TRIAL IN PROGRESS: PHASE 1 TRIAL OF NEXT GENERATION MEK1/2 INHIBITOR PAS-004 IN ADULTS WITH INOPERABLE PLEXIFORM NEUROFIBROMAS

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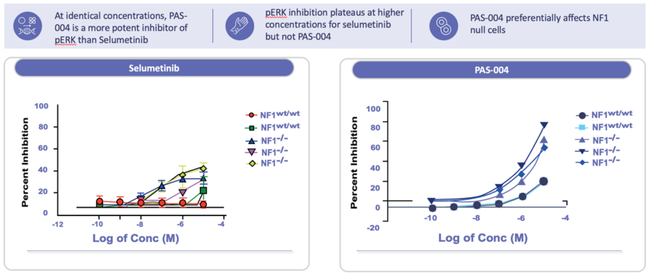
BACKGROUND

Neurofibromatosis Type 1 (NF1) is a genetic nerve sheath tumor predisposition syndrome associated with benign plexiform neurofibromas (PNs) that cause deformity, debility, and pain, and have a high risk of malignant transformation into a poorly treatable sarcoma. Prior research led to the FDA approval of both selumetinib (pediatric population), and mirdametinib (pediatric and adult population) with unresectable symptomatic PNs. These treatments are highly effective with an approximate target tumor response rate of 40% when given twice daily orally, however nearly all patients experience adverse events.

The current study (NCT06961565) will investigate a next-generation MEK inhibitor, PAS-004 (Pasithea Therapeutics). PAS-004 is a macrocyclic small molecule allosteric inhibitor of MEK 1/2. In NF1 wildtype and null cell proliferation assays, PAS-004 was highly efficient at inhibiting the downstream pharmacodynamic (PD) biomarker of MEK activity, phosphorylated ERK (pERK), studies suggested increased tolerability and favorable pharmacokinetics (PK). Here, we report the study methodology, endpoints, and timeline for a Phase I dose escalation study of PAS-004 as a once-daily oral monotherapy in NF1 patients with symptomatic unresectable PNs.

PRECLINICAL AND EARLY CLINICAL TRIAL DATA

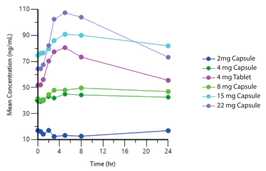
Preliminary results from a concurrent Phase I dose-escalation study of PAS-004 in capsule and tablet formulations for advanced solid tumors with MAPK pathway mutations. Preliminary PK data indicates a linear dose-response curve with an estimated t ½ of >60 hours and up to 91% pERK inhibition of circulating nucleated cells. No dose-limiting toxicities (DLTs) or treatment-related SAEs were observed and the maximum tolerated dose (MTD) has not been met.



Unpublished Data - Dr. Raymond Mattingly,Wayne State Univ.

Pharmacokinetics (PK) parameters by cohort

PAS-004 Study Cohort	C_{max} (ng/mL) [mean CV%]	AUC_{0-24} (ng*h/mL) [mean CV%]	T_{max} (h) [mean CV%]	AR_{AUC} [mean CV%]
2 mg Capsule (N=3)	16.2 (89.7)	354 (95.2)	1 - 5	4.1 (16.2)
4 mg Capsule (N=3)	38.7 (94.8)	859 (101.3)	2 - 24	8.4 (37.8)
8 mg Capsule (N=3)	42.1 (100.9)	889 (118.0)	3-8	6.2 (11.3)
15 mg Capsule (N=3)	91.3 (27.6)	1990 (32.5)	2-24	4.02 (14.8)
22 mg Capsule (N=3)	108 (19.9)	2160 (16.4)	3-8	4.64 (50.6)
4 mg Tablet (N=4)	76.8 (37.9)	1550 (33.8)	3-5	4.17 (21.7)



Summary of Clinical Safety: Adverse Events (AEs) at least Possibly related to PAS-004 during the DLT period

		Grade 1		Grade 2		Grade 3	
	AE Preferred Term	Possible	Probable	Possible	Probable	Possible	Grand Total
Cohort 1 - 2mg	Nausea				1		1
	Urinary incontinence			1			1
	Vomiting		1		1		2
Cohort 2 - 4mg	Dehydration				1		1
Cohort 3 - 8mg	Nausea		1				1
Cohort 4A - 15mg	Creatine phosphokinase increased	1		1			2
	Diarrhoea	1					1
Cohort 4B - 4mg tablet	Diarrhoea	1	1	1			3
	Fatigue		1				1
	Lacrimation increased		1				1
	Nail disorder		1				1
	Nausea	1	1				2
	Scleral disorder		1				1
	Vomiting	1	2				3
Cohort 5 - 22mg	Constipation		1				1
	Vomiting		1				1
Grand Total		5	12				23

METHODS

This is an international Phase 1 dose-expansion clinical trial for adult NF1 patients with symptomatic plexiform neurofibromas ≥3 cm in axial imaging that follows a modified 3+3 dose escalation dose-discovery design ("Part A") followed by a safety expansion portion of two selected doses ("Part B") to evaluate the safety, tolerability, PK, PD, and preliminary efficacy of PAS-004 for unresectable symptomatic plexiform neurofibromas in NF1 patients.

Key Endpoints:

Primary: Safety and tolerability of PAS-004 (Part A)
- Identify 2 doses at or below the MTD in Part A to study further in Part B, and then select a recommended Phase 2 dose (RP2D)

Secondary: Evaluate PK and PD specifically in cutaneous neurofibromas (CNs)
- Assess preliminary anti-tumor activity against PNs

Tertiary: Evaluate the impact of PAS-004 on Response Evaluation in NF and Schwannomatosis (REiNS)-validated quality of life (QOL) measures
- Plexi-QOL, cNF-Skindex, NRS-11 pain scale, PGI-S and PROMIS© Physical function (PF) assessments

Quantify PK, PD, and anti-tumor effects of PAS-004 on cutaneous neurofibromas (CNs)

Outcome Measures:

- Toxicities according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
- PN measurements per MRI with volumetric analysis
  - Partial Response (PR) ≥ 20% reduction in the sum of the volume of all target PN lesions for ≥ 4 weeks.
  - Stable Disease (SD) <20% increase and/or a <20% reduction in the sum of the volume of all target lesions for ≥ 4 weeks.
  - Progressive Disease (PD): ≥20% increase in the volume of at least one of the target PN compared to the pretreatment volume.
- CN measurements per calipers and 2D/3D photography
  - CR no measurable lesion
  - PR ≥ 20% reduction in the sum of the ellipsoid areas or the sum of the calculated surface areas (∑EA or ∑SA); OR ≥2 CN with ≥30% reduction in EA or SA
  - SD between a 20% reduction and a 30% increase in ∑EA or ∑SA; OR <2 CN with ≥30% reduction in EA or SA
  - PD ≥ 30% increase in ∑EA or ∑SA; OR ≥40% increase in EA or SA in ≥ CNs

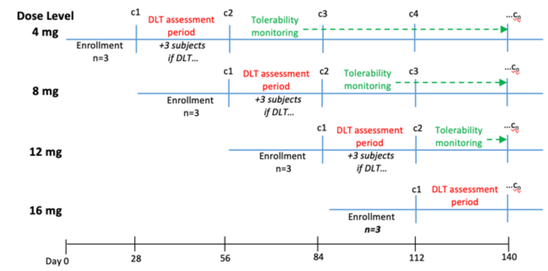
EXPERIMENTAL PLAN

Three patients per dosing cohort will be sequentially enrolled in Part A, for 28 days of a DLT assessment period prior to the next cohort being enrolled. An estimate of 12 subjects is expected including the four dose groups of 4, 8, 12, and 18 mg per day PAS-004. Participants in the Dose Escalation Phase (Part A) will remain on their assigned dose for six 28-day treatment cycles (168 days). If the RP2D has not yet been selected after 6 cycles, participants may continue treatment for up to 6 more cycles. Two doses at or below a MTD (if determined) will be selected for further study in the Part B.

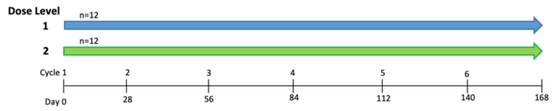
Participants from Part A may be eligible for continued PAS-004 study treatment in Part B only if their assigned dose was selected for Part B. Participants in Part A on a dose that is selected for Part B will be included in the data analysis for Part B must have completed 4 contiguous cycles as well as the MRI post cycle 4.

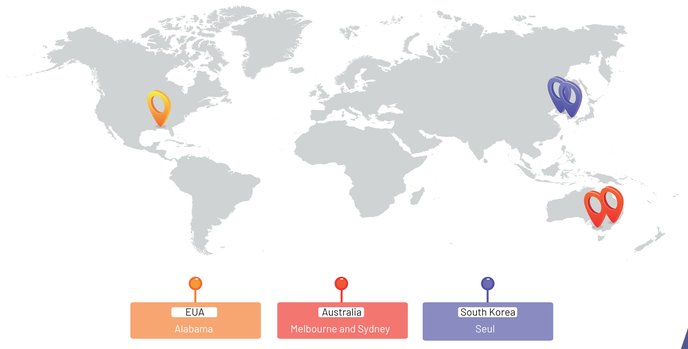
Participants in the Expansion Phase (Part B) will remain on their assigned dose for six 28-day treatment cycles. Twelve subjects will be enrolled/included on each of the selected RPBDs for a total of 24 patients in Part B.

Part A Dose-Finding Schema



Part B Expansion Schema





ENROLLMENT AND PREDICTED STUDY COMPLETION DATE:
Enrollment will be open at the first site in June 2025;
Predicted duration of the study is 2-3 years.