6</td>
<td>1.9</td>
<td>225</td>
<td>296</td>
<td>21</td>
<td>Y</td>
</tr>
<tr>
<td>Patient 3</td>
<td>F</td>
<td>35</td>
<td>59.2</td>
<td>1200 mg</td>
<td>x2w</td>
<td>7.4</td>
<td>1.8</td>
<td>535</td>
<td>160</td>
<td>7</td>
<td>N</td>
</tr>
<tr>
<td>Patient 4</td>
<td>F</td>
<td>57</td>
<td>27.8</td>
<td>900 mg</td>
<td>x1w</td>
<td>10.5</td>
<td>2.0</td>
<td>211</td>
<td>272</td>
<td>20</td>
<td>Y</td>
</tr>
<tr>
<td>Patient 5*</td>
<td>F</td>
<td>38</td>
<td>25.6</td>
<td>1200 mg</td>
<td>x2w</td>
<td>9.8</td>
<td>1.3</td>
<td>307</td>
<td>515</td>
<td>8</td>
<td>N</td>
</tr>
<tr>
<td>Patient 6</td>
<td>F</td>
<td>48</td>
<td>45.9</td>
<td>900 mg</td>
<td>x1w</td>
<td>7.0</td>
<td>2.7</td>
<td>204</td>
<td>398</td>
<td>20</td>
<td>Y</td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>8.8</strong></td>
<td><strong>280 x1.3 ULN</strong></td>
<td><strong>1.9 X1.6 ULN</strong></td>
<td><strong>334 (x3 ULN)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Investigator and patient decision to stepwise change to standard of care based on effect observed:
- Reduce Soliris to approved dose of 900 mg bi-weekly
- Soliris withdrawal and continue with APL-2 monotherapy

* Number given is true baseline in year before entering study for the 1st time
PHAROAH (interim): APL-2 shows potential to improve eculizumab outcomes as add-on therapy in PNH – 270 mg/day, (n=6)

Interim data as reported June 2017

Mean Hemoglobin

- Normal range: 14 - 17 g/dL
- Dosing timeline:
  - Months 0 - 1: Treatment started
  - Months 2 - 4: Eculizumab
  - Months 5 - 7: Off APL-2 for 3 Weeks

Mean LDH

- Normal range: 0.4 - 1.0 ULN
- BMI 59 Under-dosed?

- Patient transfusions:
  - Patient 1
  - Patient 2
  - Patient 3
  - Patient 4
  - Patient 5
  - Patient 6

Apellis

89
2 Patients discontinued from the study:

**Patient 3**: Discontinued at month 7
- Morbidly obese (BMI 59)
- History of MS and renal/urinary co-morbidities
- Required x2 transfusions whilst on APL-2
- APL-2 dose increase to 360 mg appeared to improve response but subject had to withdraw after 28 days

**Patient 5**: Discontinued at month 8
- Subject participated in 3 dose-escalation cohorts at her request
- APL-2 was temporarily discontinued to allow investigation of a biliary obstruction
- Required transfusion while off APL-2 for 3 weeks
- Withdrawn from study due to pregnancy at month 8

Both Patients and their Physicians have requested that patients resume APL-2

4 Patients ongoing and continue to receive daily doses of APL-2
PHAROAH: APL-2 add-on to Soliris® four patients -1 yr.
PHAROAH other measures of anemia meaningfully improved with APL-2 including reticulocytes and bilirubin (n=4)

**Mean Reticulocytes**

-2 0 2 4 6 8 10 12 14 16 18 20 22

**Mean Bilirubin**

-2 0 2 4 6 8 10 12 14 16 18 20 22

Only for patients on study at 1 year (Patients 1,2,4,6)
PHAROAH: C3d deposition

C3d Deposition on PNH RBCs (Type II and III)
Patient #1

Hemoglobin (g/dL)

LDH (xULN)

ED - every day

EOV - every other week

Soliris 1,200mg EOW

Soliris 900mg EOW

APL-2 270mg ED

APL-2 360mg ED

Patient #1 transfusions

Months

0 2 4 6 8 10 12 14 16 18 20 22 24

0 0.5 1.0 1.5 2.0 2.5 3.0 3.5

10 12 14

10 12 14

0.5 1.0 1.5 2.0 2.5 3.0 3.5
Patient #2

- Soliris 900mg EOW
- APL-2 270mg ED
- Hemoglobin (g/dL)
- LDH (xULN)

Hemoglobin:
- Months:
  - LDH (xULN):
  - Patient #2 transfusions:

EOW - every other week
ED - every day
Patient #4

Hemoglobin (g/dL) vs. Months

- EW - every week
- EOW - every other week
- ED - every day

LDH (xULN)

- Soliris 900mg EW
- Soliris 900mg EOW
- APL-2 270mg ED
- APL-2 360mg ED

Patient #4 transfusions
Patient #6

- **Soliris 900mg EW**
- **APL-2 270mg ED**
- **Soliris 900mg EOW**
- **APL-2 360mg ED**
- **APL-2 440mg ED**

**Months**

**Hemoglobin (g/dL)**

**LDH (xULN)**

**EW** - every week
**EOW** - every other week
**ED** - every day

**Transfusions**
APL-2 in PNH: PHAROAH - Key Takeaways

4 Patients Ongoing

- Hemoglobin stable & transfusion independent

Soliris Dose Reduction

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APL-2 In PNH – Phase III Program

Anita Hill, MBChB (Hons), MRCP, FRCPath, PhD
Consultant Haematologist and Lead Clinician
for the National PNH Service, UK
Phase III Program - Key Takeaways

- Phase III designed for superiority and patient/physician reality

- Data to date suggest markedly improved hematology vs. Soliris

- Blocking extravascular hemolysis likely to translate into clinically meaningful improvement in Hb (e.g. transfusion avoidance), reticulocytes, bilirubin, and comparable LDH to C5 inhibitors
Study outline

**PEGASUS (n=70)**

- **Population**: PNH patients on eculizumab who continue to be anemic (Hb < 10.5 g/dL at screening)

- **Primary Endpoint**: Week 16 change from baseline in hemoglobin level

- **Design**: Randomized 1:1 APL-2:eculizumab. 1 Month Run In; 4 Month Randomization; 6 Month Open Label; 1 Month Follow Up

- **Posology**: Dose 1080 mg 2/week, SC infusion via injection pump

- **Sample size**: 70 patients (35/group) randomized 1:1 provides 90% power with 2-sided=0.05 to detect a difference of 1 mg/dL.

*Open Label extension may be offered to all participants if clinical benefit is evident*
**Parameter**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Patients with PNH (not on eculizumab)</td>
</tr>
<tr>
<td><strong>1° Endpoint</strong></td>
<td>Hb stabilization, defined as avoidance of a decrease in Hb levels from baseline in the absence of transfusion through Week 16</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Randomized 2:1 APL-2:No-treatment, 4 months No-treatment controlled period followed by 8 months open label period</td>
</tr>
<tr>
<td><strong>Posology</strong></td>
<td>Dose 1080 mg, twice/week SC injection via injection pump</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>48 patients randomized 2:1 (32:16) to APL-2:No-treatment provides 90% power with 2-sided =0.05 to detect a 45% difference in Hb stabilization (assuming a No-treatment rate of 5% and an APL-2 rate of 50%).</td>
</tr>
</tbody>
</table>
Phase III Program - Key Takeaways

- Phase III designed for superiority and patient/physician reality
- Data to date suggest markedly improved hematology vs. Soliris
- Blocking extravascular hemolysis likely to translate into clinically meaningful improvement in Hb (e.g. transfusion avoidance), reticulocytes, bilirubin, and comparable LDH to C5 inhibitors
APL-2 in PNH - Key Takeaways

- Hematological correction significant & clinically meaningful
- Only one patient out of 20 required transfusions while on adequate APL-2 (5%), likely under-dosed (BMI = 59)
- Switch from eculizumab (C5) achieved with retained superior hematology to eculizumab monotherapy
- Well tolerated
APL-2 In Paroxysmal Nocturnal Hemoglobinuria

Q&A
Early Stage Pipeline
Early Stage Pipeline: APL-2 in Autoimmune Hemolytic Anemia (AIHA) & Complement Dependent Nephropathies (CDN)

Cedric Francois, MD, PhD, Founder and Chief Executive Officer, Apellis Pharmaceuticals
APL-2 in Autoimmune Hemolytic Anemia (AIHA)
AIHA Overview

DISEASE

- Increased destruction of RBCs due to the presence of autoantibodies (decreased RBC life span)
- Estimated incidence 1-3 per 100,000/year, prevalence 17 per 100,000, mortality 8-11%
- Hemolysis mediated by complement:
  - Warm antibody (wAIHA): ~20% of patients
  - Cold agglutinin disease (CAD): majority of patients

STANDARD OF CARE

- wAIHA: Corticosteroids, Rituximab, splenectomy and transfusion.
- CAD: no effective treatment therapy, corticosteroids, alkylating agents, Rituximab (off label), IVIG, or transfusion.

Role of Complement in Warm AIHA

**Optimum 37° C**

Autoantibody antigen complex activates complement classical pathway

IgG auto-antibodies → C1q → Autoantibody antigen complex activates complement classical pathway → C3b → Phagocytosis through C3bR → Extravascular hemolysis
Role of Complement in CAD

At 37°C
- Production of cold agglutinin (CA) autoantibodies

Below 30°C
- In body extremities: IgM mediates RBC agglutination leads strong activation of CP

At 37°C
- Hemolysis upon recirculation to central parts of the body

- IgM → C1q → C5/MAC → C3b
- Extravascular hemolysis (Liver mainly)
- Intravascular hemolysis (patients w/ severe acute exacerbation)
- Phagocytosis through C3bR
Unmet Need in AIHA

EFFICACY

• wAIHA: 15-30% non-responders to corticosteroids. Splenectomy: 33% patients w/ relapses.
• CAD: Steroids and splenectomy are not generally effective (10-14% response). Rituximab overall response: 45-66%, median time to response: 1.5 months, median duration of remission: 11 months.

SAFETY

• Long-term safety issue associated with high doses of corticosteroids
• Toxicity, clinically significant AE (neutropenia, infection) associated with Rituximab
• Rituximab also associated with rare disastrous outcomes, including fatal pulmonary fibrosis and PML
• Splenectomy associated with sepsis, postoperative thrombosis and pulmonary embolism. Transfusion can be life threatening.

### OVERVIEW

The study is to assess the safety, tolerability, preliminary efficacy, and pharmacokinetics of multiple subcutaneous (SC) doses of APL-2 in subjects with Warm Antibody Autoimmune Hemolytic Anemia (wAIHA) or Cold Agglutinin Disease (CAD).

### PRIMARY SAFETY ENDPOINT

The incidence and severity of treatment emergent adverse events (TEAEs) following administration of multiple doses of subcutaneous (SC) APL-2.

### SECONDARY ENDPOINTS

**Change from baseline in:**
- Hb
- RBC transfusions during study
- absolute reticulocyte count
- LDH
- Haptoglobin
- Bilirubin
- Functional Assessment of Chronic Illness Therapy (FACIT) Scale
- Linear Analog Scale Assessment scale (LASA)
### AIHA Proof of Concept Phase II Study Overview

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Patients with warm or cold AIHA (treatment naïve or previously treated)</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>1:1 APL-2 270 mg/day: APL-2 360 mg/day, 12-month treatment</td>
</tr>
<tr>
<td><strong>Posology</strong></td>
<td>270 mg and 360 mg daily SC injection</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>12 patients, 6 patients with warm AIHA and 6 patients with cold AIHA</td>
</tr>
</tbody>
</table>

**Phase 2 study in US**

- **Cohort 1:** Warm AIHA (N=6)
  - APL-2 Daily 270 mg N=3
  - APL-2 Daily 360 mg N=3
- **Cohort 2:** Cold AIHA (N=6)
  - APL-2 Daily 270 mg N=3
  - APL-2 Daily 360 mg N=3
AIHA Key Inclusion Criteria

1. >18 years of age, <125 kg

2. Subjects must have a primary diagnosis of wAIHA or CAD defined by the presence of hemolytic anemia and positive DAT for wAIHA (IgG) or CAD (C3).

3. Hemoglobin <11 g/dL.

4. Specific for wAIHA: Relapsed from, did not respond to, or did not tolerate at least one prior wAIHA treatment regimen (such as prednisone, rituximab).
AIHA Key Exclusion Criteria

1. Prior treatment with rituximab within 90 days.

2. Deficiency of iron, folic acid and vitamin B12 prior to treatment phase.

3. Abnormal liver function (direct bilirubin above normal, and/or an AST/ALT level >2x upper limit of normal). Elevated indirect bilirubin due to hemolysis is not an exclusion criteria.

4. Active aggressive lymphoma requiring therapy or an active nonlymphatic malignant disease other than basal cell carcinoma or carcinoma in situ (CIS) of the cervix.

5. Presence or suspicion of active bacterial or viral infection at screening or severe recurrent bacterial infections

6. Pregnant, breast-feeding, or intending to conceive during the course of the study, including the Post-Treatment Phase.

7. Myocardial infarction, CABG, coronary or cerebral artery stenting and/or angioplasty, stroke, cardiac surgery, or hospitalization for congestive heart failure within 3 months or > Class 2 Angina Pectoris or NYHA Heart Failure Class >2
APL-2 in Cold Agglutinin Disease (n=2)

**Hemoglobin**

![Hemoglobin chart showing changes over days with two treatment groups: 270 mg/d - CAD and 360 mg/d - CAD.]

**Reticulocytes**

![Reticulocytes chart showing changes over days with two treatment groups: 270 mg/d - CAD and 360 mg/d - CAD.]

---

**Days**

-28 -21 -14 -7 0 7 14 21 28 35 42 49 56

**g/dL**

- 4 5 6 7 8 9 10 11 12 13 14 15

**10/1**

- 0 25 50 75 100 125 150 175 200 225 250
APL-2 in Warm Antibody AIHA (n=2)

Hemoglobin

Reticulocytes

Days

-28 -21 -14 -7 0 7 14 21 28

g/dL

4 5 6 7 8 9 10 11 12 13 14 15

APL-2 in Warm Antibody AIHA (n=2)

Days

-28 -21 -14 -7 0 7 14 21 28

10^9/L

0 25 50 75 100 125 150 175 200 225 250

270 mg/d - wAIHA

360 mg/d - wAIHA

270 mg/d - wAIHA

360 mg/d - wAIHA

Hemoglobin

Reticulocytes
A Phase 2 Study to Evaluate the Safety and Biologic Activity of APL-2 in Patients With IgA Nephropathy, Lupus Nephritis, Primary Membranous Nephropathy, or C3 Glomerulopathy (C3 Glomerulonephritis and Dense Deposit Disease)
APL-2 Prevents Inflammation and MAC Formation

Lectin Pathway  Classical Pathway  Alternative Pathway

APL-2  C3  C3b  Cell removal  Antigen uptake

Inflammation  C3a  Amplification loop  (C5 Inhibition)

Inflammation  C5a  C5b  MAC  Direct Cell Lysis
### Rationale for APL-2 in Glomerulopathies

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Complement pathways activated</th>
<th>Incidence/Prevalence(^*)</th>
<th>End-stage Renal Disease (ESRD) Hemodialysis</th>
<th>Competition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgA nephropathy</strong></td>
<td>• Alternative</td>
<td>• Inc: 6,200*</td>
<td>• ESRD: 40% within 20 years</td>
<td>• OMS721 (Omeros) phase 2</td>
</tr>
<tr>
<td></td>
<td>• Lectin (more severe cases)</td>
<td>• Prev: 130,000</td>
<td>• Hemodialysis: 72%</td>
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<tr>
<td><strong>Membranous nephropathy</strong></td>
<td>• Lectin</td>
<td>• Inc: 2,980*</td>
<td>• ESRD: 30-40% within 5-15 years</td>
<td>• Eculizumab - did not reach primary clinical endpoints</td>
</tr>
<tr>
<td></td>
<td>• Alternative</td>
<td>• Prev: Not determined</td>
<td>• Hemodialysis: 82%</td>
<td>• OMS721 (Omeros) phase 2</td>
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</tr>
<tr>
<td><strong>Lupus Nephritis</strong></td>
<td>• Alternative</td>
<td>• Inc: 17,000*</td>
<td>• ESRD: 10-30% within 15 years</td>
<td>• Rituximab phase 3</td>
</tr>
<tr>
<td></td>
<td>• Classical</td>
<td>• Prev: 80,000</td>
<td>• Hemodialysis: 85%</td>
<td>• Eculizumab, one case report</td>
</tr>
<tr>
<td></td>
<td>• Lectin</td>
<td></td>
<td></td>
<td>• OMS721 (Omeros) phase 2</td>
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<tr>
<td><strong>C3 glomerulopathy</strong></td>
<td>• Alternative</td>
<td>• Inc: Not determined</td>
<td>• ESRD: ~50% within 10 years</td>
<td>• Eculizumab ~15 promising cases studies, C3 deposition on biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prev: 600</td>
<td></td>
<td>• OMS721 (Omeros) phase 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• ACH-0144471 (Achillion) phase 2</td>
</tr>
</tbody>
</table>

\(^*\) Based on US adult population, 2016 248 million adults
1. National Organization for Rare Diseases, IgA Nephropathy, 2005, [www.rarediseases.org](http://www.rarediseases.org)
### APL2-201: Study Design

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Patients with either: IgA Nephropathy (IgAN), Lupus Nephritis (LN), Primary Membranous Nephropathy (Primary MN) or C3 Glomerulopathy (C3G)</td>
</tr>
<tr>
<td><strong>1º Endpoint</strong></td>
<td>Proteinuria reduction</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Single, open-label, treatment arm with APL-2 daily dosing</td>
</tr>
<tr>
<td><strong>Posology</strong></td>
<td>360mg (40mg/mL) subcutaneous infusion</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>Up to 48 patients (6-12 per indication)</td>
</tr>
</tbody>
</table>

#### Study Timeline

- **Screen/Observation**: 4 or 12 weeks
- **Enrollment**: 16 weeks
- **Treatment**: 16 weeks
- **Follow Up**: 24 weeks

**Open-Label Cohort**

IgAN, LN, C3G, Primary MN
APL2-201: Key Inclusion Criteria (Following Protocol Amendment)

1. 18+ years of age at screening
2. Urinary protein to creatinine ratio >750mg/g (~1.0g/day)
3. Stable blood pressure (<140/90mmHg)
4. 3+ months of optimized ACE/ARB therapy (if applicable)
5. 2+ months of optimized immunosuppressive therapy (if applicable)
6. eGFR ≥ 30 mL/min/1.73 m² calculated by CKD-EPI
7. Prior diagnosis by renal biopsy
8. 4 Week Screening Eligibility:
   - 6+ months of uPCR levels >750mg/g, stable blood pressure (<140/90mmHg), and optimized ACE/ARB
APL2-201: Key Exclusion Criteria

1. Use of belimumab, eculizumab, or rituximab within 6 months prior to Screening
2. Previous treatment with APL-2
3. History of organ transplant
4. Current unstable kidney function for other reasons, e.g. toxin induced acute kidney injury
Key Milestones for 2018

GA:
- Phase 2: 18 month safety & efficacy data

PNH:
- Phase 1b: monotherapy expansion (interim)
  - Phase 1b: Soliris weaning in add-on study

AIHA:
- Phase 2: POC monotherapy data

CDN:
- Phase 2: POC monotherapy data

PNH:
- Start of Phase 3 program

GA:
- Start of Phase 3 program