P839 PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA TREATED WITH PEGCETACOPLAN SHOW IMPROVEMENTS IN D-DIMER NORMALIZATION AND DECREASE IN INCIDENCE OF THROMBOSIS

**Topic:** 12. Bone marrow failure syndromes incl. PNH - Clinical

Ilene Weitz¹, Mohammed Al-Adhami², Jinny Min², Emmelie Persson³, Michael Yeh², Jessica Savage², David Dingli⁴

¹ Jane Anne Nohl Division of Hematology, Keck-USC School of Medicine, Los Angeles, United States;² Apellis Pharmaceuticals, Waltham, United States;³ Swedish Orphan Biovitrum AB, Stockholm, Sweden;⁴ Mayo Clinic, Rochester, United States

**Background:** Thrombosis is the main life-threatening complication of paroxysmal nocturnal hemoglobinuria (PNH), a rare acquired hematologic disease. Pegcetacoplan (PEG) is a C3 complement-inhibitor approved by the FDA/EMA for treatment of adults with PNH.

**Aims:** This post hoc analysis examined incidence of thrombosis, anti-thrombotic therapy (ATT), and D-dimer normalization in adult patients with PNH treated with PEG in the Phase 3 PEGASUS (NCT03500549) and PRINCE (NCT04085601) studies.

**Methods:** PEGASUS enrolled adult patients with PNH with prior suboptimal response to eculizumab (ECU) despite stable ECU treatment (≥3 months) and hemoglobin (Hb) levels ≤10.5 g/dL at screening. For the randomized controlled period (RCP), patients were randomized 1:1 to ECU (n=39) or PEG (n=41; 1080 mg subcutaneously [sc] 2x weekly) for 16 weeks. Thereafter, ECU patients were switched to PEG monotherapy and PEG RCP patients remained on PEG during the open-label period (OLP, n=77) through Week 48. PRINCE compared PEG treatment (n=35; 1080 mg sc 2x weekly) in complement-inhibitor-naïve patients to patients receiving control treatment (CTRL; excluding complement-inhibitors i.e., ECU/ravulizumab; n=18). CTRL patients had the option to escape to the PEG group if Hb levels decreased ≥2 g/dL from baseline (n=11). Safety analyses in all trials included monitoring of thrombotic events. D-dimer normalization, defined as D-dimer level less than the upper limit of normal (0.5 µg/mL) was examined at baseline, Week 8, and the end of the study period (PEGASUS: 16 weeks [RCP] and 48 weeks [OLP], PRINCE: 26 weeks).

**Results:** Prior to study entry, 31% (n=25) of PEGASUS patients (6 of these while on ECU therapy) and 9% (n=5) of PRINCE patients experienced at least one type of thrombosis. During the PEGASUS OLP, 2 of 77 patients experienced a thrombotic event, one in the setting of non-Hodgkin’s lymphoma and one during sepsis; neither event was deemed related to PEG. No patients in the PEGASUS RCP or PRINCE trial experienced a thrombotic event.

Pooled analysis of completed clinical trials of PEG including PEGASUS and PRINCE indicated there were 2 cases of thrombosis in 164 patients comprising 130 patient-years (1.54 events per 100 patient-years), compared to 1.77 events per 100 patient-years for patients on ECU treatment before entry into PEGASUS.

In PEGASUS, 34% (n=27) of patients were on ATT prior to study entry. During the PEGASUS RCP, concomitant ATT was observed in 37% (PEG, n=15) and 33% (ECU, n=13) of patients, and during the PEGASUS-OLP in 23% (n=18) of patients (PEG monotherapy). In PRINCE, concomitant ATT decreased from 21% (n=11) prior to the study to 7% (PEG, n=3) and 0% (CTRL, n=0) during the study.

In PEGASUS, D-dimer normalization in the PEG arm increased from 73% (baseline, n=30) to 89% (Week 8, n=33)
and was largely sustained at Week 16 and Week 48 (Table 1). D-dimer normalization in the ECU arm increased once ECU patients switched to PEG monotherapy, from 76% (Week 16, n=29) to 89% (Week 48, n=17) (Table 1). In PRINCE, D-dimer normalization in the PEG arm increased from 51% (baseline, n=18) to 67% (Week 8, n=18) and increased further to 68% (n=19) at Week 26 (Table 1).

### Table 1. D-dimer Normalization in PEGASUS and PRINCE

|          | Baseline, n/N (%) | Week 8, n/N (%) | End of study period, n/N (%) |
|----------|-------------------|----------------|------------------------------|
|          |                   |                | Week 16 (ECU) | Week 48 (OLP) |
| **PEGASUS** |                   |                | ECU, n=41 | PEG, n=39 |
| RCP group |                   |                | 20/41 (72%) | 33/37 (89%) |
| ECU      |                   |                | 29/32 (90%) | 26/28 (92%) |
| **PRINCE** |                   |                |               |               |
| Treatment group |                   |                | 7/11 (63%) | 3/4 (75%) |
| CTRL N=7 to 15 |                   |                | 19/35 (54%) | 19/37 (57%) |
| CTRL escape to PEG N=11 |                   |                | 2/6 (22%) | 3/11 (27%) |
| Last measure before escape |                   |                | 3/11 (27%) | 0/11 (0%) |
| First measure after escape |                   |                | 6/6 (100%) | 5/5 (100%) |

* n is the number of patients with available lab readings at each time point
* Includes patients randomized to prophylactic treatment and patients who had escaped from the control arm to prophylaxis during treatment at each time point.

**Summary/Conclusion:** Overall, these results demonstrate that PEG treatment can increase D-dimer normalization and reduces incidence of thrombotic events in patients with PNH who are complement-inhibitor naïve or remained anemic after ECU treatment, suggesting that PEG treatment is as effective as ECU in these outcomes.