

CONCLUSIONS

- ✓ PEGASUS trial injection site reactions (ISRs) observed with pegcetacoplan treatment decreased over time as patients became more comfortable and experienced with self-injection
- ✓ Injection site reactions were often mild or manageable; pegcetacoplan-treated patients, on average, reported higher quality of life than eculizumab-treated patients, indicating that these events are likely not a barrier to treatment
- ✓ Comparable trends for reported ISRs have been observed with drugs delivered similarly to pegcetacoplan; management strategies for ISRs with these drugs may potentially be useful for reactions observed with pegcetacoplan

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired, rare, chronic, potentially life-threatening hematologic disease

- Pegcetacoplan (PEG) is a C3-complement inhibitor recently approved by the FDA for the treatment of PNH
- PEG was superior to eculizumab (ECU; C5-inhibitor) in improving hemoglobin (Hb) levels at Week 16 in patients with suboptimal response to prior ECU treatment (Phase 3 PEGASUS trial NCT03500549).
- PEG is self-administered subcutaneously with an injection volume of 10 mL at each of two distinct sites, which may lead to injection site reactions (ISRs) relating to the injection volume, frequency, or molecular structure

OBJECTIVE

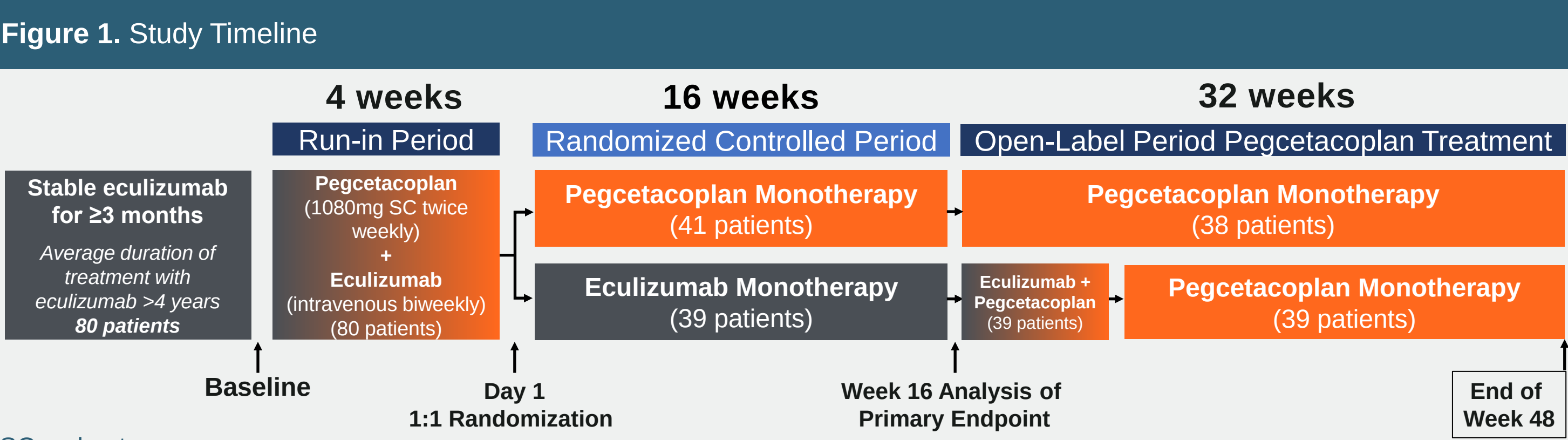
We report detailed ISR safety outcomes from the PEGASUS trial along with an analysis of ISRs and management strategies for treatments administered similarly to PEG, from published literature.

METHODS

The PEGASUS trial (NCT03500549) was an open-label, head-to-head trial of PEG (twice weekly subcutaneous injections of 1080 mg) compared with intravenously administered ECU in adults with PNH (**Figure 1**) who were on ECU treatment ≥3 months and had Hb levels <10.5 g/dL.

All patients completed a 4-week run-in with ECU+PEG before 1:1 randomization to PEG (n=41) or ECU monotherapy (n=39). After the randomized control period (RCP), PEG patients could continue directly to the 32-week PEG monotherapy open-label period (OLP) (PEG-to-PEG). ECU patients completed a 4-week run-in prior to continuing to the PEG monotherapy OLP through Week 48 (ECU-to-PEG).

- PEGASUS trial endpoints:
 - Primary endpoints included change from baseline in Hb level at Week 16
 - Secondary endpoints included ISR and adverse event (AE) monitoring
- Situational analysis was performed to identify subcutaneously administered therapies with injection volume similar to PEG (≥10 mL) or PEGylation (with ≥0.5 mL injections) in order to compare to ISR incidences in PEGASUS
- ISR management strategies reported with identified drugs were evaluated from the prescribing information and published literature



SC, subcutaneous

RESULTS

PEGASUS 48-Week Treatment Emergent AEs (TEAEs) and Injection Site Reaction (ISR) Incidences

- Incidences of TEAEs were comparable across the PEGASUS study periods:
 - Combined run-in periods: 71 patients (89%)
 - RCP: 36 PEG patients (88%) and 36 ECU patients (92%)
 - OLP: 33 PEG-to-PEG patients (87%) and 37 ECU-to-PEG patients (95%)
- Most ISRs occurred during treatment initiation. In the combined RIP 59% of patients experienced ISRs, compared to 37% in the RCP; in the OLP, 33% of ECU-to-PEG and 18% of PEG-to-PEG patients experienced ISRs (**Table 1**)
- In the total cohort, most ISRs were mild; there were a few moderate ISRs (3 in RIP, 1 in RCP in PEG group, and 2 in OLP [1 in ECU-to-PEG group, 1 in PEG-to-PEG group])
- No ISR TEAEs were serious (requiring medical intervention), severe (medically significant but not immediately life-threatening), or led to study drug discontinuation

Table 1. Injection Site Reaction (ISR) Severity and Injection Site Reactions (ISRs) Occurring in ≥5% of Patients Within Any Treatment Group by System Organ Class and Preferred Term, by Study Periods and Treatment Group

Study Period	RIP	RCP		OLP	
Therapy	PEG+ECU ^a	ECU	PEG	ECU-to-PEG	PEG-to-PEG
N	80	39	41	39	38
Any ISR TEAE, n (%) ^b	47 (58.8)	1 (2.6)	15 (36.6)	13 (33.3)	7 (18.4)
Mild	44 (55.0)	1 (2.6)	14 (34.1)	12 (30.8)	6 (15.8)
Moderate	3 (3.8)	0 (0.0)	1 (2.4)	1 (2.6)	1 (2.6)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
System Organ Class/ Preferred Term					
General Disorders and Administration Site Conditions ^c , n (%)	47 (58.8)	1 (2.6)	15 (36.6)	13 (33.3)	7 (18.4)
Injection site erythema ^d , n (%)	33 (41.3)	0 (0.0)	7 (17.1)	6 (15.4)	3 (7.9)
Injection site pruritus ^d , n (%)	12 (15.0)	0 (0.0)	1 (2.4)	4 (10.3)	1 (2.6)
Injection site bruising ^d , n (%)	1 (1.3)	0 (0.0)	2 (4.9)	2 (5.1)	1 (2.6)
Injection site induration ^d , n (%)	5 (6.3)	0 (0.0)	3 (7.3)	2 (5.1)	3 (7.9)
Injection site reaction ^d , n (%)	8 (10.0)	0 (0.0)	4 (9.8)	1 (2.6)	1 (2.6)
Injection site swelling ^d , n (%)	10 (12.5)	0 (0.0)	4 (9.8)	1 (2.6)	0 (0.0)
Injection site pain ^d , n (%)	6 (7.5)	0 (0.0)	1 (2.4)	2 (5.1)	2 (5.3)
Injection site hemorrhage ^d , n (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.7)	0 (0.0)

^a Includes the run-in period and the open-label run-in period
^b Data is presented as n = number of patients reporting that type of event (% of patients). Patients could report more than one event.
^c Medical dictionary for regulatory affairs (MedDRA): System organ class
^d MedDRA: Preferred term
ECU, eculizumab; ECU-to-PEG, patients received eculizumab during the randomized controlled period and switched to pegcetacoplan during the open-label period after a 4-week run-in; ISR, injection site reaction; OLP, open-label period; PEG, pegcetacoplan; PEG-to-PEG, patients received pegcetacoplan during the randomized controlled period and continued through Week 48 of the open-label period; RCP, randomized controlled period; RIP, run-in period; TEAE, treatment emergent adverse event

RESULTS, continued

Situational Analysis of Drugs Similar to Pegcetacoplan (PEG)

Reported ISR incidences from published literature varied between evaluated drugs (1-67%) but were generally mild, resolved quickly, and decreased following the initial treatment (**Table 2**).

Table 2. Situational Analysis of Injection Site Reactions (ISRs)

Drug name	Drug type	Volume per site (mL)	Delivery	Frequency	Most frequent ISRs ^a	ISR incidence
Pegcetacoplan ^b	PEGylated peptide	~10	20-40 min over 2 sites	Twice weekly	Erythema, pruritus ^c	36% ^c
Immunoglobulin with hyaluronidase	Immunoglobulin	≤600	~1-2 mL/min over 2 sites	Monthly	Discomfort, pain, erythema	38-65% ¹⁻³
Deferoxamine	Small molecule	10-20	Continuous pump over 8-24 hours	Daily	Pain, swelling, reddening	45% ⁴
Daratumumab and hyaluronidase	Monoclonal antibody	15	Injected over 3-5 min	Weekly to monthly	Erythema, itching, swelling	11-67% ⁵⁻⁷
Certolizumab pegol ^b	PEGylated antibody fragment	~1	Short injections at up to 2 sites	Monthly	Erythema, bruising, discoloration	1-10% ⁸⁻¹⁰
Pegfilgrastim ^b	PEGylated growth factor	0.6	Single injection at 1 site	Once per chemotherapy cycle	Pain, redness	8% ¹¹

^a Per prescribing information
^b PEGylated molecule
^c From PEGASUS pegcetacoplan monotherapy across randomized controlled period and open-label period
ISR, injection site reaction

Injection Site Reaction (ISR) Management Strategies from Published Literature
Prevention or management strategies for ISRs included ice packs, injection site rotation, education, and empowering patients to gain comfort in self-administration through training and other initiatives (**Figure 2**). Management strategies for ISRs with these drugs may potentially be useful for ISRs observed with PEG.

Figure 2. A Review of Injection Site Reaction (ISR) Prevention and Management Strategies from the Published Literature

