

## **SUPPLEMENTARY MATERIAL**

**Title:** Comparative effectiveness of pegcetacoplan versus ravulizumab and eculizumab in complement inhibitor-naïve patients with paroxysmal nocturnal hemoglobinuria: A matching-adjusted indirect comparison

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A bias factor analysis based on studies by Jiang and Ni (2020) and VanderWeele et al. (2020) was performed to estimate bias due to unmeasured confounders for the following binary variables: age  $\geq 65$  years, overweight or obese, aplastic anemia, impaired renal function, bone marrow failure, and glycosyl-phosphatidylinositol (GPI)-deficient granulocyte clone size  $>70\%$ . The steps of this analysis were as follows: 1) perform a targeted literature review to extract prevalence estimates of binary variables in the broader PNH population; 2) conduct multivariate regressions using the PRINCE IPD to calculate the effect of the risk factor on each outcome, after adjusting for the variables used to match the IPD data to the aggregate data in the MAIC; and 3) use the above results to calculate a bias factor to adjust the unanchored comparisons from the MAIC. The literature review encompassed 115 publications; where multiple estimates were available for a given prevalence, a population-weighted average was calculated. The prevalence estimates were as follows: age at first infusion  $>65$  years, 12.8%; overweight or obese, 50.8%; aplastic anemia, 59.1%; impaired renal function, 31.7%; bone marrow failure, 62.6%; age at diagnosis  $>36.8$  years, 50%; GPI-deficient granulocyte clone size  $>70\%$ , 76.9%; GPI-deficient monocyte clone size  $>90\%$ , 45.2%.

Unanchored indirect comparisons were adjusted for each bias factor by subtracting the factor from the effect estimate and 95% CIs. Results are shown in **Supplementary Table S1**.

**Supplementary Table S1. Bias factor-adjusted comparisons**

| Endpoint <sup>1</sup>                                | Bias factor <sup>2</sup> | Bias factor-adjusted<br>pegcetacoplan vs. ravulizumab<br>mean (95% CI) <sup>3</sup> | Bias factor-adjusted<br>pegcetacoplan vs. eculizumab<br>mean (95% CI) <sup>3</sup> |
|------------------------------------------------------|--------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| <b>Primary endpoints</b>                             |                          |                                                                                     |                                                                                    |
| <b>LDH level (change from baseline), U/l</b>         |                          |                                                                                     |                                                                                    |
| <b>Unadjusted</b>                                    | n/a                      | -764.05 (-1,093.48, -434.63)                                                        | -886.85 (-1,277.32, -496.38)                                                       |
| Age ≥65 years                                        | -465.91                  | -298.14 (-627.57, 31.28)                                                            | -420.94 (-811.41, -30.47)                                                          |
| Overweight or obese                                  | 76.21                    | -840.26 (-1,169.69, -510.84)                                                        | -963.06 (-1,353.53, -572.59)                                                       |
| Aplastic anemia                                      | 39.41                    | -803.46 (-1,132.89, -474.04)                                                        | -926.26 (-1,316.73, -535.79)                                                       |
| Impaired renal function                              | -53.43                   | -710.62 (-1,040.05, -381.20)                                                        | -833.42 (-1,223.89, -442.95)                                                       |
| Bone marrow failure                                  | 135.02                   | -899.07 (-1,228.50, -569.65)                                                        | -1,021.87 (-1,412.34, -631.40)                                                     |
| Diagnosis age >36.8 years                            | 453.07                   | -1,217.12 (-1,546.55, -887.70)                                                      | -1,339.92 (-1,730.39, -949.45)                                                     |
| GPI-deficient granulocyte clone size >70%            | -233.95                  | -530.10 (-859.53, -200.68)                                                          | -652.90 (-1,043.37, -262.43)                                                       |
| GPI-deficient monocyte clone size >90%               | -266.41                  | -497.64 (-827.07, -168.22)                                                          | -620.44 (-1,010.91, -229.97)                                                       |
| <b>LDH level (percentage change from baseline)</b>   |                          |                                                                                     |                                                                                    |
| <b>Unadjusted</b>                                    | n/a                      | -11.89 (-16.13, -7.65)                                                              | -12.42 (-16.03, -8.81)                                                             |
| Age ≥65 years                                        | -3.23                    | -8.66 (-12.90, -4.42)                                                               | -9.19 (-12.80, -5.58)                                                              |
| Overweight or obese                                  | 3.65                     | -15.54 (-19.78, -11.30)                                                             | -16.07 (-19.68, -12.46)                                                            |
| Aplastic anemia                                      | -0.90                    | -10.99 (-15.23, -6.75)                                                              | -11.52 (-15.13, -7.91)                                                             |
| Impaired renal function                              | -0.68                    | -11.21 (-15.45, -6.97)                                                              | -11.74 (-15.35, -8.13)                                                             |
| Bone marrow failure                                  | 0.12                     | -12.01 (-16.25, -7.77)                                                              | -12.54 (-16.15, -8.93)                                                             |
| Diagnosis age >36.8 years                            | 3.67                     | -15.56 (-19.80, -11.32)                                                             | -16.09 (-19.70, -12.48)                                                            |
| GPI-deficient granulocyte clone size >70%            | -4.72                    | -7.17 (-11.41, -2.93)                                                               | -7.70 (-11.31, -4.09)                                                              |
| GPI-deficient monocyte clone size >90%               | -4.86                    | -7.03 (-11.27, -2.79)                                                               | -7.56 (-11.17, -3.95)                                                              |
| <b>LDH normalization<sup>4</sup></b>                 |                          |                                                                                     |                                                                                    |
| <b>Unadjusted</b>                                    | n/a                      | 25.94 (6.40, 45.48)                                                                 | 26.56 (5.07, 48.05)                                                                |
| Age ≥65 years                                        | 0.15                     | 25.79 (6.25, 45.33)                                                                 | 26.41 (4.92, 47.90)                                                                |
| Overweight or obese                                  | -0.26                    | 26.20 (6.66, 45.74)                                                                 | 26.82 (5.33, 48.31)                                                                |
| Aplastic anemia                                      | -0.05                    | 25.99 (6.45, 45.53)                                                                 | 26.61 (5.12, 48.10)                                                                |
| Impaired renal function                              | 0.10                     | 25.84 (6.30, 45.38)                                                                 | 26.46 (4.97, 47.95)                                                                |
| Bone marrow failure                                  | -0.07                    | 26.01 (6.47, 45.55)                                                                 | 26.63 (5.14, 48.12)                                                                |
| Diagnosis age >36.8 years                            | 0.03                     | 25.91 (6.37, 45.45)                                                                 | 26.53 (5.04, 48.02)                                                                |
| GPI-deficient granulocyte clone size >70%            | 0.06                     | 25.88 (6.34, 45.42)                                                                 | 26.50 (5.01, 47.99)                                                                |
| GPI-deficient monocyte clone size >90%               | -0.39                    | 26.33 (6.79, 45.87)                                                                 | 26.95 (5.46, 48.44)                                                                |
| <b>Hemoglobin level (change from baseline), g/dl</b> |                          |                                                                                     |                                                                                    |
| <b>Unadjusted</b>                                    | n/a                      | 1.58 (0.26, 2.90)                                                                   | 1.78 (0.18, 3.37)                                                                  |
| Age ≥65 years                                        | 0.87                     | 0.71 (-0.61, 2.03)                                                                  | 0.91 (-0.69, 2.50)                                                                 |

| Endpoint <sup>1</sup>                                     | Bias factor <sup>2</sup> | Bias factor-adjusted<br>pegcetacoplan vs. ravulizumab | Bias factor-adjusted<br>pegcetacoplan vs. eculizumab |
|-----------------------------------------------------------|--------------------------|-------------------------------------------------------|------------------------------------------------------|
|                                                           |                          | mean (95% CI) <sup>3</sup>                            | mean (95% CI) <sup>3</sup>                           |
| Overweight or obese                                       | -0.02                    | 1.60 (0.28, 2.92)                                     | 1.80 (0.20, 3.39)                                    |
| Aplastic anemia                                           | -0.37                    | 1.95 (0.63, 3.27)                                     | 2.15 (0.55, 3.74)                                    |
| Impaired renal function                                   | 0.27                     | 1.31 (-0.01, 2.63)                                    | 1.51 (-0.09, 3.10)                                   |
| Bone marrow failure                                       | -0.43                    | 2.01 (0.69, 3.33)                                     | 2.21 (0.61, 3.80)                                    |
| Diagnosis age >36.8 years                                 | -1.80                    | 3.38 (2.06, 4.70)                                     | 3.58 (1.98, 5.17)                                    |
| GPI-deficient granulocyte clone size >70%                 | -0.04                    | 1.62 (0.30, 2.94)                                     | 1.82 (0.22, 3.41)                                    |
| GPI-deficient monocyte clone size >90%                    | -2.03                    | 3.61 (2.29, 4.93)                                     | 3.81 (2.21, 5.40)                                    |
| <b>Hemoglobin level (percentage change from baseline)</b> |                          |                                                       |                                                      |
| Unadjusted                                                | n/a                      | 16.84 (2.40, 31.28)                                   | 19.49 (1.98, 37.00)                                  |
| Age ≥65 years                                             | 9.92                     | 6.92 (-7.52, 21.36)                                   | 9.57 (-7.94, 27.08)                                  |
| Overweight or obese                                       | -0.02                    | 16.86 (2.42, 31.30)                                   | 19.51 (2.00, 37.02)                                  |
| Aplastic anemia                                           | -3.17                    | 20.01 (5.57, 34.45)                                   | 22.66 (5.15, 40.17)                                  |
| Impaired renal function                                   | 2.87                     | 13.97 (-0.47, 28.41)                                  | 16.62 (-0.89, 34.13)                                 |
| Bone marrow failure                                       | -3.99                    | 20.83 (6.39, 35.27)                                   | 23.48 (5.97, 40.99)                                  |
| Diagnosis age >36.8 years                                 | -23.63                   | 40.47 (26.03, 54.91)                                  | 43.12 (25.61, 60.63)                                 |
| GPI-deficient granulocyte clone size >70%                 | -1.35                    | 18.19 (3.75, 32.63)                                   | 20.84 (3.33, 38.35)                                  |
| GPI-deficient monocyte clone size >90%                    | -13.78                   | 30.62 (16.18, 45.06)                                  | 33.27 (15.76, 50.78)                                 |
| <b>Hemoglobin stabilization<sup>5</sup></b>               |                          |                                                       |                                                      |
| Unadjusted                                                | n/a                      | 26.35 (14.83, 37.86)                                  | 27.73 (13.93, 41.53)                                 |
| Age ≥65 years                                             | 0.00                     | 26.35 (14.83, 37.86)                                  | 27.73 (13.93, 41.53)                                 |
| Overweight or obese                                       | 0.00                     | 26.35 (14.83, 37.86)                                  | 27.73 (13.93, 41.53)                                 |
| Aplastic anemia                                           | 0.00                     | 26.35 (14.83, 37.86)                                  | 27.73 (13.93, 41.53)                                 |
| Impaired renal function                                   | 0.00                     | 26.35 (14.83, 37.86)                                  | 27.73 (13.93, 41.53)                                 |
| Bone marrow failure                                       | 0.00                     | 26.35 (14.83, 37.86)                                  | 27.73 (13.93, 41.53)                                 |
| Diagnosis age >36.8 years                                 | 0.00                     | 26.35 (14.83, 37.86)                                  | 27.73 (13.93, 41.53)                                 |
| GPI-deficient granulocyte clone size >70%                 | 0.00                     | 26.35 (14.83, 37.86)                                  | 27.73 (13.93, 41.53)                                 |
| GPI-deficient monocyte clone size >90%                    | 0.00                     | 26.35 (14.83, 37.86)                                  | 27.73 (13.93, 41.53)                                 |
| <b>Transfusion avoidance<sup>6</sup></b>                  |                          |                                                       |                                                      |
| Unadjusted                                                | n/a                      | 20.75 (9.55, 31.94)                                   | 26.13 (12.39, 39.87)                                 |
| Age ≥65 years                                             | 0.00                     | 20.75 (9.55, 31.94)                                   | 26.13 (12.39, 39.87)                                 |
| Overweight or obese                                       | 0.00                     | 20.75 (9.55, 31.94)                                   | 26.13 (12.39, 39.87)                                 |
| Aplastic anemia                                           | 0.00                     | 20.75 (9.55, 31.94)                                   | 26.13 (12.39, 39.87)                                 |
| Impaired renal function                                   | 0.00                     | 20.75 (9.55, 31.94)                                   | 26.13 (12.39, 39.87)                                 |
| Bone marrow failure                                       | 0.00                     | 20.75 (9.55, 31.94)                                   | 26.13 (12.39, 39.87)                                 |
| Diagnosis age >36.8 years                                 | 0.00                     | 20.75 (9.55, 31.94)                                   | 26.13 (12.39, 39.87)                                 |
| GPI-deficient granulocyte clone size >70%                 | 0.00                     | 20.75 (9.55, 31.94)                                   | 26.13 (12.39, 39.87)                                 |
| GPI-deficient monocyte clone size >90%                    | 0.00                     | 20.75 (9.55, 31.94)                                   | 26.13 (12.39, 39.87)                                 |

| Endpoint <sup>1</sup>                                                   | Bias factor <sup>2</sup> | Bias factor-adjusted<br>pegcetacoplan vs. ravulizumab<br>mean (95% CI) <sup>3</sup> | Bias factor-adjusted<br>pegcetacoplan vs. eculizumab<br>mean (95% CI) <sup>3</sup> |
|-------------------------------------------------------------------------|--------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| <b>Secondary endpoints</b>                                              |                          |                                                                                     |                                                                                    |
| <b>Transfusion requirements (total number of PRBC units transfused)</b> |                          |                                                                                     |                                                                                    |
| Unadjusted                                                              | n/a                      | -4.07 (-5.69, -2.46)                                                                | -4.62 (-6.69, -2.55)                                                               |
| Age ≥65 years                                                           | -0.36                    | -3.71 (-5.33, -2.10)                                                                | -4.26 (-6.33, -2.19)                                                               |
| Overweight or obese                                                     | 0.89                     | -4.96 (-6.58, -3.35)                                                                | -5.51 (-7.58, -3.44)                                                               |
| Aplastic anemia                                                         | -0.04                    | -4.03 (-5.65, -2.42)                                                                | -4.58 (-6.65, -2.51)                                                               |
| Impaired renal function                                                 | 0.03                     | -4.10 (-5.72, -2.49)                                                                | -4.65 (-6.72, -2.58)                                                               |
| Bone marrow failure                                                     | -0.32                    | -3.75 (-5.37, -2.14)                                                                | -4.30 (-6.37, -2.23)                                                               |
| Diagnosis age >36.8 years                                               | 2.51                     | -6.58 (-8.20, -4.97)                                                                | -7.13 (-9.20, -5.06)                                                               |
| GPI-deficient granulocyte clone size >70%                               | -1.27                    | -2.80 (-4.42, -1.19)                                                                | -3.35 (-5.42, -1.28)                                                               |
| GPI-deficient monocyte clone size >90%                                  | 0.56                     | -4.63 (-6.25, -3.02)                                                                | -5.18 (-7.25, -3.11)                                                               |
| <b>Time to first LDH normalization<sup>7</sup>, days</b>                |                          |                                                                                     |                                                                                    |
| Unadjusted                                                              | n/a                      | -8.29 (-12.30, -4.29)                                                               | -13.07 (-22.94, -3.20)                                                             |
| Age ≥65 years                                                           | 0.81                     | -9.10 (-13.11, -5.10)                                                               | -13.88 (-23.75, -4.01)                                                             |
| Overweight or obese                                                     | 9.18                     | -17.47 (-21.48, -13.47)                                                             | -22.25 (-32.12, -12.38)                                                            |
| Aplastic anemia                                                         | 0.56                     | -8.85 (-12.86, -4.85)                                                               | -13.63 (-23.50, -3.76)                                                             |
| Impaired renal function                                                 | 0.85                     | -9.14 (-13.15, -5.14)                                                               | -13.92 (-23.79, -4.05)                                                             |
| Bone marrow failure                                                     | 0.64                     | -8.93 (-12.94, -4.93)                                                               | -13.71 (-23.58, -3.84)                                                             |
| Diagnosis age >36.8 years                                               | 0.99                     | -9.28 (-13.29, -5.28)                                                               | -14.06 (-23.93, -4.19)                                                             |
| GPI-deficient granulocyte clone size >70%                               | 1.05                     | -9.34 (-13.35, -5.34)                                                               | -14.12 (-23.99, -4.25)                                                             |
| GPI-deficient monocyte clone size >90%                                  | 0.93                     | -9.22 (-13.23, -5.22)                                                               | -14.00 (-23.87, -4.13)                                                             |
| <b>Breakthrough hemolysis<sup>8</sup></b>                               |                          |                                                                                     |                                                                                    |
| Unadjusted                                                              | n/a                      | -4.00 (-7.44, -0.56)                                                                | -10.70 (-16.21, -5.19)                                                             |
| Age ≥65 years                                                           | 0.00                     | -4.00 (-7.44, -0.56)                                                                | -10.70 (-16.21, -5.19)                                                             |
| Overweight or obese                                                     | 0.00                     | -4.00 (-7.44, -0.56)                                                                | -10.70 (-16.21, -5.19)                                                             |
| Aplastic anemia                                                         | 0.00                     | -4.00 (-7.44, -0.56)                                                                | -10.70 (-16.21, -5.19)                                                             |
| Impaired renal function                                                 | 0.00                     | -4.00 (-7.44, -0.56)                                                                | -10.70 (-16.21, -5.19)                                                             |
| Bone marrow failure                                                     | 0.00                     | -4.00 (-7.44, -0.56)                                                                | -10.70 (-16.21, -5.19)                                                             |
| Diagnosis age >36.8 years                                               | 0.00                     | -4.00 (-7.44, -0.56)                                                                | -10.70 (-16.21, -5.19)                                                             |
| GPI-deficient granulocyte clone size >70%                               | 0.00                     | -4.00 (-7.44, -0.56)                                                                | -10.70 (-16.21, -5.19)                                                             |
| GPI-deficient monocyte clone size >90%                                  | 0.00                     | -4.00 (-7.44, -0.56)                                                                | -10.70 (-16.21, -5.19)                                                             |
| <b>MAVEs</b>                                                            |                          |                                                                                     |                                                                                    |
| Unadjusted                                                              | n/a                      | -1.60 (-3.80, 0.60)                                                                 | -0.83 (-2.44, 0.79)                                                                |
| Age ≥65 years                                                           | 0.00                     | -1.60 (-3.80, 0.60)                                                                 | -0.83 (-2.44, 0.79)                                                                |
| Overweight or obese                                                     | 0.00                     | -1.60 (-3.80, 0.60)                                                                 | -0.83 (-2.44, 0.79)                                                                |
| Aplastic anemia                                                         | 0.00                     | -1.60 (-3.80, 0.60)                                                                 | -0.83 (-2.44, 0.79)                                                                |

| Endpoint <sup>1</sup>                                               | Bias factor <sup>2</sup> | Bias factor-adjusted<br>pegcetacoplan vs. ravulizumab<br>mean (95% CI) <sup>3</sup> | Bias factor-adjusted<br>pegcetacoplan vs. eculizumab<br>mean (95% CI) <sup>3</sup> |
|---------------------------------------------------------------------|--------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Impaired renal function                                             | 0.00                     | -1.60 (-3.80, 0.60)                                                                 | -0.83 (-2.44, 0.79)                                                                |
| Bone marrow failure                                                 | 0.00                     | -1.60 (-3.80, 0.60)                                                                 | -0.83 (-2.44, 0.79)                                                                |
| Diagnosis age >36.8 years                                           | 0.00                     | -1.60 (-3.80, 0.60)                                                                 | -0.83 (-2.44, 0.79)                                                                |
| GPI-deficient granulocyte clone size >70%                           | 0.00                     | -1.60 (-3.80, 0.60)                                                                 | -0.83 (-2.44, 0.79)                                                                |
| GPI-deficient monocyte clone size >90%                              | 0.00                     | -1.60 (-3.80, 0.60)                                                                 | -0.83 (-2.44, 0.79)                                                                |
| <b>FACIT-Fatigue score (change from baseline)</b>                   |                          |                                                                                     |                                                                                    |
| Unadjusted                                                          | n/a                      | 2.70 (-2.38, 7.79)                                                                  | 3.60 (-1.50, 8.69)                                                                 |
| Age ≥65 years                                                       | -3.52                    | 6.22 (1.14, 11.31)                                                                  | 7.12 (2.02, 12.21)                                                                 |
| Overweight or obese                                                 | -0.63                    | 3.33 (-1.75, 8.42)                                                                  | 4.23 (-0.87, 9.32)                                                                 |
| Aplastic anemia                                                     | -2.70                    | 5.40 (0.32, 10.49)                                                                  | 6.30 (1.20, 11.39)                                                                 |
| Impaired renal function                                             | 1.62                     | 1.08 (-4.00, 6.17)                                                                  | 1.98 (-3.12, 7.07)                                                                 |
| Bone marrow failure                                                 | -2.42                    | 5.12 (0.04, 10.21)                                                                  | 6.02 (0.92, 11.11)                                                                 |
| Diagnosis age >36.8 years                                           | 1.02                     | 1.68 (-3.40, 6.77)                                                                  | 2.58 (-2.52, 7.67)                                                                 |
| GPI-deficient granulocyte clone size >70%                           | 1.05                     | 1.65 (-3.43, 6.74)                                                                  | 2.55 (-2.55, 7.64)                                                                 |
| GPI-deficient monocyte clone size >90%                              | -3.78                    | 6.48 (1.40, 11.57)                                                                  | 7.38 (2.28, 12.47)                                                                 |
| <b>General health status (EORTC QLQ-C30) (change from baseline)</b> |                          |                                                                                     |                                                                                    |
| Unadjusted                                                          | n/a                      | 12.91 (3.27, 22.56)                                                                 | 12.52 (2.60, 22.44)                                                                |
| Age ≥65 years                                                       | 0.06                     | 12.85 (3.21, 22.50)                                                                 | 12.46 (2.54, 22.38)                                                                |
| Overweight or obese                                                 | 5.27                     | 7.64 (-2.00, 17.29)                                                                 | 7.25 (-2.67, 17.17)                                                                |
| Aplastic anemia                                                     | 0.20                     | 12.71 (3.07, 22.36)                                                                 | 12.32 (2.40, 22.24)                                                                |
| Impaired renal function                                             | 0.32                     | 12.59 (2.95, 22.24)                                                                 | 12.20 (2.28, 22.12)                                                                |
| Bone marrow failure                                                 | -0.44                    | 13.35 (3.71, 23.00)                                                                 | 12.96 (3.04, 22.88)                                                                |
| Diagnosis age >36.8 years                                           | -1.06                    | 13.97 (4.33, 23.62)                                                                 | 13.58 (3.66, 23.50)                                                                |
| GPI-deficient granulocyte clone size >70%                           | -3.64                    | 16.55 (6.91, 26.20)                                                                 | 16.16 (6.24, 26.08)                                                                |
| GPI-deficient monocyte clone size >90%                              | -1.84                    | 14.75 (5.11, 24.40)                                                                 | 14.36 (4.44, 24.28)                                                                |
| <b>Physical functioning (EORTC QLQ-C30) (change from baseline)</b>  |                          |                                                                                     |                                                                                    |
| Unadjusted                                                          | n/a                      | -5.56 (-11.53, 0.42)                                                                | -3.82 (-9.96, 2.31)                                                                |
| Age ≥65 years                                                       | 1.75                     | -7.31 (-13.28, -1.33)                                                               | -5.57 (-11.71, 0.56)                                                               |
| Overweight or obese                                                 | -2.08                    | -3.48 (-9.45, 2.50)                                                                 | -1.74 (-7.88, 4.39)                                                                |
| Aplastic anemia                                                     | -4.07                    | -1.49 (-7.46, 4.49)                                                                 | 0.25 (-5.89, 6.38)                                                                 |
| Impaired renal function                                             | 6.07                     | -11.63 (-17.60, -5.65)                                                              | -9.89 (-16.03, -3.76)                                                              |
| Bone marrow failure                                                 | -6.75                    | 1.19 (-4.78, 7.17)                                                                  | 2.93 (-3.21, 9.06)                                                                 |
| Diagnosis age >36.8 years                                           | 9.73                     | -15.29 (-21.26, -9.31)                                                              | -13.55 (-19.69, -7.42)                                                             |
| GPI-deficient granulocyte clone size >70%                           | 6.16                     | -11.72 (-17.69, -5.74)                                                              | -9.98 (-16.12, -3.85)                                                              |
| GPI-deficient monocyte clone size >90%                              | -12.27                   | 6.71 (0.74, 12.69)                                                                  | 8.45 (2.31, 14.58)                                                                 |

| Endpoint <sup>1</sup>                                          | Bias factor <sup>2</sup> | Bias factor-adjusted<br>pegcetacoplan vs. ravulizumab<br>mean (95% CI) <sup>3</sup> | Bias factor-adjusted<br>pegcetacoplan vs. eculizumab<br>mean (95% CI) <sup>3</sup> |
|----------------------------------------------------------------|--------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| <b>Fatigue symptoms (EORTC QLQ-C30) (change from baseline)</b> |                          |                                                                                     |                                                                                    |
| <b>Unadjusted</b>                                              | n/a                      | <i>-4.36 (-16.64, 7.93)</i>                                                         | <i>-7.33 (-20.79, 6.13)</i>                                                        |
| Age ≥65 years                                                  | -18.50                   | 14.14 (1.86, 26.43)                                                                 | <i>11.17 (-2.29, 24.63)</i>                                                        |
| Overweight or obese                                            | 7.52                     | -11.88 (-24.16, 0.41)                                                               | -14.85 (-28.31, -1.39)                                                             |
| Aplastic anemia                                                | 1.45                     | <i>-5.81 (-18.09, 6.48)</i>                                                         | <i>-8.78 (-22.24, 4.68)</i>                                                        |
| Impaired renal function                                        | -2.76                    | <i>-1.60 (-13.88, 10.69)</i>                                                        | <i>-4.57 (-18.03, 8.89)</i>                                                        |
| Bone marrow failure                                            | 4.76                     | <i>-9.12 (-21.40, 3.17)</i>                                                         | <i>-12.09 (-25.55, 1.37)</i>                                                       |
| Diagnosis age >36.8 years                                      | -7.15                    | <i>2.79 (-9.49, 15.08)</i>                                                          | <i>-0.18 (-13.64, 13.28)</i>                                                       |
| GPI-deficient granulocyte clone size >70%                      | -3.11                    | <i>-1.25 (-13.53, 11.04)</i>                                                        | <i>-4.22 (-17.68, 9.24)</i>                                                        |
| GPI-deficient monocyte clone size >90%                         | 37.61                    | -41.97 (-54.25, -29.68)                                                             | -44.94 (-58.40, -31.48)                                                            |

**Abbreviations:** CI, confidence interval; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; GPI, glucose phosphate isomerase; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; n/a, not available; PRBC, packed red blood cell; ULN, upper limit of normal.

**Notes:**

1. The following baseline characteristics were used for weighting: Asian race, age at first infusion, female sex, and baseline EORTC QLQ-C30 general health score.
2. Bias factor estimates were derived using population-level proportions found in the literature. The proportions assumed for this table were as follows: age at first infusion >65 years, 12.8%; overweight or obese, 50.8%; aplastic anemia, 59.1%; impaired renal function, 31.7%; bone marrow failure, 62.6%; age at diagnosis >36.8 years, 50%; GPI-deficient granulocyte clone size >70%, 76.9%; GPI-deficient monocyte clone size >90%, 45.2%. Sensitivity analyses were performed on bias factor-adjusted estimates by varying population prevalence values; results are shown in Table 6.
3. Italics indicate CI's that overlap with zero.
4. LDH normalization was defined as LDH <1× ULN (246 U/l) in the absence of transfusions during the randomized controlled period.
5. Hemoglobin stabilization was defined as avoidance of a ≥2 g/dl decrease in hemoglobin level in the absence of transfusions during the randomized controlled period.
6. Transfusions received during the randomized controlled period.
7. Time to first LDH normalization in days were median values from the ALXN1210-PNH-301 study.
8. The required reporting for breakthrough hemolysis differed between the PRINCE and ALXN1210-PNH-301 studies, where the PRINCE study required reports from both scheduled and unscheduled visits and the ALXN1210-PNH-301 study only required reports from scheduled visits.

## References

1. Jiang Y, Ni W. Performance of unanchored matching-adjusted indirect comparison (MAIC) for the evidence synthesis of single-arm trials with time-to-event outcomes. *BMC Med Res Methodol* 20, 241 (2020).
2. VanderWeele TJ, Mathur MB, Chen Y. Outcome-Wide Longitudinal Designs for Causal Inference: A New Template for Empirical Studies. *Statistical Science* 35(3) (2020)