PNH: A Historical Perspective

- 1882: Strübing: First reported case.
- 1928: Enneking: “paroxysmal nocturnal hemoglobinuria”.
- 1938: Ham: PNH RBCs lysis in an acidified serum by an antibody-independent complement-like factors.
- 1961: Dacie: PNH cells in BM failure /Link to somatic mutation: “abnormal cells must have as yet, not understood biological advantage”.

PNH: A Historical Perspective

- **1966**: Rosse: PNH RBC’s were 25 times more sensitive to lysis by complement than normal RBC’s. C3 binding with complement activation.
- **1970**: Luzzatto: Clonal nature of PNH / G6PD iso-typing.
- **1989**: Parker: MIRL (CD-59) which inhibited reactive lysis of PNH cells.
- **1993**: Kinoshita: Loss of GPI anchor is the result of a somatic mutation in *PIG-A* gene.

The Etiology of PNH:

- An acquired / somatic mutation in the X-linked \textit{PIG-A} gene in hematopoietic stem cells.
- Inability to synthesize/display the GPI-anchor on cell surface.
- Loss of GPI-anchored complement-shielding CD-55/CD-59
- One mutation is required in either males or females to cause disease.
PNH : Epidemiology

- A rare disorder.
- Incidence: 1-10 cases per million.
- Median age of onset in the 30’s.
- Can affect the elderly and rarely children.
- No ethnic or geographic distribution.

The Complement System

Intravascular Hemolysis

Inflammation

C3

C3b

C3a

C5a

C5b

MAC

Extravascular Hemolysis

C5b on RBC

Amplification loop

Immune cells

Proximal

Classical Pathway

Alternative Pathway

Terminal

Lectin Pathway

Inflammation

C5

Intravascular Hemolysis

Classical Pathway

Alternative Pathway
CD59 Deficiency and MAC* Formation

* Membrane Attack Complex

The Clinical Triad of PNH

- Hemolysis/Hemoglobinuria
- Thrombosis
- Bone Marrow Failure*
Clinical Manifestations of PNH

- **Intravascular Hemolysis**
  - Anemia and fatigue
  - Hemoglobinuria
  - Renal failure
  - Esophageal spasms
  - Abdominal pain
  - Headache
  - Erectile dysfunction

- **Bone Marrow Failure**
  - Pancytopenia
  - Propensity for infection
  - Bleeding

- **Thrombotic Events**
  - Venous thromboembolism DVT/PE
  - Intra-abdominal vein thrombosis
    - Budd-Chiari
    - Splenic/mesenteric/renal vein thrombosis
  - Cerebral vein thrombosis
  - Retinal and dermal vein thromboses
  - Arterial thromboses: MI/Strokes
## Classification of PNH

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classic</strong></td>
<td>Florid (macroscopic hemoglobinuria is frequent or persistent)</td>
</tr>
<tr>
<td></td>
<td>Cellular marrow with erythroid hyperplasia and normal or near-normal morphology</td>
</tr>
<tr>
<td><strong>PNH in the setting of another marrow failure syndrome</strong></td>
<td>Mild to moderate (macroscopic hemoglobinuria is intermittent or absent)</td>
</tr>
<tr>
<td><strong>Subclinical</strong></td>
<td>No clinical or biochemical evidence of intravascular hemolysis</td>
</tr>
<tr>
<td></td>
<td>Evidence of a concomitant marrow failure syndrome</td>
</tr>
</tbody>
</table>

PNH: An Approach To Diagnosis
Time to Diagnosis of PNH

Average time to diagnosis from onset of symptoms <2 years

## Providers Consulted Prior to PNH Diagnosis

<table>
<thead>
<tr>
<th>PROVIDER</th>
<th>n</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiologist</td>
<td>114</td>
<td>4 (4%)</td>
<td>3 (3%)</td>
<td>4 (4%)</td>
<td>3 (3%)</td>
<td>5 (5%)</td>
<td>95 (83%)</td>
</tr>
<tr>
<td>Emergency</td>
<td>124</td>
<td>24 (19%)</td>
<td>27 (22%)</td>
<td>3 (2%)</td>
<td>3 (2%)</td>
<td>5 (2%)</td>
<td>52 (42%)</td>
</tr>
<tr>
<td>Hematologist</td>
<td>150</td>
<td>19 (13%)</td>
<td>50 (33%)</td>
<td>42 (28%)</td>
<td>17 (11%)</td>
<td>12 (8%)</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Nephrologist</td>
<td>102</td>
<td>2 (2%)</td>
<td>7 (7%)</td>
<td>7 (7%)</td>
<td>3 (3%)</td>
<td>3 (3%)</td>
<td>76 (74%)</td>
</tr>
<tr>
<td>Neurologist</td>
<td>99</td>
<td>0 (0%)</td>
<td>4 (4%)</td>
<td>4 (4%)</td>
<td>2 (2%)</td>
<td>5 (5%)</td>
<td>84 (85%)</td>
</tr>
<tr>
<td>OB/GYN</td>
<td>82</td>
<td>11 (13%)</td>
<td>10 (12%)</td>
<td>5 (6%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>53 (66%)</td>
</tr>
<tr>
<td>PCP</td>
<td>148</td>
<td>90 (61%)</td>
<td>18 (12%)</td>
<td>4 (3%)</td>
<td>4 (3%)</td>
<td>5 (4%)</td>
<td>19 (12.8%)</td>
</tr>
<tr>
<td>Mental Health</td>
<td>94</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
<td>4 (4%)</td>
<td>84 (89%)</td>
</tr>
<tr>
<td>Pulmonologist</td>
<td>99</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>3 (3%)</td>
<td>2 (2%)</td>
<td>91 (92%)</td>
</tr>
<tr>
<td>Urologist</td>
<td>107</td>
<td>5 (5%)</td>
<td>8 (8%)</td>
<td>6 (6%)</td>
<td>2 (2%)</td>
<td>3 (3%)</td>
<td>83 (77%)</td>
</tr>
<tr>
<td>Other</td>
<td>65</td>
<td>7 (11%)</td>
<td>10 (15%)</td>
<td>8 (12%)</td>
<td>4 (6%)</td>
<td>5 (7%)</td>
<td>30 (46%)</td>
</tr>
</tbody>
</table>

Diagnostic Testing for PNH

- Flow cytometry of peripheral blood:
  - Gold standard test for diagnosis of PNH
    - Stains with monoclonal antibodies for CD55 and CD59
    - FLAER (fluorescein-tagged pro-aerolysin variant) that binds a portion of GPI anchor
  - More than one cell lineage should be evaluated
    - Granulocytes
    - Monocytes
    - Red Blood Cells (RBC)
  - Sensitivity Level ~ 0.01%
Flow Cytometric Analysis in PNH

80.1% of Granulocytes lack GPI proteins

31.4% RBCs are Type III PNH cells
Identifying patients for PNH Testing

- All Patients with AA
- Select patients with MDS.
- Unexplained Coombs- negative hemolytic anemia.
- Hemoglobinuria/ Intravascular hemolysis.
- Young patients with Unexplained thromboses.
- Thromboses at unusual sites.
- Thrombotic events despite adequate anticoagulation.
- Thrombotic events with iron deficiency, granulocytopenia, and or hemolytic anemia.
- Patients with unexplained cytopenias

Dezern et al. clinical cytometry, 94b: 16-22 (2018)
PNH: Treatment
Treatment options for PNH

- **Supportive care**
  - Transfusions.
  - Iron/folate.
  - Androgens.
  - Erythropoiesis stimulating agents.

- **Prednisone**
  - Dose required (20-30 mg/day).

- **Allogeneic Bone marrow transplantation.**

- **Complement Inhibition:**
  - Eculizumab (Soliris).
  - Ravulizumab (ultomiris)

- **Clinical trials/Novel agents.**

Eculizumab: Anti-C5 Antibody

Human Framework Regions
- No mutations
- Germline

Human IgG₂ Heavy Chain
Constant Region 1 and Hinge

Complementarity Determining Regions
(murine origin)

Human IgG₄ Heavy Chain
Constant Regions 2 and 3

Rother R et al. Nat Biotech 2007;25:1256
Eculizumab Clinical Studies

Pilot Study – *NEJM*. 2004
N = 11
Primary endpoint: reduction of hemolysis

TRIUMPH – *NEJM*. 2006
Pivotal Phase III, Double-Blind, Placebo-Controlled Trial, N = 87

Broader patient population, including those receiving minimal transfusions or with thrombocytopenia, N = 97

Long-Term Extension Trial Hillmen *Blood*. 2007
Evaluated long-term safety, efficacy and effect on thrombosis; Placebo patients switched to Eculizumab N = 187
TRIUMPH – LDH

LDH (IU/L)

Placebo
P < 0.001

Eculizumab

Study Week

Normal

Screening

CASE 1

- Treated with immunosuppressive therapy.

- In 2005, he presented with worsening anemia:
  - HGB: 9.8 gm/dl, MCV:115, WBC/ANC/Plt. WNL
CASE 1: Results of Diagnostic Testing

- Bone marrow biopsy:
  - Normocellular bone marrow
  - Erythroid hyperplasia.
  - No overt dysplasia seen.
  - Absent storage iron.

- Flow cytometry results:
  - RBC Type I: Normal CD59 level. 74.81%
  - RBC Type II: Partial CD59 deficiency 1.13%
  - RBC Type III: Complete CD59 deficiency 24.06%
  - Granulocytes FLAER/CD24 deficiency 76.06%
  - Monocytes FLAER/CD14 deficiency 83.65%
CASE 1: LDH
CASE 1: Hemoglobin

Eculizumab
Impact of eculizumab treatment on paroxysmal nocturnal hemoglobinuria: a treatment versus no-treatment study

- A retrospective comparison study between 123 patients treated with eculizumab in the recent period (>2005) and 191 historical controls (from the French registry).

- Overall survival (OS) at 6 years was 92% in the eculizumab cohort versus 80% in historical controls diagnosed after 1985. (HR 0.38 [0.15 to 0.94], P = 0.037).

- There were significantly fewer thrombotic events in the group of patients treated with eculizumab (4%) as compared to the historical cohort (27%).

ALXN -1210: Ravulizumab

- A humanized monoclonal antibody to C5.
- Enhanced Fc receptor recycling.
- Half-life of 42 days (4x longer than Eculizumab).
- Administered IV q 8 weeks.
- Weight-based dosing.
- A sq. version is under investigation.
Ravulizumab: Phase 3 Trials

- **PNH-301:**
  - A randomized, open-label trial in treatment-naïve PNH patients (n: 246).
  - To evaluate the efficacy and safety of ALXN1210 VS. Eculizumab.
  - Co-primary endpoint: Transfusion avoidance, and LDH normalization.
  - ALXN 1210 reported to be noninferior to eculizumab (Lee, EHA 2018).

- **PNH-302:**
  - A randomized noninferiority trial of ALXN1210 versus eculizumab.
  - Previously-treated adult patients with PNH (n: 197).
  - At least 6 months of eculizumab therapy, LDH < 1.5 X ULN.
  - Primary efficacy endpoint was hemolysis /percentage change in LDH level from baseline to day 183.
Ravulizumab (ALXN1210) vs ecuvilizumab in adult patients with PNH naive to complement inhibitors: the 301 study

by Jong Wook Lee, Flore Sicre de Fontbrune, Lily Wong Lee Lee, Viviani Pessoa, Sandra Gualandro, Wolfgang Fürderer, Vadim Ptushkin, Scott T Rottinghaus, Lori Volles, Lori Shafner, Rasha Aguzzi, Rajendra Pradhan, Hubert Schrezenmeier, and Anita Hill

Blood
Volume 133(6):530-539
February 7, 2019

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Efficacy of ravulizumab and eculizumab in complement inhibitor–naive PNH patients

**Coprimary Endpoints**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ravulizumab (N=123)</th>
<th>Eculizumab (N=121)</th>
<th>Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion Avoidance (%)</td>
<td>73.6</td>
<td>66.1</td>
<td>6.8 (-4.66, 10.14)</td>
</tr>
<tr>
<td>LDH Normalization (%)</td>
<td>53.6</td>
<td>49.4</td>
<td>1.19 (0.8, 1.77)</td>
</tr>
</tbody>
</table>

**Key Secondary Endpoints**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ravulizumab (N=123)</th>
<th>Eculizumab (N=121)</th>
<th>Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent Change in LDH</td>
<td>-76.84</td>
<td>-76.02</td>
<td>0.83 (-1.56, 3.21)</td>
</tr>
<tr>
<td>Change in FACIT-Fatigue</td>
<td>7.07</td>
<td>6.40</td>
<td>0.67 (-1.21, 2.55)</td>
</tr>
<tr>
<td>Breakthrough Hemolysis (%)</td>
<td>4.0</td>
<td>10.7</td>
<td>6.7 (0.18, 14.21)</td>
</tr>
<tr>
<td>Hemoglobin Stabilization</td>
<td>68.0</td>
<td>64.5</td>
<td>2.9 (-0.30, 14.64)</td>
</tr>
</tbody>
</table>

* CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria.
* For transfusion avoidance, percent change in LDH, breakthrough hemolysis, and hemoglobin stabilization, difference (95% CI) was based on estimated differences in percentage with 95% CI. For LDH normalization, adjusted prevalence within each treatment was displayed. For change in FACIT-Fatigue, difference (95% CI) was based on estimated difference in change from baseline with 95% CI. Treatment differences are displayed as ravulizumab – eculizumab for all endpoints except breakthrough hemolysis, which is displayed as eculizumab – ravulizumab. The red triangle indicates the noninferiority margin.

Jong Wook Lee et al. Blood 2019;133:530-539

©2019 by American Society of Hematology
Proportion of patients achieving LDH-N over time in the ravulizumab and eculizumab treatment groups.

Jong Wook Lee et al. Blood 2019;133:530-539

©2019 by American Society of Hematology
Mean (95% CI) free C5 concentrations in the ravulizumab and eculizumab groups over time.

Jong Wook Lee et al. Blood 2019;133:530-539
Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor–experienced adult patients with PNH: the 302 study

by Austin G. Kulasekhararaj, Anita Hill, Scott T. Rottinghaus, Saskia Langemeijer, Richard Wells, F. Ataulfo Gonzalez-Fernandez, Anna Gaya, Jong Wook Lee, Emilio Ojeda Gutierrez, Caroline I. Piatek, Jeff Szer, Antonio Risitano, Shinji Nakao, Eric Bachman, Lori Shafner, Andrew I. Damokosh, Stephan Ortiz, Alexander Röth, and Regis Peffault de Latour

Blood
Volume 133(6):540-549
February 7, 2019
Efficacy of Ravulizumab and Eculizumab in PNH Patients Stable on Eculizumab

**Primary Endpoint**

**Percent Change in LDH**

<table>
<thead>
<tr>
<th></th>
<th>Ravulizumab (N=97)</th>
<th>Eculizumab (N=98)</th>
<th>Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.82</td>
<td>0.39</td>
<td>0.02 (0.62, 0.84)</td>
</tr>
</tbody>
</table>

**Key SecondaryEndpoints**

**Breakthrough Hemolysis (%)**

<table>
<thead>
<tr>
<th></th>
<th>Ravulizumab (N=97)</th>
<th>Eculizumab (N=98)</th>
<th>Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>5.1</td>
<td>5.1 (0.09, 8.19)</td>
</tr>
</tbody>
</table>

**Change in FACT-Fatigue**

<table>
<thead>
<tr>
<th></th>
<th>Ravulizumab (N=97)</th>
<th>Eculizumab (N=98)</th>
<th>Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.01</td>
<td>0.54</td>
<td>1.47 (0.21, 3.15)</td>
</tr>
</tbody>
</table>

**Transfusion Avoidance (%)**

<table>
<thead>
<tr>
<th></th>
<th>Ravulizumab (N=97)</th>
<th>Eculizumab (N=98)</th>
<th>Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>87.6</td>
<td>92.7</td>
<td>5.5 (4.37, 15.68)</td>
</tr>
</tbody>
</table>

**Hemoglobin Stabilization (%)**

<table>
<thead>
<tr>
<th></th>
<th>Ravulizumab (N=97)</th>
<th>Eculizumab (N=98)</th>
<th>Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>76.3</td>
<td>75.5</td>
<td>1.4 (10.41, 15.31)</td>
</tr>
</tbody>
</table>

CI, confidence interval; FACT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria.

*For percent change in LDH, breakthrough hemolysis, transfusion avoidance, and hemoglobin stabilization, difference (95% CI) was based on estimated difference in percentages with 95% CI. For change in FACT-Fatigue, difference (95% CI) was based on estimated difference in change from baseline with 95% CI. For change in FACT-Fatigue, transfusion avoidance, and hemoglobin stabilization, treatment difference is displayed as eculizumab - ravulizumab. For percent change in LDH and breakthrough hemolysis, treatment difference is displayed as ravulizumab - eculizumab. The red triangle indicates the noninferiority margin.

Austin G. Kulasekaran et al. Blood 2019;133:540-549
Percentage of patients achieving LDH normalization overtime in the ravulizumab and eculizumab treatment groups.

![Graph showing percentage of patients achieving LDH normalization over time. The x-axis represents visit days (1 to 183) and the y-axis represents percentage of patients achieving LDH normalization. The graph shows two lines, one for Ravulizumab and one for Eculizumab.](image)

_Austin G. Kulasekararaj et al. Blood 2019;133:540-549_
(A) Impact of donor: matched sibling versus unrelated donors. (B) Impact of transplant indication: BMT performed RHC, AA or TE.
PNH Treatment Algorithm

Hemolysis
- Mild
  - Supportive care
- Severe
  - No thrombosis
  - Anti-complement therapy: eculizumab
    - Response
    - No response

Thrombophilia
- No thrombosis
  - Anti-coagulants, ± thrombolysis
- Thrombosis
  - Supportive care

Aplastic anemia
- Moderate AA
  - Supportive care
- Severe AA
  - No sibling donor
  - Sibling donor
    - ATG + CyA
    - No response
    - Response

BMT option contraindicated due to high transplant-related mortality

Novel anti-complement therapies???

BMT (MUD)

BMT (sibling)
CASE 2

- A 25 year old woman with no prior medical history presented to PCP with fatigue and exercise intolerance.

- A CBC was performed:
  - Hemoglobin 4.5 g/dl, MCV 103.8 Fl
  - WBC 2.8 th/mL, ANC: 1.18 th/mL
  - Platelets 59 th/mL.

- LDH (> 3000), Total bilirubin: 3.5, mostly unconjugated

- Coombs negative.

- Extensive workup for causes of hemolytic anemia was negative.
CASE 2: Results of Diagnostic Testing

- Bone marrow biopsy: Normocellular marrow with erythroid hyperplasia. No dysplasia present.
- Flow cytometry on a peripheral blood sample for PNH was performed:
  - Type I RBC 69.29%
  - Type II RBC 20.26%
  - Type III RBC 10.45%
- Granulocytes FLAER/CD24 deficiency: 86%
- Monocytes FLAER/CD14 deficiency: 84.99%
CASE 2: Hgb

Eculizumab

Stem Cell Transplantation
CASE 2: Platelets
CASE 2: PNH Clone Kinetics

- **Pre-BMT:**
  - **RBCS**
    - Type I: Normal CD59 level. 54.64%
    - Type II: Partial CD59 deficiency 6.49%
    - Type III: Complete CD59 deficiency 38.87%
  - GRANULOCYTES FLAER/CD24 deficiency 94.34%
  - MONOCYTES FLAER/CD14 deficiency 96.93%

- **1 Month Post BMT**
  - **RBCS**
    - Type I: Normal CD59 level. 99.08%
    - Type II: Partial CD59 deficiency 0.59%
    - Type III: Complete CD59 deficiency 0.33%
  - GRANULOCYTES FLAER/CD24 deficiency 1.11%
  - MONOCYTES FLAER/CD14 deficiency 0.66%

- **4 Months Post BMT**
  - No flow cytometric evidence of paroxysmal nocturnal hemoglobinuria (PNH).
PNH: Novel Agents
PNH: Ongoing Dilemmas

- C5 polymorphism/lack of response to Eculizumab
- Breakthrough hemolysis
- Concomitant bone marrow failure
- Extravascular hemolysis (+ DAT/C3 deposits)
- Increased risk for meningococcal infection.
- Need for frequent infusions (q 2 week).
- Cost of therapy.
Novel Agents

Anti-C5 mAb
- REGN3918
- LFG316
- Eculizumab biosimilars
- Coversin
- SKY59/RO711268/Crovalimab

Interference with C5 production
ALN-CC5
Zilucoplan: C5 Complement Inhibitor

- Zilucoplan (RA101495 SC): self-administered, subcutaneous C5 inhibitor
- Binds to C5 and C5b
- Phase 2 studies completed
- Phase 3 studies in paroxysmal nocturnal hemoglobinuria (PNH) planned for 2019
Inhibitors of the Proximal Complement

Broad inhibitors of C3: two compstatin analogs
- AMY-101
- APL-2)

Selective inhibitors of the alternative pathway
ACH-4471: Anti complement factor D (FD)
LNP023: Anti complement factor B (FB).
APL-2: Central Inhibition of Complement

Inflammation

C3

APL-2

Amplification loop

C3a

C3b

C3

EXTRAVASCULAR HEMOLYSIS

C5

C5a

C5b

MAC

Eculizumab

Peptides of the APL-2 family bind to a pocket of C3 and inhibit activation

PHAROAH: APL-2 Add-on Therapy in Eculizumab Tx’d Pts *

**Patient Population:**
- Diagnosis of PNH (WBC clone > 10%)
- At least 3 months of eculizumab treatment
- Hb < 10.5 g/dL at screening, LDH > 2X ULN 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

PADDOCK: APL-2 Monotherapy in eculizumab-Naïve PNH

**Patient Population:**
- Diagnosis of PNH (WBC clone > 10%)
- LDH > 2X ULN
- Last transfusion within 12 months prior to screening
- Platelet count of > 30,000/mm³ and ANC > 500 x 10⁹/L

---

**Study designs – Open label MADs**

| Dose (mg) | Screen | Treat 28 days | Observe Country
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>Screen</td>
<td>Treat 28 days</td>
<td></td>
</tr>
<tr>
<td>270</td>
<td>Screen</td>
<td>Treat 28 days</td>
<td>Continue treatment for 2 years</td>
</tr>
</tbody>
</table>

* Poster presentation on Sunday, abstract 2314*
**Parameter**

<table>
<thead>
<tr>
<th><strong>Population</strong></th>
<th>PNH patients on eculizumab who continue to be anemic (Hb &lt; 10.5 g/dL at screening), elevated retic counts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>Week 16 change from baseline in hemoglobin level</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Randomized 1:1 APL-2:eculizumab. 1 Month Run In; 4 Month Randomization; 6 Month Open Label; 1 Month Follow Up</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Dose 1080 mg 2/week, SC infusion via injection pump</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>70 patients (35/group) randomized 1:1</td>
</tr>
</tbody>
</table>
Key Takeaways

- PNH is a rare disease with serious consequences.
- Testing for PNH should be performed in high-yield patient populations.
- Flow cytometry of the peripheral blood is the diagnostic procedure of choice for PNH.
- PNH clones should be monitored periodically.
- SCT is reserved for patients with PNH/severe bone marrow failure, or those who do not respond to complement inhibition.
- Multiple novel agents are being evaluated.