A MULTICENTER, PHASE 2, OPEN-LABEL STUDY EVALUATING THE SAFETY AND EFFICACY OF SIROLIMUS 3.9% TOPICAL GEL (PTX-022) IN THE TREATMENT OF MICROCYSTIC LYMPHATIC MALFORMATIONS

Protocol Number:	PALV-06
Compound Number	PTX-022
Sponsor Name:	Palvella Therapeutics, Inc.
Legal Registered Address:	125 Strafford Ave, Suite 360 Wayne, PA 19087
Regulatory Agency Identifying Number(s):	[redacted]
Approval Date	27June2022

1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Title of Study: A Phase 2, Open Label Study Evaluating the Safety and Efficacy of PTX-022 (sirolimus) Topical Gel 3.9% in the Treatment of Microcystic Lymphatic Malformations
Name of Sponsor/Company: Palvella Therapeutics
Name of Finished Product: PTX-022 (sirolimus) Topical Gel 3.9% w/w
Name of Active Ingredient: Sirolimus
Objectives: *Safety Objective:* The primary objective of the study is to evaluate the safety of PTX-022. *Efficacy Objective:* The secondary objective of the study is to evaluate the effectiveness of PTX-022 in treating microcystic LM.
Study Design and Duration: This is an open-label study to evaluate the safety and effectiveness of PTX-022. The study will consist of a screening and baseline period, 12-week treatment period and 4-week follow up period. Participants will have 8 visits (remote or on-site) which include: • Screening • Day 1 +4 days • Day 7 (blood draw only done remote or onsite) ± 2 days • Day 28 ± 4 days, Day 56 ±4 days, Day 84 ± 4 days • Day 14 ± 4 and Day 112 ± 4 (remote)
Number of Study Centers: Approximately 5 sites in the United States Sample Size: ~10-20 subjects dosed
Duration of Participation: Each subject will participate in the study for approximately 20 weeks from the time the subject signs the ICF through the safety follow-up period.

Duration of Study: The study will require approximately 12 months from the beginning to the end of the study (first subject signing the ICF to last contact with last subject).

Screening Period Inclusion Criteria:

Participants are eligible to participate in the screening period only if all the following inclusion criteria apply:

1) The participant must be at least 6 years of age.
2) If less <18 years of age, the participant and legal guardian must provide written informed consent/assent prior to any study procedures.
3) The participant must have a clinically confirmed vascular malformation which contains within it a superficial (visible on the skin) microcystic lymphatic malformation (LM). [redacted]
4) The microcystic LM to be treated (lesion) must have a defined total area of [redacted]
5) The participant is willing to abstain from application of other topical medications (prescription or over the counter) [redacted]
6) [redacted]
7) At least [redacted] have elapsed since the participant has had any major surgery.
8) At least [redacted] have elapsed since the participant has completed therapy with a Growth Factor (GF) that supports platelet, red or white cell number or function.
9) Participants must not have received any investigational drug or biologic within [redacted] whichever is longer, prior to starting treatment with and during treatment with PTX-022.
10) [redacted]
11) The participant is willing to have blood collected for safety and PK testing.

Screening Period Exclusion Criteria:

Participants are not eligible to participate in the screening period if any of the following exclusion criteria apply:

1) The participant has used sirolimus in the past 6 weeks.
2) The participant has previously participated in a clinical trial evaluating an investigational product for treatment of Vascular Anomalies, including microcystic LM in the last 3 months.
3) The participant has used a topical, oral, or interventional treatment that might interfere with the evaluation of the study IP. Among these are use of the following: [redacted]

[redacted]

4) The participant has had either COVID-19 or the COVID-19 Vaccine within the last 6 weeks.
5) Participants who require medications and OTC supplements that inhibit/ induce CYP3A4 activity to control concurrent medical conditions.
6) [redacted]
7) Participants with known hypersensitivity to any of the ingredients in the study medication formulation.
8) Known history of HIV seropositivity or known immunodeficiency.
9) [redacted]
10) Concurrent severe and/or uncontrolled medical disease which could compromise compliance with safety monitoring requirements for sirolimus
11) Participants previously treated for invasive cancer within the past 5 years unless the Investigator concludes history of cancer is not confounding to safety.
12) [redacted]
13) [redacted]
14) The participant has any condition or situation which, in the Investigator's opinion, may put the subject at significant risk, could confound the study results, or could interfere significantly with the subject's participation in the study.
15) Participants deemed by the investigator as unwilling or unable to remain compliant with all tests and procedures, adherence to the study drug administration regimen and other protocol-required activities.

Baseline Period Inclusion Criteria

Participants are eligible to participate in the baseline period only if all the following inclusion criteria apply:

1) Participant has completed the screening period
2) In the Investigator's opinion, the participant's overall health status, including adequate organ function, LDL and cholesterol levels, should be appropriate to permit participation in this clinical trial.
3) The participant has adequate Renal Function.
    a. eGFR>90 mL/min/1.73m^2 or CrCl >90 mL/min

Baseline Period Exclusion Criteria

Participants are not eligible to participate in the baseline period if any of the following exclusion criteria apply:

1) Participants deemed by the investigator as unwilling or unable to remain compliant with all tests and procedures, including adherence to the study drug administration regimen and allowing healthcare workers into the home and other protocol-required activities.

Open-Label Treatment Period Inclusion Criteria:

Participants are eligible to participate in the open-label treatment period only if all the following inclusion criteria apply:

1) Maintained [redacted] compliance with completion of the PDD during the Baseline period.

Open-Label Treatment Period Exclusion Criteria:

Participants are not eligible to participate in the open-label treatment period if any of the following exclusion criteria apply:

1) Participants deemed by the investigator as unwilling or unable to remain compliant with all tests and procedures, including adherence to the study drug administration regimen and other protocol-required activities.

Investigational Product (IP), Dose, Route of Administration, and Regimen:

Test product: PTX-022 (sirolimus) Topical Gel 3.9% w/w

In accordance with study participant safety and tolerability, treatment will be applied according to this administration schedule:

- All subjects shall complete 12 weeks of therapy.
- PTX-022 will be topically administered each day [redacted] PTX-022 should be applied once daily to the lesion area [redacted] [redacted]Specific instructions will be available in the Participant Instruction for Use manual. If [redacted]

Study Assessments:

The study will be conducted as outlined in the Schedule of Assessments. For all safety and efficacy measurements, study participants and investigators will be provided with study specific training to ensure consistent evaluations.

Safety Assessments:

Safety will be assessed through adverse event (AE) evaluations. During the study, subjects will be assessed for the occurrence of new and ongoing AEs. Descriptions of AEs will include the dates of onset and resolution (if resolved), maximum severity, and seriousness, action taken regarding the study drug, corrective treatment, outcome, and the Investigator's assessment of causality. AEs

present at any visit will be followed to resolution (return to normal or to the baseline state) or until clinically stable as determined by the Investigator.

Safety Laboratory Tests: Routine safety laboratory tests (complete blood count/differential urinalysis and serum chemistry) will be performed. Laboratory samples may be obtained from a central or local laboratory facility. Any out-of-range laboratory result that is considered clinically significant by the Investigator will be recorded as an AE and should be confirmed by repeat testing at the discretion of the Investigator. Clinically significant laboratory abnormalities at any visit will be followed to resolution (return to normal or to the baseline state) or until clinically stable as determined by the Investigator.

Physical Examinations: Investigator will evaluate body systems with trial participant.

All Adverse Events will be evaluated using Common Toxicity Criteria for Adverse Events (CTCAE) version TBD at time of final protocol.

[redacted]

Statistical Methods:

This is a descriptive, open-label pilot study. Primary and secondary outcomes will be reported by mean or percentage and 95% confidence interval.

All statistical processing will be performed using SAS® or R3.6.1 or later version unless otherwise stated. Summary tables (descriptive statistics and/or frequency tables) will be provided for baseline variables and safety and efficacy variables. Continuous variables will be described by descriptive statistics (n, mean, standard deviation, minimum, median, and maximum). Frequency counts and percentage of subjects within each category will be provided for categorical data.

Adverse Event Coding

AEs will be coded by system-organ-class and preferred term using the most current Medical Dictionary for Regulatory Activities (MedDRA). Events will be recorded from signing of informed consent through 30 days following the last dose of PTX-022 and will be tabulated by maximum severity according to NCI-CTCAE (v.4.03). The calculation of AE incidence will be based on the number of participants per AE category. For each participant who has multiple AEs classified to the same category, that participant will be tabulated under the worst toxicity grade for that AE category. Summary tables will be presented by dose level, seriousness, severity, and relatedness.

Analysis Populations:

Safety/Intent to Treat (ITT) population: All subjects who received at least one application of study intervention.

Per Protocol Population: All subjects who completed treatment without major protocol violations affecting the efficacy endpoints.

1.2. SCHEDULE OF ASSESSMENTS (SOA)

Table 2. Schedule of Assessments

	Screening	Baseline	Open-Label Treatment[2]						Post-treatment follow-up[2]
	Visit 1 Screening[1]	Remote	Visit 2[2]	Blood Draw	Phone Contact	Visit 3	Visit 4	Visit 5	Visit 6 Phone contact
Visit Day[3]	Up to 6 weeks	14-28 days	Day 1	Day 7	Day 14	Day 28	Day 56	Day 84	Day 112
Informed Consent	X								
Eligibility Criteria	X		X[3]						
Med History/ Demographics	X								
Physical Exam	X							X	
Height and Weight	X[4]							X	
Vital Signs	X		X[3]			X	X	X	
Clinical Laboratory Tests[6]	X			X[5]		X		X	
PK Tests						X	X	X	
Urine Pregnancy Test	X		X[3]					X	
CGI-S			X[3]			X	X	X	
CGI-C						X	X	X	
Photography	X		X[3]			X	X	X	

[1] Re-screening is permitted as described in Section 5.5.1

[2] Visit window is +/4 days for all visits during the open-label treatment period and Post-treatment follow-up period, excluding Day 1 and 7. Day 1 visit window is +4 days and Day 7 blood draw window is +/- 2 days.

[3] Assessments on Day 1 of OLT should be conducted prior to application of study intervention and are considered part of Baseline

[4] Height is obtained at screening only

[5] Day 7 is sirolimus only and does not need to be fasting.

[6] Fasting labs are required for Visit 3 and Visit 5.

Assessment of lesion leakage		----------✓[7]----------							
Assessment of lesion bleeding		----------✓[7]----------							
Assessment of lesion impact on function		----------✓[7]----------							
LM Symptom Severity Scale (Pain)		----------✓[7]----------							
LM Symptom Severity Scale (Crusting)		----------✓[7]----------							
PGI-SL		----------✓[8]----------							
PGI-SB		----------✓[8]----------							
PGI-CL				----------✓[8]----------					
PGI-CB				----------✓[8]----------					
Overall PGI-S[11]			✓[3]			✓	✓	✓	
Overall PGI-C						✓	✓	✓	
DLQI			✓[3]					✓[10]	
TSQM								✓[10]	
Adverse Events	X[9]		X	X	X	X	X	X	X
Application Site Reaction Assessment			X			X	X		
Concomitant Medications	X		X	X	X	X	X	X	X
Dispense/Collect IP			X			X	X	X	
Accountability/Compliance			X			X	X	X	
Exit Interview									X[12]

[7] Daily in the PDD
[8] Weekly in the PDD
[9] SAEs will be captured from time of informed consent. AEs not meeting SAE criteria will be captured starting at time of first dose.
[10] Collected after the PGI-S/C
[11] If parent is completing daily and in-person questionnaires for a child, it should be the same parent completing them throughout the course of the study.
[12] Interviews can occur any time after end of treatment. Interviews will be conducted by an independent, third party. Please refer to the Interview Guide for more information on conduct.