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Safety and Efficacy of Long-Term Treatment of Type 1 Plasminogen Deficient Patients With Intravenous Plasminogen Replacement Therapy

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ABSTRACT

Introduction: Type 1 plasminogen deficiency (PLGD-1), or hypoplasminogenaemia, is an ultra-rare autosomal-recessive disorder characterised by fibrin-rich lesions on mucous membranes, often leading to serious complications if left untreated. Prior treatments have shown limited and inconsistent success, but IV PLG concentrate (Ryplazim) offers a targeted therapy.

Aim: This study investigated the long-term safety and efficacy of IV PLG concentrate treatment for PLGD-1 patients.

Methods: A long-term study (NCT03642691) followed 12 participants who had previously been included in pivotal or expanded access trials of IV PLG concentrate. Participants received 6.6 mg/kg IV PLG concentrate infusions, with dosing frequency adjusted based on clinical response and plasminogen levels. Safety assessments and plasminogen level measurements were conducted.

Results: The median treatment duration during this long-term follow-up study was 41 months (range: 25–42 months). The median total exposure for participants in this study throughout the clinical development was 68 months (range: 28–71 months). No new or recurring ligneous lesions occurred when participants adhered to the prescribed regimen. Temporary disruptions in the drug supply led to some lesion recurrences, which resolved upon resuming the prescribed dosing frequency. A total of 2165 infusions were administered in this study, and most adverse events were mild. No anti-plasminogen antibodies or treatment-related fatalities occurred.

Conclusion: Long-term treatment with IV PLG concentrate is safe and effective for PLGD-1, demonstrating the potential for tailored dosing regimens. This study highlights the importance of individualised treatment and provides valuable insights into managing this ultra-rare disorder.

Summary

- Type 1 plasminogen deficiency (PLGD-1), also known as hypoplasminogenaemia, is a very rare genetic disorder where the body does not produce enough plasminogen, an important protein involved in breaking down clots and in other important functions in the body. This condition leads to the formation of lesions rich in fibrin (a key protein in your blood that forms a sticky network of fibres when you get an injury, acting like a glue to stop bleeding by creating a clot at the wound or injury site) on mucous membranes (the moist inner lining) of many systems of the body including eyes, ears, nose, mouth and respiratory, gastrointestinal, genital and urinary systems, which can cause serious health problems. Previous treatment options have had limited success.
- This study evaluated the long-term safety and effectiveness of an intravenous plasminogen concentrate for PLGD-1. It included 12 participants, who were followed for a median of 41 months after participating in earlier trials (median of total exposure was 68 months). All participants received regular infusions of plasminogen concentrate, with the frequency adjusted based upon their symptoms, plasminogen levels and product availability.
- The results showed that when patients followed their prescribed treatment schedule, no new or recurring lesions occurred. If treatment was interrupted, lesions reappeared but resolved once treatment resumed. Across more than 2100 infusions, the medication was well-tolerated, with only mild side effects reported and no anti-plasminogen antibodies or serious complications were observed.
- This research demonstrates that long-term treatment with plasminogen concentrate is both safe and effective for managing PLGD-1. It highlights the importance of personalised treatment plans for this ultra-rare condition, offering hope to affected patients.

1 | Introduction

Type 1 plasminogen deficiency (PLGD-1), also known as hypoplasminogenaemia, is an ultra-rare autosomal recessive disorder with an estimated prevalence of symptomatic cases of approximately 1.6 per million individuals [1]. PLGD-1 is caused by pathogenic variants in the *PLG* gene, which encodes plasminogen [2], a key regulator of fibrinolysis, inflammation, wound healing and tissue remodelling [3, 4]. Plasminogen circulates in an inactive zymogen form.

Upon binding to cross-linked fibrin or the cell surface, plasminogen is cleaved and activated by tissue plasminogen activator or urinary plasminogen activator, resulting in the formation of the serine protease plasmin. Plasmin regulates fibrinolysis through fibrin degradation within blood clots and fibrin-rich deposits in the extravascular milieu.

PLGD-1 is a chronic condition that intermittently or continuously affects multiple systems and is characterised by the formation of fibrin-rich lesions on mucosa throughout the body [5]. These lesions often occur at sites of injury, infection, or surgery where the normal wound-healing process is impaired due to insufficient plasminogen activity [1, 6, 7]. The most prevalent symptom of PLGD-1 is ligneous conjunctivitis, characterised by the development of woody, inflamed growths on the conjunctival membranes of the eyes [1, 7-18]. If left untreated, this condition can lead to visual impairment or blindness. Lesions may additionally occur in the respiratory tract, oropharynx/gingiva, ears, central nervous system (CNS), genitourinary tract and gastrointestinal tract [1, 2, 5, 14, 19-21]. These lesions can lead to complications such as respiratory compromise or failure, tooth loss, hearing loss, hydrocephalus, infertility, renal impairment, as well as abdominal pain and diarrhoea.

Several therapies for treating ligneous lesions associated with PLGD-1 have been evaluated. Some treatments designed to alleviate symptoms rather than address the underlying plasminogen deficiency have shown limited or inconsistent success [5, 19]. Fresh frozen plasma has occasionally been used to elevate plasminogen levels; however, in many instances, the plasminogen concentration in these products is insufficient to restore plasminogen to normal physiologic levels. There are also risks of transfusion-related infections and reactions, as well as the potential for volume overload [9, 22]. Plasminogen eye drops effectively treated ocular manifestations and prevented lesion regrowth after surgical removal, but they are not yet commercially available. Additionally, topical plasminogen applications are insufficient for treating systemic conditions [17].

In 2021, the US Food and Drug Administration (FDA) authorised IV PLG concentrate (Kedrion Biopharma, Inc., New Jersey, USA), a purified plasminogen derived from human plasma, as the first specific treatment for PLGD-1 [23]. The pivotal Phase 2/3 trial included 15 paediatric and adult participants who completed up to 124 weeks of IV PLG concentrate treatment. This therapy improved clinical symptoms and reduced or resolved fibrin-rich lesions by increasing circulating plasminogen levels [24, 25].

Plasminogen replacement therapy has become the primary treatment for PLGD-1 in regions where it is approved and available. Still, managing PLGD-1 requires a multidisciplinary approach and careful consideration of patient needs. Individualised therapeutic plans and routine monitoring are essential, given the variability in disease presentation and response to treatment [24–26]. This paper explores the safety, efficacy and individualised treatment responses of 12 participants who received long-term IV PLG concentrate treatment for PLGD-1. This research expands our understanding of the safety and efficacy of this newly approved drug and provides new examples of how dose frequency can be tailored to meet patient needs.

2 | Materials and Methods

2.1 | IV PLG Concentrate Clinical Development

This is a long-term repeat-dose investigation of adult and paediatric PLGD-1 participants in the United States receiving IV PLG concentrate therapy. The participants had previously completed the End of Study visit in either the Phase 2/3 pivotal trial 2002C0011G (NCT02690714) or in individual expanded

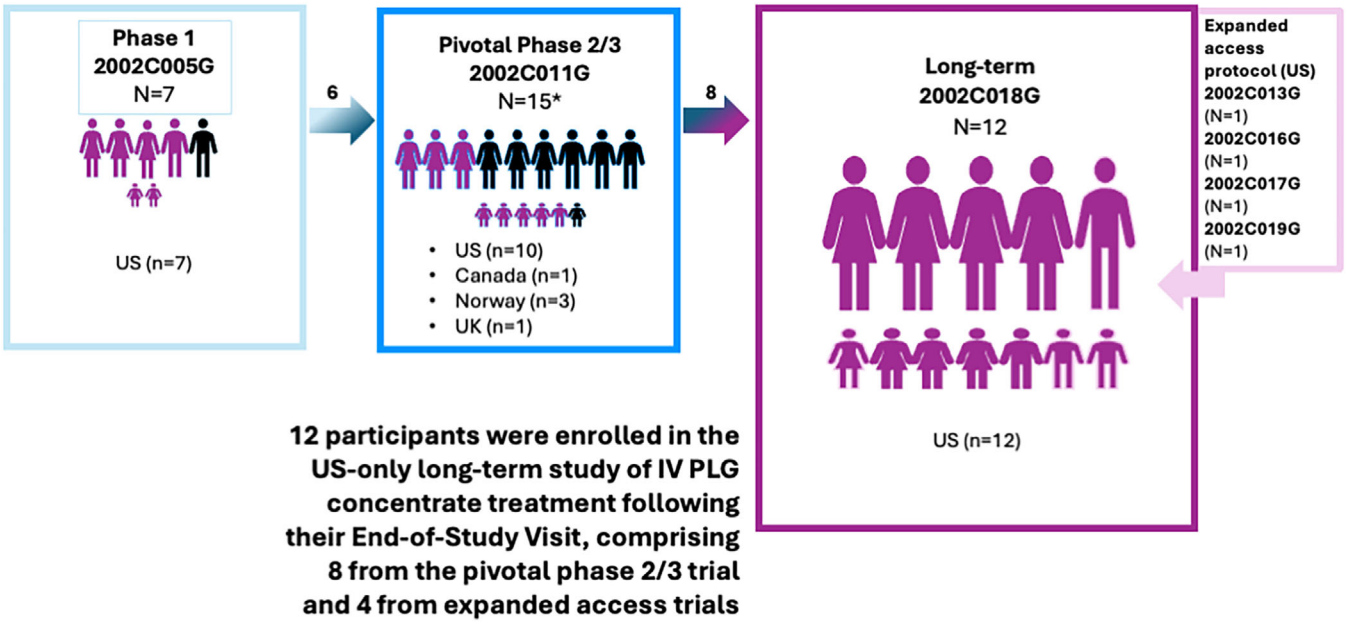

FIGURE 1 | Clinical development of IV PLG concentrate. The purple colour denotes participants who continued into the subsequent trial. Adults were ≥18 years old, whilst participants <18 years were designated as children *Six participants from the Phase 1 trial continued into the Phase 2/3 pivotal trial of IV PLG concentrate. Two participants discontinued the study after 84 weeks and 117 weeks of IV PLG concentrate treatment due to non-compliance.

access trials 2002C013G, 2002C016G, 2002C017G and 2002C019G (NCT0364291). The clinical development program for IV PLG concentrate is illustrated in Figure 1. One adult from the Phase 1 trial did not continue into the international Phase 2/3 pivotal trial of IV PLG concentrate. Four adults and four children transitioned from the Phase 2/3 study, and one adult and three children who had received IV PLG concentrate treatment through expanded access protocols were enrolled in the long-term maintenance study 2002C018G (NCT03642691) described in this paper. The expanded access protocols allowed treatment for patients who were not eligible for the pivotal Phase 2/3 study, either because they received the drug prior to its start or after enrolment had closed. This ensured that these patients had access to the drug as quickly as possible.

2.2 | Study Design

A long-term study of IV PLG concentrate treatment (NCT03642691) efficacy and safety was conducted at three US locations (California, Indiana and Tennessee) from September 2018 to April 2022. Twelve participants received IV PLG concentrate at a dose of 6.6 mg/kg at an initial frequency of every 3–7 days. Each infusion lasted 10–30 min and was performed at home or during study site visits. The site investigators adjusted the dosing frequency based on clinical response, plasminogen activity trough levels and the availability of IV PLG concentrate. During the clinical development program, there were two brief delays in manufacturing the IV PLG concentrate, which affected the availability of the investigational drug. The study protocol indicated that safety assessments and measurements of plasminogen levels were to take place at the study site every 26 weeks; however, due to the COVID-19 pandemic, remote assessments were conducted at the investigators' discretion. Treatment was continued until FDA approval of Ryplazim, the licensed IV PLG concentrate product. Inclusion criteria required that participants had completed the End of Study visit in a prior IV PLG concentrate clinical trial, either the Phase 2/3 pivotal trial or expanded access studies, receiving 6.6 mg/kg of plasminogen every 1–7 days.

2.3 | Laboratory Assays

The quantitative determination of human plasminogen activity in plasma was performed using Diagnostica Stago's STA-STACHROM Plasminogen kit (cat# 00658). Human plasminogen antigen in plasma was quantified using the Cell Sciences Human Plasminogen Total Antigen enzyme-linked immunosorbent assay kit (cat# CSI19819A). Laboratory assays were previously described in detail [24, 25].

3 | Results

3.1 | Participants Treated With IV PLG Concentrate

During the Phase 1 and 2/3 clinical trials, expanded access programs, and compassionate use programs, 29 participants underwent treatment with IV PLG concentrate (Figure 1). The pivotal Phase 2/3 trial included 15 participants with baseline plasminogen activity levels of <5%–43% of the normal range. This report presents findings from a long-term safety and efficacy study involving 12 participants, including 8 who continued from the pivotal trial and 4 who received IV PLG concentrate treatment through expanded access protocols.

TABLE 1 | Baseline characteristics: Lesion presentation during pivotal or expanded access trials.

Original trial	Participant ID/sex	Age at 1st dose[a]	Endogenous plasminogen activity (%)[b]	Clinical manifestations in prior studies	
				Baseline at prior study	End of study
Pivotal trial	01-001/female	39 years	29	Both eyes, cervix	Resolved
	01-008/female	37 years	<5	Both eyes, gums, nasal-right nare	Resolved
				Bronchus, kidney,	Improved
				Genital tract	Not assessed
	01-009/female	24 years	31	Cervix	Resolved
	01-010/female	5 years	22	Right eye	Resolved
				Vagina	Improved
	01-011/female	16 years	20	Colon, vagina	Resolved
	01-012/female	11 years	17	Left eye	Resolved
				Colon	Not assessed
	01-013/male	6 years	29	No lesion	No change
	01-014/female	4 years	18	No lesion	No change
Expanded access trial	03-001/male	33 years	11	Non-healing postsurgical wound on right hand ureteral obstruction	Resolved
	02-010/female	16 months	12	Life-threatening airway involvement: stridor, hypercapnia, tachypnoea, tracheobronchial lesions, airway narrowing	Resolved
	01-015/male	16 months	<5[d]	Life-threatening airway involvement: bronchiectasis, lesions on vocal cords and main bronchi, worsening hoarseness, ligneous conjunctivitis, CNS lesions with ascites	Resolved[c]
	01-016/male	3 years	<14	Respiratory lesions, hoarseness, chronic ligneous conjunctivitis	Resolved

[a]First dose in pivotal trial or expanded access protocol; participants 01-001 and 01-008 received one or two previous doses during Phase 1 study.
[b]At baseline, normal range = 70%–130%.
[c]Bronchiectasis likely not resolved.
[d]Plasminogen activity level increased to 30% after four infusions of 10 ml/kg fresh frozen plasma (Nakar 2024).

3.2 | Participants

At the time of enrolment in the pivotal trial or expanded access program, the participant age range was 16 months–39 years, comprising 8 females (5 children, 3 adults) and 4 males (3 children, 1 adult). Two children (1 female, 1 male) entered the pivotal clinical trial with no lesions. The remaining participants exhibited lesions in multiple anatomic regions, including eyes, gingiva, genitourinary tract, respiratory tract, CNS and colon. For two participants, respiratory tract lesions were considered life-threatening. At the initiation of the long-term maintenance study, all measured lesions were resolved or improved from the baseline measured during the prior study (Table 1).

3.3 | Total Drug Exposure

All participants in this long-term study were enrolled from the pivotal trial or expanded access protocols. The duration of the initial studies varied among participants, with a median treatment time of 27 months (range: 3–46 months). The 12 participants in the long-term study were treated with IV PLG concentrate for a median of 41 months (range: 25–42 months). When IV PLG concentrate use from initial and long-term studies was combined, the median treatment length was 68 months (range: 28–71 months) (Figure 2). During the study, the median number of infusions per participant was 172 (range: 88–331), or a median and mean of 5 (range: 2–8) infusions per month.

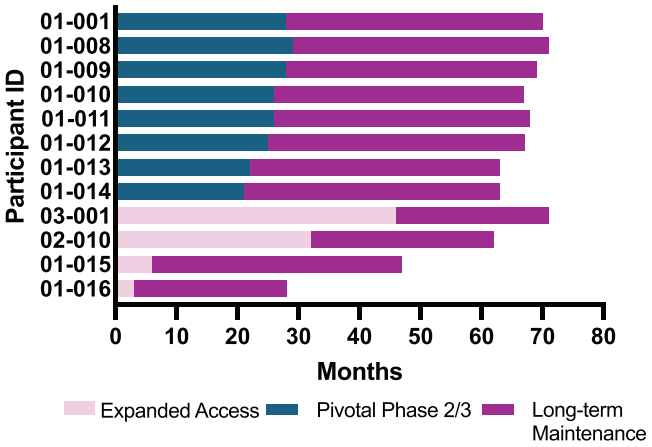

FIGURE 2 | Total IV PLG concentrate exposure of all participants enrolled in the long-term treatment study.

3.4 | Dosage and Lesion Occurrence During the Long-Term PLG Study

The frequency of IV PLG concentrate maintenance treatment varied from every 3 days to every 15 days, attributable to delays in drug manufacturing. During the long-term study, no new or recurring ligneous lesions were observed when participants were able to adhere to the prescribed treatment regimens. However, due to a manufacturing delay resulting in reduced availability of IV PLG concentrate, the investigators extended the dosing frequency for participants. Two adults (1 female, 1 male) and two children (2 female) experienced lesion recurrences (Figure 3). The lesions resolved quickly upon resumption of their prescribed IV PLG concentrate dosing frequency. These data suggest that treatment dose and frequency impact lesion control and that lesions typically resolve after participants return to the regular dosing schedule. Notably, 66.7% (8/12) of participants maintained stable conditions even with changes in dose frequency (Figure 3). Three participants underwent surgical procedures during IV PLG concentrate treatment, one during the pivotal trial (tympanomastoidectomy due to tympanic membrane perforation), one under the expanded access protocol (rigid and flexible bronchoscopy) and one during the long-term maintenance study (lumpectomy) (Figure 3). The dosing frequency was temporarily increased to provide improved coverage. These surgical procedures did not lead to new or recurrent lesions.

3.5 | Safety

A total of 2165 infusions were administered to the 12 trial participants, who initially received 6.6 mg/kg of IV PLG concentrate every 1–4 days. The site investigators adjusted the dosing frequency based on the clinical response, plasminogen activity trough levels and the availability of clinical supply. No neutralising plasminogen antibodies were detected. No fatalities occurred during the study, and no treatment-emergent adverse events (TEAEs) required the permanent discontinuation of the study drug. Five participants reported a total of five serious adverse events that were deemed unrelated to the study drug by the investigator, including three cases of COVID-19, one case of left pyelonephritis and pyeloureteritis, and one case of dysfunctional port-a-cath.

Ninety-three TEAEs were reported during the study, with a median of six events (range: 1–25) per participant. Seventy-five percent of reported TEAEs (70/93) were of mild severity, and 67% (8/12) of participants experienced only mild to moderate TEAEs. The median number of mild events experienced per participant was 5, and the median number of moderate events experienced per participant was 0. One participant experienced two infusion-reaction incidents that were resolved by relocating the infusion site. Overall, five TEAEs were reported by three or more participants. These included abdominal pain (3/12), ear infection (5/12), pyrexia (3/25), pharyngitis streptococcal (3/12) and urinary tract infection (3/12) (Table 2).

4 | Discussion

This study demonstrates the long-term efficacy and safety of personalised IV PLG concentrate treatment, expands understanding of how changes in dosing frequencies may impact lesion development, and describes potential adjustments in dosing frequency during the perioperative period. The 12 study participants remained lesion-free during periods of administration of 6.6 mg/kg IV PLG concentrate at a tailored frequency with an average number of infusions per month of 4.8 (range: 2–8). Overall, participants used a median of 172 infusions (range: 88–331) over a median of 41 months (range: 25–42). During a manufacturing delay, dosing was extended for all participants and 67% (8/12) did not experience lesion recurrence, indicating that their dosing frequency could potentially be extended. The remaining four participants (33%) experienced lesion recurrence, with rapid improvement observed after resuming the therapy, highlighting the requirement for individualised treatment regimens.

Overall, IV PLG concentrate therapy was well tolerated in this population, who received a total of 2165 infusions. Most adverse events were of mild severity. No study participants developed neutralising antibodies against plasminogen, and all participants stayed on the product following its approval by the U.S. FDA. These safety data confirm the results of the previous Phase 1 and Phase 2/3 clinical trials [24, 25, 27].

This trial is the first long-term maintenance study of IV PLG concentrate, significantly extending the duration of treatment by more than three-fold. The duration from the treatment initiation to the resolution of lesions varies based on the overall disease burden, the duration of the lesions and the number of affected systems, including any associated functional impairments. Newly developed lesions tend to respond rapidly, whilst older lesions may take months or up to a year to respond to therapy.

For ultra-rare diseases such as PLGD-1, only a small number of participants are available to enrol in clinical studies, making large, prospective randomised trials often unfeasible. Enrolment for the present study was limited to 12 participants who had completed End of Study visits in prior IV PLG concentrate trials, reflecting the low frequency of PLGD-1. Nevertheless, this cohort size was sufficient to demonstrate how dosing frequency can be successfully tailored to support individual patient needs.

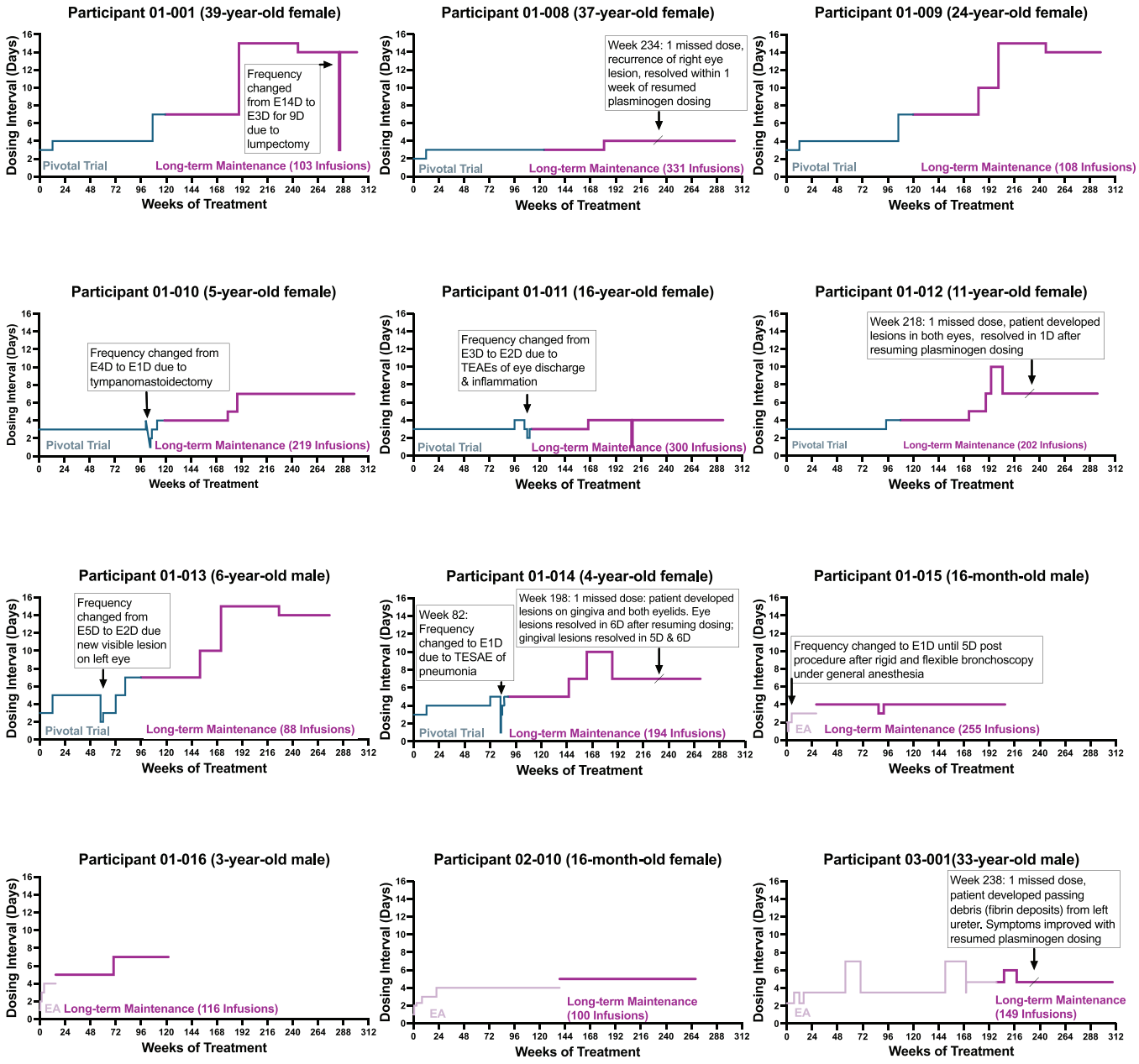

FIGURE 3 | Dosing frequency and lesion occurrence. Blue lines indicate participant dosing frequency during the pivotal trial. Pink lines indicate participant dosing frequency during the expanded access protocol. Purple lines indicate dosing frequency during the long-term maintenance trial. D, day; E, every; EA, expanded access.

TABLE 2 | Adverse events.

Treatment-emergent adverse events[a]	Population, number (%)		
	Children ($n = 7$)	Adults ($n = 5$)	Combined ($N = 12$)
Abdominal pain	1 (14.2)	2 (40.0)	3 (25.0)
Ear infection	2 (28.6)	3 (60.0)	5 (41.7)
Pyrexia	3 (42.9)	0 (0.0)	3 (25.0)
Pharyngitis streptococcal	3 (42.9)	1 (20.0)	4 (33.3)
Urinary tract infection	1 (14.2)	2 (40.0)	3 (25.0)

Note: Adverse events were coded by Version 19.0 of the Medical Dictionary for Regulatory Activities using preferred terms.

[a]Events that occurred in ≥3 participants as of the data cutoff date; none were considered related to the study drug.

Notably, the oldest participant was 38 years old. Therefore, close observation of older individuals prescribed the licensed product is important to gather information on safety and efficacy in this population.

Additional programs have been designed to address the significant knowledge gaps regarding the treatment of PLGD-1, including identifying contributing factors and triggers of lesion development, predicting disease progression, severity classification and better understanding the treatment regimen required, such as intermittent therapy, shorter-term prophylaxis versus long term prophylaxis and so forth. Due to the limited availability of real-world data, an international data collection system, HISTORY (https://www.plgdeficiency.com/, https://clinicaltrials.gov/study/NCT03797495) has been established. This system focuses on a substantial cohort of individuals affected by PLGD-1, as well as all first-degree family members [16]. Another valuable tool for improving our understanding of PLGD-1 treatment is the development of a Ryplazim specific module on WAPPS-Hemo [18], an online clinical calculator that allows for determining a personalised pharmacokinetic profile, including trough levels and optimal dosage, with just 1–2 data points. As IV PLG concentrate is now commercially available to PLGD-1 patients in the United States, safety and efficacy will be monitored continuously.

5 | Conclusion

Ryplazim is the only disease-specific treatment for PLGD-1 approved in the United States [13]. Other available therapies are used for symptom management and do not address the underlying cause of the disorder [17]. This study presents the first evidence of the long-term safety and efficacy of plasminogen replacement therapy using IV PLG concentrate in PLGD-1. Administration of IV PLG concentrate effectively resolved ligneous conjunctivitis and lesions at other body sites. After initial treatment and lesion clearance, dosing intervals were tailored in accordance with participant needs, including for participants undergoing surgery or who experienced trauma or infection. Further research is required to determine the optimal treatment approach for this ultra-rare disorder. Untreated or inappropriately treated PLGD-1 can lead to significant morbidity, mortality and a decline in overall quality of life. IV PLG concentrate represents a significant advancement in treatment for patients with PLGD-1, one that can be individualised for optimal health outcomes.

Author Contributions

Amy D. Shapiro designed the study. Amy D. Shapiro, Charles Nakar, Heather McDaniel and Robert W. Decker enrolled and followed patients in the study. Neelam Thukral was the study coordinator. Joseph M. Parker was the Medical Officer responsible for the study. Karen Thibaudeau was the clinical project manager for the study and performed the PK analysis for plasminogen. Karen Thibaudeau and Joseph M. Parker conceptualised the paper and developed the first outline for the manuscript. All authors provided critical revisions, gave final approval and agreed to be accountable for the work.

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Ethics Statement

The protocol was approved by the institutional review board or ethics committee at each study centre. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonization Tripartite Guidelines for Good Clinical Practice. All participants provided written informed consent, with assent obtained from children between 7 and <18 years old.

Conflicts of Interest

A.D.S. received compensation paid directly to the Indiana Hemophilia & Thrombosis Center (IHTC) for consultation, speaker's bureau, or participation in advisory boards from Be Biopharma, BioMarin, Genentech/Roche, HEMA Biologics, Kedrion Biopharma, Novo Nordisk, Pfizer, Sanofi-Genzyme/Bioverativ, and research support from Centessa Pharmaceuticals/ApcinteX Ltd, Genentech/Roche, Kedrion Biopharma, Novo Nordisk, Pharmacosmos A/S, Pfizer, Regeneron, Sanofi-Genzyme/Bioverativ and Takeda Pharmaceuticals and sits on the board of the Novo Nordisk Haemophilia Foundation. H.M. has acted as a paid consultant and clinical trial investigator to Kedrion (legacy Prometic Biotherapeutics). C.N. received compensation paid directly to the IHTC for honoraria, reimbursement for lectures from Kedrion Biopharma, and research support from Kedrion Biopharma and Prometic Biotherapeutics. J.M.P. is a paid consultant to Kedrion Biopharma. K.T. is an employee of Kedrion Biopharma. R.W.D., J.L. and N.T. report no conflict of interest.

Data Availability Statement

The data supporting this study's findings are available upon request of the corresponding author.

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