PAS-004-103: a Phase 1/1b study of the safety, tolerability, pharmacokinetics and clinical activity of PAS-004, a macrocyclic MEK inhibitor, in patients with NF1-associated plexiform neurofibroma (PN)

Rebecca Brown[2], Yemima Berman[3], James Whittle[4], Beom Hee Lee[5], Ji Young Oh[6], Kartik Krishnan[1], Mathew Lazarus[1], Joy Cannon[1], Tiago Reis Marques[1]

1 Pasithea Therapeutics Corp, Miami Beach, FL, USA · 2 University of Alabama at Birmingham, AL, USA · 3 Royal North Shore Hospital, St Leonards, NSW, Australia · 4 Peter MacCallum Cancer Centre, Melbourne, VIC, Australia · 5 Asan Medical Center, Seoul, South Korea · 6 Severance Hospital, Yonsei University, Seoul, South Korea

Background

PAS-004 is the first small-molecule allosteric MEK1/2 inhibitor under clinical development that has a macrocyclic ultrastructure. Its unique ring formation confers a long terminal half-life of 40–60 h by shielding metabolically labile side groups. The high stability of PAS-004 is permissive of once-daily dosing and confers a flat concentration profile (steady-state Cmax/Ctrough < 2) that can be fine-tuned within the target therapeutic window while avoiding spikes into toxic concentrations or troughs into subtherapeutic concentrations.

PAS-004 was developed for long-term, continuous, once-daily dosing with excellent efficacy and tolerability. It inhibits cellular pERK with an IC_{50} of 2.0 nM and showed strong activity in both NF1-mutant cell lines and in an NF1 mouse model (reduced neurofibroma number and volume).

We report preliminary Part A results of study PAS-004-103 (NCT06961565).

Methods

Multicenter, international, open-label, two-part Phase 1/1b study of once-daily PAS-004 tablets.

Part A:

- 3+3 dose escalation including Safety Review Committee approval between each dose escalation
- Six 28-day cycles with optional extension to 18 cycles

Part B:

- Participants randomized between two dose levels selected from Part A to identify the recommended Phase 2 dose

Population:

- Adults with NF1 and ≥1 symptomatic Target PN ≥3 cm that is inoperable, incompletely resected (≥15% residual) or recurrent

Primary endpoint:

Safety and tolerability:

- Dose-limiting toxicities (DLTs)
- All adverse events (AEs), and AEs leading to interruption/discontinuation of study drug

Secondary endpoints:

- Day 1 and Day 28 PK — Cmax, Ctrough, Tmax, $AUC_{0-\tau}$ and drug accumulation
- Target PN volume by volumetric MRI — clinical benefit rate (CR, PR, SD, PD), best objective response rate, and time to maximal response per REiNS criteria
- PROMs: PROMIS Physical Function and Plexi-QOL
- Recommended Part B dose (RPBD)

Imaging read:

As of 30 September 2026, Target PN volumes are reported by a blinded independent central read by a single reader. The imaging charter specifies two independent central readers with averaging of their measurements; the second read is pending. Local investigator reads are shown alongside where available.

Figure 1. Part A dose escalation — six once-daily tablet cohorts, 3 participants each



Figure 2. PN assessment schedule — volumetric MRI at Screening and end of each cycle shown

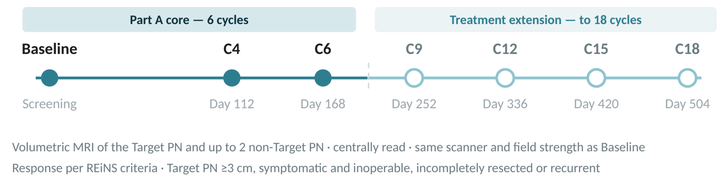


Figure 3. Five sites in three countries



Results

Demographics and disposition

Nineteen participants were enrolled across the six dose-escalation cohorts (3 per cohort; 4 in the 18 mg cohort, where one participant was replaced) at five study sites (Table 1). As of 15 September 2026, 18 remain on study; one participant (18 mg) was discontinued by Sponsor for dosing non-compliance.

Table 1. Participants and baseline characteristics (N=19)

Characteristic	N = 19
Age, years, mean (SD)	36.4 (13.0)
Sex, female / male, n	9 / 10
Asian, n (%)	9 (47.4)
White, n (%)	9 (47.4)
Black or African American, n (%)	1 (5.3)
BMI, kg/m², mean (SD)	23.7 (3.1)

Target PN	N = 18
Location, n (%)	
Head and neck	6 (33.3)
Lower limb	5 (27.8)
Trunk / paraspinal	4 (22.2)
Pelvis / sacral	3 (16.7)
Mean volume, mm³ *	456,156

* Target PN baseline volume from the Screening MRI

Safety

Table 2. Treatment-related adverse events (TRAE) — overall summary (N=19)

Treatment-related adverse events (TRAE)	N = 19
Dose-limiting toxicity (DLT), n	0
Participants with any TRAE, n (%)	16 (84.2)
Grade 1, n (% of events)	62 (73.8)
Grade 2, n (% of events)	20 (23.8)
Grade 3, n (% of events) *	2 (2.4)
Grade 4 or 5, n (% of events)	0
Discontinuation due to TRAE, n	0
Dose interruption due to TRAE, n (%)	3 (15.8)
Dose modification due to TRAE	not permitted

* Two asymptomatic Grade 3 blood CPK elevations (4 mg and 8 mg), each resolved after a one-week dose interruption. The third interruption was for Grade 2 dermatitis acneiform (18 mg).

The two Grade 3 asymptomatic CPK elevations (at 4 mg and 8 mg) each resolved after a one-week interruption and both participants remain on treatment.

Table 3. Treatment-related adverse events by dose cohort — all grades and Grade ≥3

Related adverse event	Participants	4 mg		8 mg		12 mg		15 mg		18 mg		24 mg	
	n (%) of 19	All	G≥3	All	G≥3	All	G≥3	All	G≥3	All	G≥3	All	G≥3
Any related adverse event	**16 (84.2)**												
Dermatitis acneiform	11 (57.9)	1	–	1	–	1	–	2	–	3	–	3	–
Blood CPK increased	5 (26.3)	2	1	2	1	1	–	–	–	–	–	–	–
Oedema peripheral	3 (15.8)	–	–	–	–	1	–	–	–	–	–	2	–
Diarrhoea	2 (10.5)	–	–	1	–	–	–	–	–	1	–	–	–
Nausea	2 (10.5)	–	–	1	–	–	–	–	–	1	–	–	–
Constipation	2 (10.5)	–	–	–	–	–	–	–	–	1	–	1	–
Fatigue	2 (10.5)	–	–	1	–	1	–	–	–	–	–	–	–
Neutrophil count decreased	2 (10.5)	–	–	1	–	–	–	–	–	1	–	–	–
Platelet count decreased	2 (10.5)	–	–	–	–	–	–	–	–	1	–	1	–
Paronychia	2 (10.5)	–	–	1	–	–	–	–	–	–	–	1	–
Pruritus	2 (10.5)	–	–	–	–	–	–	–	–	–	–	2	–
Stomatitis	2 (10.5)	–	–	–	–	–	–	1	–	–	–	1	–

Preferred terms reported by two or more participants are shown; 14 further terms occurred in a single participant each. Safety population N = 19, clinical cut-off 15 Sep 2026.

Pharmacokinetics

Steady-state (Day 28) exposure increased approximately proportionally with dose across 4–24 mg, with 3- to 4-fold accumulation from Day 1, consistent with a long terminal half-life (approximately 40–60 h). The profile is flat, with Cmax/Ctau 1.5–2.0 in every cohort (Table 4).

Table 4. Steady-state (Day 28) PK parameters by cohort — geometric mean (GeoCV%)

Cohort	Cmax (ng/mL)	AUC_{0-24} (ng·h/mL)	Ctau (ng/mL)	Tmax (h)	AR (AUC)
4 mg (n=3)	58.1 (35.7)	1,120 (39.8)	37.6 (42.4)	3	3.3 (17.2)
8 mg (n=3)	118 (28.0)	2,290 (24.8)	75.4 (24.2)	3–6	2.9 (8.3)
12 mg (n=3)	215 (32.5)	3,680 (11.9)	109 (20.7)	3–6	2.9 (20.6)
15 mg (n=3)	PK data still being analyzed				
18 mg (n=3)	422 (34.3)	8,270 (42.3)	280 (48.8)	3–6	4.1 (52.7)
24 mg (n=3)	452 (25.4)	8,500 (33.2)	268 (39.8)	3–6	3.8 (46.7)

N=15 with Day 28 PK · AR = accumulation ratio (Day 28 / Day 1) · interim PK analysis · 15 mg cohort: bioanalysis in progress

Efficacy — plexiform neurofibroma

- 18 participants with on-study MRI volumetric evaluation
  - Median time on therapy 10.7 months (first dose to MRI cut-off)
  - For patients on doses >12 mg, median time on therapy is 5.2 months
- All participants showed a reduction at best assessment by Blinded Independent Central Review (BICR)
- 2 patients showed a reduction over 20% in volume (partial response by REiNS criteria) at best assessment by BICR
  - 1 patient on 12 mg
  - 1 patient on 15 mg
- One site contributed investigator-assessed volumetrics
  - 2 SD, 1 PR
  - Patient with PR at the dose of 8 mg
- The BICR was completed by a single reader; the second independent central read and averaged volumes are pending

Figure 4. Centrally read Target PN MRIs per cohort, Baseline to Cycle 15 (MRI cut-off 30 Sep 2026)

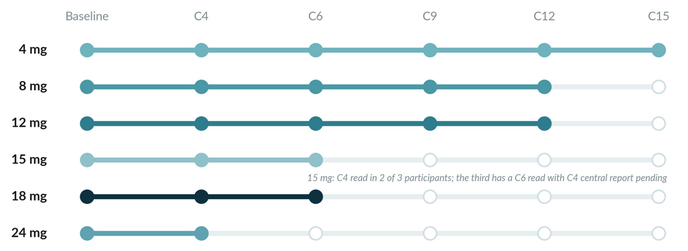
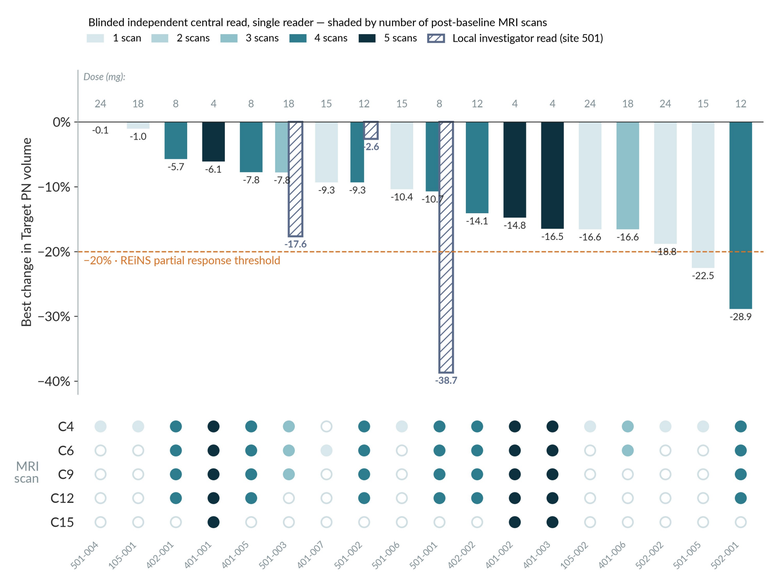


Figure 5. Best change in Target PN volume (n=18) — central read to 30 Sep 2026, and local read



Conclusions

- **PAS-004 is well tolerated in adults with NF1-associated PN**
  - No DLTs
  - No related SAEs
  - No discontinuations due to AE
  - Related AEs all Grade 1 or 2, except two asymptomatic Grade 3 elevations in CK
- **PK of PAS-004 is conducive to once-daily, long-term dosing**
  - Long half-life (40–60 h)
  - Dose proportionality
  - Peak-to-trough ratio below 2 at steady state
- **Efficacy has been seen, but time on study is too short for definitive conclusions**
  - Two patients with PRs by BICR, including one at C4
  - Median time on study for higher dose cohorts is under 6 months

These findings support continued follow-up of Part A, selection of the RPBD, and progression into Part B of this study, which will randomize participants between two doses of PAS-004 to select a dose for a registrational study in PN.

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Contact: Tiago Reis Marques — tiago@pasithea.com