Patient-Reported Outcomes of Pain Severity and Pain Interference From ReNeu: Pivotal Phase 2b Trial of Mirdametinib in Adults and Children With Neurofibromatosis Type 1-Associated Plexiform Neurofibroma (NF1-PN)

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Financial and Competing Interests and Disclosure

Dusica Babovic-Vuksanovic, MD: Employment with Mayo Clinic; research funding: SpringWorks Therapeutics Inc, Alexion Pharmaceuticals, and Recursion; consultancy/advisory role: SpringWorks Therapeutics Inc, Alexion Pharmaceuticals.

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Background

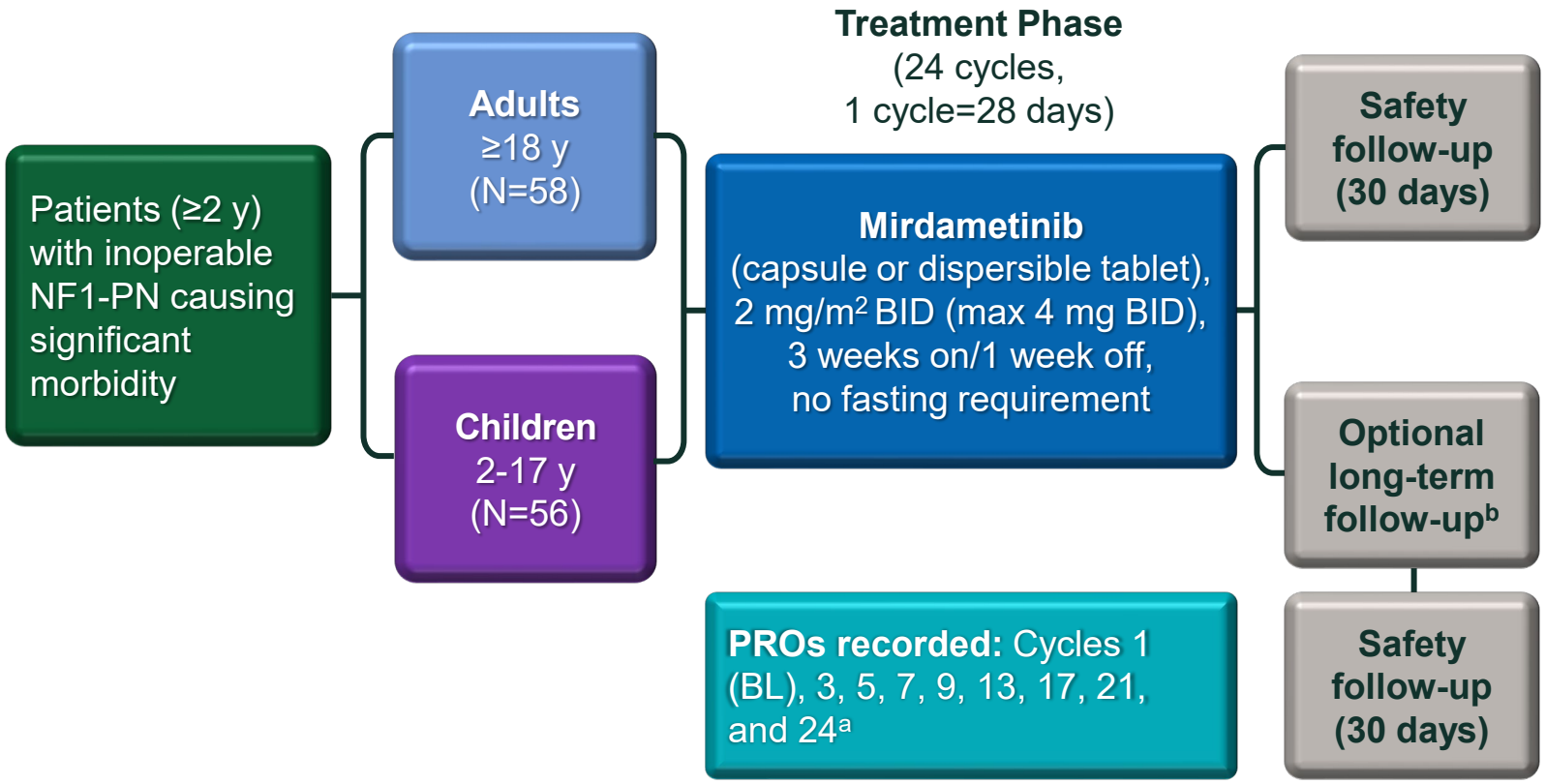
- Plexiform neurofibromas (PNs) are nonmalignant nerve sheath tumors reported in 30% to 50% of people with neurofibromatosis type 1 (NF1)[1,2]
- Pain is one of the most common morbidities among people with NF1-PN and has a considerable impact on physical functioning and health-related quality of life[3,4]
- Mirdametinib is an investigational, highly-selective, allosteric, CNS-penetrant, small-molecule MEK1/2 inhibitor[5-8,a]
- ReNeu (NCT03962543) is a pivotal, phase 2 trial of mirdametinib in patients with NF1-PN, which met the primary endpoint of confirmed ORR (41% of adults and 52% of children)[9]
- No pharmacologic therapies for NF1-PN are approved for adults; one MEK inhibitor is FDA-approved for children (2 to 17 years)[10]

Objective: To report patient-reported outcomes (PROs) of worst tumor pain severity and pain interference in adults and children with NF1-PN treated with mirdametinib from the ReNeu trial

[a]Mirdametinib is an investigational product that has not been approved by any regulatory authority; the safety and efficacy of mirdametinib have not been established. **CNS**, central nervous system; **FDA**, US Food and Drug Administration; **NF1**, neurofibromas type 1; **ORR**, overall response rate; **PN**, plexiform neurofibroma; **PRO**, patient-reported outcome.

1. Prada CE, et al. *J Pediatr*. 2012;160:461-467. **2.** Miller DT, et al. *Pediatrics.* 2019;143:e20190660. **3.** Gutmann DH, et al. *Nat Rev Dis Primers*. 2017;3:17004. **4.** Fisher MJ, et al. *Neuro Oncol*. 2022;24(11):1827-44. **5.** Weiss BD, et al. *J Clin Oncol*. 2021;39(7):797-806. **6.** LoRusso PM, et al. *Clin Cancer Res*. 2010;16(6):1924-37. **7.** Jousma E, et al. *Pediatr Blood Cancer*. 2015;62(10):1709-16. **8.** de Gooijer MC, et al. *Int J Cancer*. 2018;142(2):381-91. **9.** Moertel, et al. American Society of Clinical Oncology Annual Meeting, May 31-Jun 4, 2024. **10.** KOSELUGO [Prescribing Information]. AstraZeneca Pharmaceuticals LP; 2024

ReNeu: A Multicenter, Open-label, Pivotal, Phase 2b Trial of Mirdametinib in Adults and Children With NF1-PN (NCT03962543)



Primary Endpoint

- Confirmed ORR (% of patients with ≥20% reduction in target tumor volume by MRI on consecutive scans during the treatment phase assessed by BICR)[c]

Secondary Endpoints

- DoR
- PROs from BL to Cycle 13:
  - **Worst tumor pain severity (NRS-11)**
  - **Pain interference (PII)**
  - HRQoL (PedsQL)
- Safety and tolerability

[a]PROs were recorded at Cycle 1 Day 1 (Baseline) and at Day 15 of subsequent cycles, and Cycle 13 was the prespecified endpoint. [b]In the LTFU, patients continue on mirdametinib at the last dose assigned in the treatment phase. [c]Per REiNS criteria. Consecutive scans for confirmation of objective response had to occur within 2-6 months. BICR with 2 reviewers and 1 adjudicator. High concordance of tumor volumes between readers (R=0.9907). **BICR**, blinded independent central review; **BID**, twice a day; **BL**, baseline; **DoR**, duration of response; **LTFU**, long-term follow-up phase; **NRS-11**, Numeric Rating Scale-11; **ORR**, objective response rate; **PedsQL**, Pediatric Quality of Life Inventory; **PII**, Pain Interference Index; **PRO**, patient-reported outcomes; **REiNS**, Response Evaluation in Neurofibromatosis and Schwannomatosis. **1.** ClinicalTrials.gov. https://www.clinicaltrials.gov/study/NCT03962543. Accessed May 9, 2024.

PRO Analysis: Change in Worst Tumor Pain Severity (NRS-11) and Pain Interference (PII) From Baseline Across the 24-Cycle Treatment Phase[1]

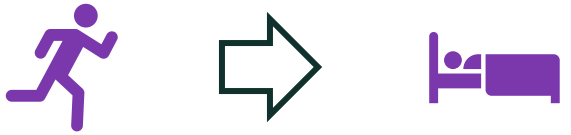
LS mean MMRM analysis of change from baseline in NRS-11 and PII scores

Worst Tumor Pain Severity – NRS-11 Score

0 – No Pain → **10 – Worst pain you can imagine**

- NRS-11 is a single-item questionnaire with a 0 to 10 (11-point) scale that assesses pain severity over the past 24 hours
- Administered over 7 consecutive days
- Self-reported by all patients ≥8 y of age

Pain Interference – PII Score



0 – No Interference → **6 – Complete Interference**

- PII is a 6-item questionnaire with a 0 to 6 (7-point) scale that assesses the degree to which pain interferes with activity over the past 24 hours
- Administered over 7 consecutive days
- Self-reported by all patients ≥6 y of age
- Parent proxy-reported for all patients 6-17 y of age

Post hoc analyses: Adults and children who could have attained a clinically meaningful change[a] from BL at Cycles 5 and 13[b]

Clinically Meaningful Improvement in NRS-11

- Calculated as a reduction from BL of ≥1 point
- Cutoff has been used in pediatric patients to evaluate clinically meaningful improvement in worst tumor pain severity[4]

Clinically Meaningful Improvement in PII

- Calculated as a reduction from BL of >0.8 points for adults and >0.6 points for children
- Reduction from BL thresholds for adults and children was calculated as a reduction from BL of >0.5*SD, using SD from BL
- Aligns with consensus recommendations for determining clinically important change in chronic pain outcome measures[5]

[a]Clinically meaningful change is the amount of individual level change over a predefined period that could be interpreted as a meaningful benefit.[2,3] [b]Patients who could have attained a clinically meaningful change had a baseline score greater than or equal to the clinically meaningful change threshold for the NRS-11, or greater than the clinically meaningful change threshold for the PII. **BL**, baseline; **LS**, least squares; **MMRM**, mixed model repeated measures; **NRS-11**, numeric rating scale; **PII**, Pain Interference Index; **PRO**, patient-reported outcomes.

1. Wolters PL, et al. *Neurology*. 2016;87(suppl 1)(7):S4-S12. **2.** FDA (2018). Accessed 7 Jun 2024. https://www.fda.gov/downloads/Drugs/NewsEvents/UCM620711.pdf. **3.** FDA (2022). Accessed 7 Jun 2024. https://www.fda.gov/media/159500/download. **4.** Hirschfeld G, et al. *J Pain*. 2014;15(1):32-9. **5.** Dworkin RH, et al. *J Pain*. 2008;9(2):105-21.

Baseline Demographics and Characteristics

	Adults (N=58)	Children (N=56)	
Age, median (range), y	34 (18 to 69)	10 (2 to 17)	
Sex, n (%)			
Female	37 (64)	30 (54)	
Male	21 (36)	26 (46)	
Type of PN-related morbidity, n (%)			
Pain	52 (90)	39 (70)	
Disfigurement or major deformity	30 (52)	28 (50)	
Motor dysfunction/weakness	23 (40)	15 (27)	
Airway dysfunction	3 (5)	7 (12)	
Other	10 (17)	12 (21)	
PRO pain scores at baseline, median (range)			
NRS-11 scores	4.7 (0-8.7) *n=51*	1.0 (0-9.2) *n=36*	
		Self-report	Parent proxy-report
PII scores	2.6 (0-5.3) *n=52*	0.5 (0-5.4) *n=45*	0.4 (0-4.3) *n=44*

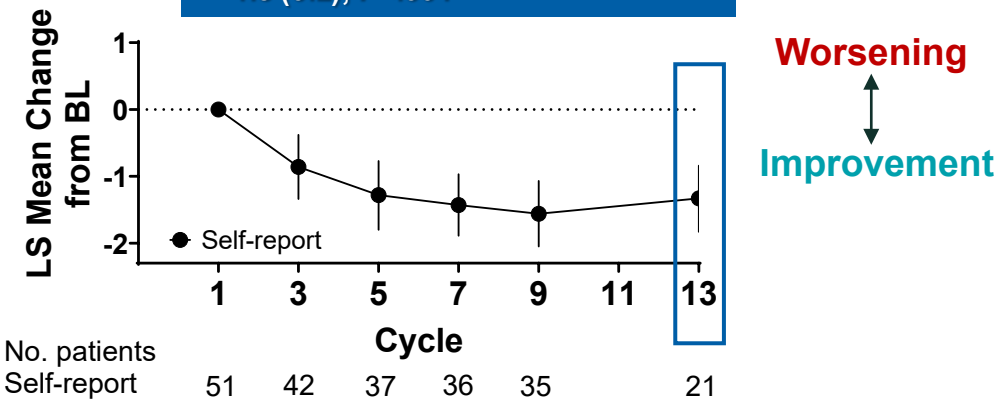
NRS-11 scores: range, 0 [no pain] to 10 [worst pain you can imagine]; higher scores indicate worse pain. PII scores: range, 0 [not at all] to 6 [completely]; higher scores indicate worse pain interference. **NRS-11,** Numeric Rating Scale-11; **PII**, Pain Interference Index; **PN**, plexiform neurofibroma.

Mirdametinib Demonstrated Improvements in Worst Tumor Pain Severity (NRS-11) and Pain Interference (PII) at Cycle 13[a]

ADULTS

Worst tumor pain severity (*NRS-11 score*)

LS mean (SE) change from BL[b] at C13
–1.3 (0.2); *P*<.001

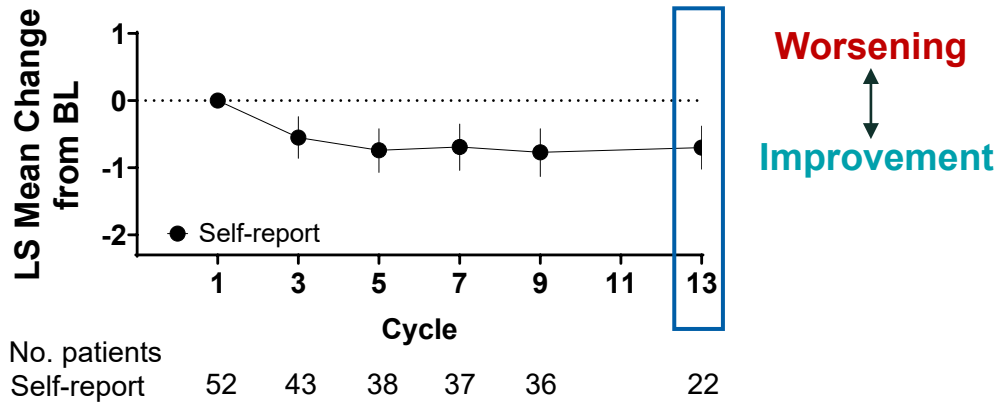


Worsening ↕ Improvement

No. patients
Self-report 51 42 37 36 35 21

Pain interference (*PII score*)

LS mean (SE) change from BL[b] at C13
–0.7 (0.2); *P*<.001

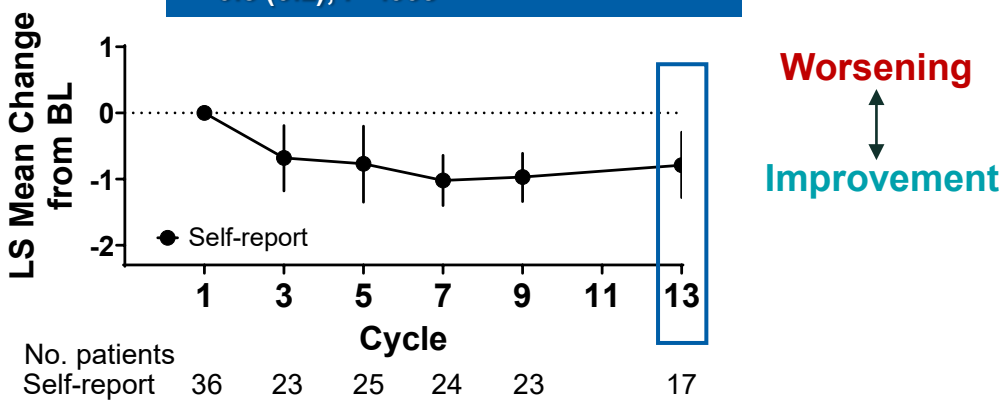


Worsening ↕ Improvement

No. patients
Self-report 52 43 38 37 36 22

CHILDREN

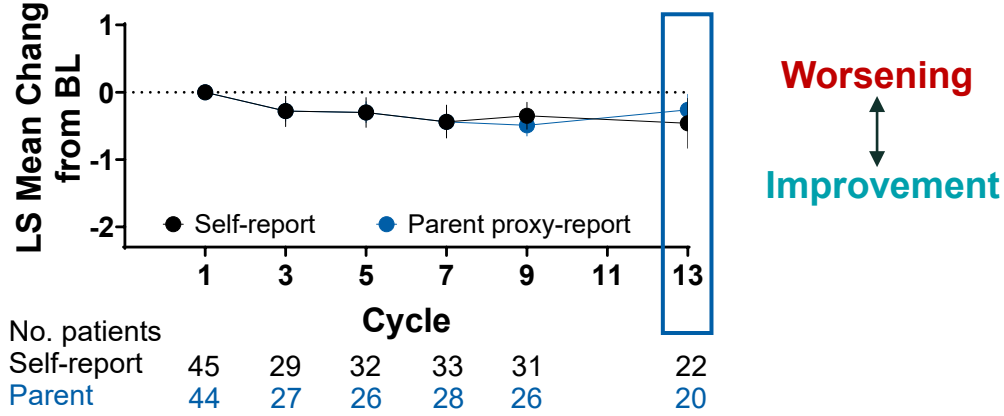
LS mean (SE) change from BL[b] at C13
–0.8 (0.2); *P*=.003



Worsening ↕ Improvement

No. patients
Self-report 36 23 25 24 23 17

LS mean (SE) change from BL[b] at C13
–0.5 (0.2); *P*=.017 (self-report)
–0.3 (0.1); *P*=.025 (parent proxy-report)



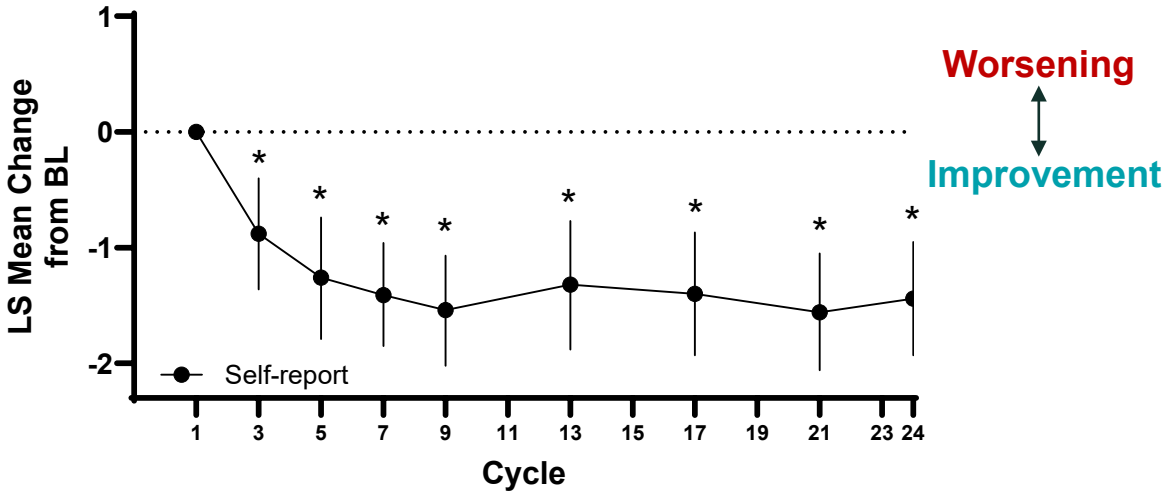
Worsening ↕ Improvement

No. patients
Self-report 45 29 32 33 31 22
Parent proxy-report 44 27 26 28 26 20

[a]Change from baseline in NRS-11 and PII scores at Cycle 13, Day 15 was a prespecified secondary endpoint. [b]BL was Cycle 1, Day 1. NRS-11 scores range from 0 (no pain) to 10 (worst pain imaginable); higher scores indicate worse pain. PII scores range from 0 (not at all) to 6 (completely); higher scores indicate greater pain interference (worsening). **BL**, baseline; **LS**, least-squares; **C**, Cycle; **No.**, number; **NRS-11**, Numeric Rating Scale-11; **PII**, Pain Interference Index.

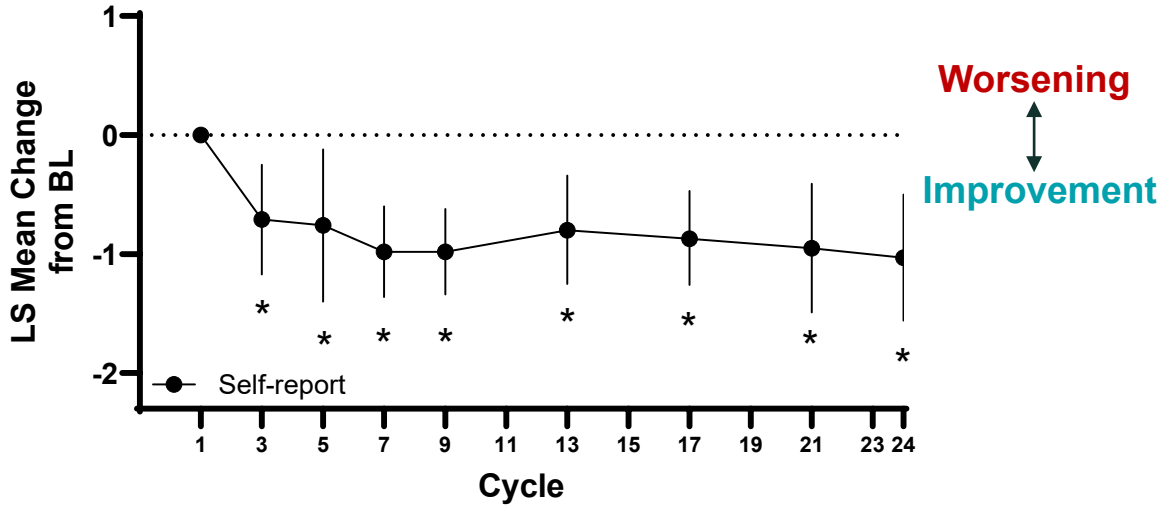
Mirdametinib Demonstrated Early and Sustained Improvement in Worst Tumor Pain Severity (NRS-11) Throughout the Treatment Phase

ADULTS



No. patients									
Self-report	51	42	37	36	35	21	21	16	17

CHILDREN



No. patients									
Self-report	36	23	25	24	23	17	18	11	8

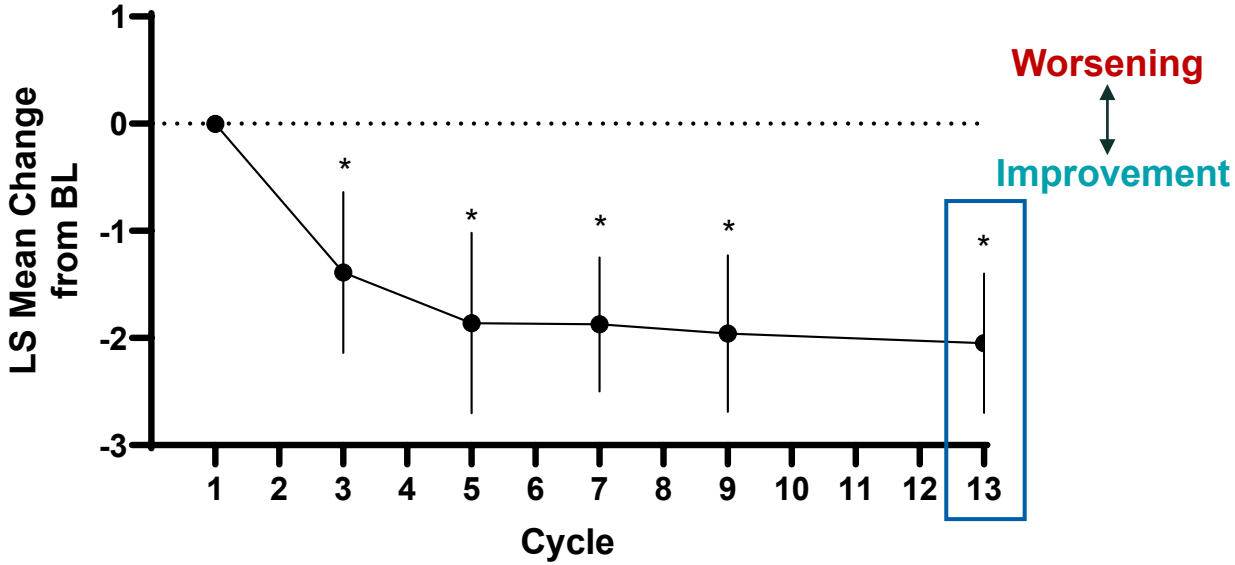
Significant improvement in **worst tumor pain severity** began early (Cycle 3, the first on-treatment assessment) and was sustained throughout the 24-cycle treatment phase

*P<.05 for a statistically significant change from BL. Vertical bars indicate 95% CIs. NRS-11 scores range from 0 (no pain) to 10 (worst pain imaginable); higher scores indicate worse pain. **BL**, baseline; **LS**, least-squares; **No.**, number; **NRS-11**, Numeric Rating Scale-11.

Mirdametinib Demonstrated Early and Sustained Improvement in Worst Tumor Pain Severity (NRS-11) in Adults and Children With Moderate-to-Severe Worst Tumor Pain Severity at Baseline

ADULTS

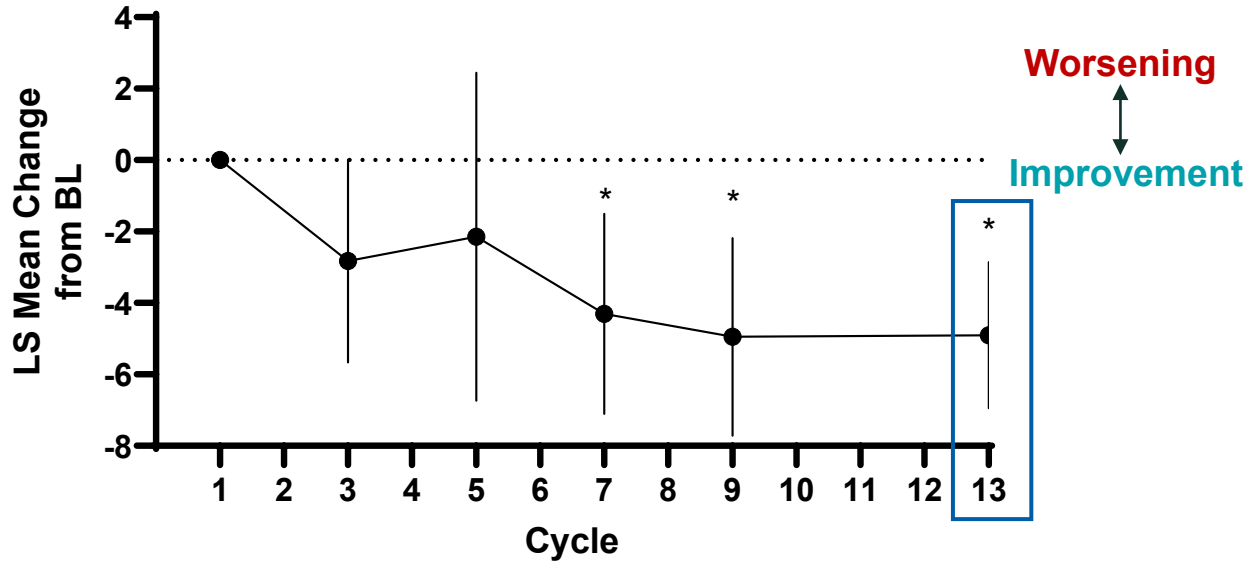
LS mean (SE) change from BL[a] at C13
–2.1 (0.3); *P*<.05



No. patients	29	23	20	18	18	9

CHILDREN

LS mean (SE) change from BL[a] at C13
–4.9 (0.8); *P*<.05



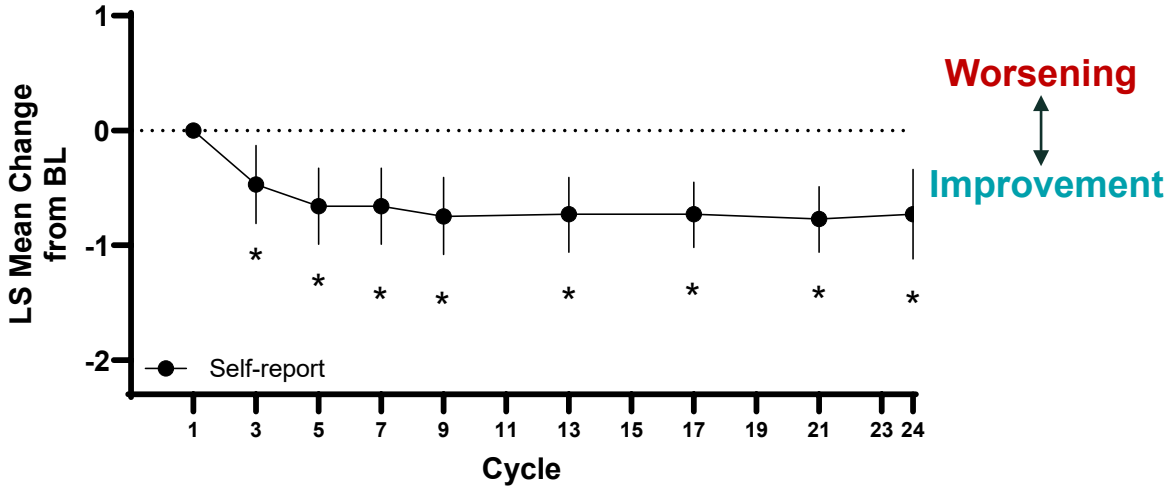
No. patients	7	4	3	5	2	4

Significant improvement in worst tumor pain severity began early (Cycle 3, the first on-treatment assessment) and was sustained in adults with moderate-to-severe pain at baseline (NRS-11 ≥4). Despite a small cohort size, significant improvement in worst tumor pain severity was seen in children as well.

*P<.05 for a statistically significant change from BL. [a]BL was Cycle 1, Day 1. Vertical bars indicate 95% CIs. NRS-11 scores: range, 0 [no pain] to 10 [worst pain you can imagine]; higher scores indicate worse pain. **BL**, baseline; **C**, Cycle; **LS**, least-squares; **No.,** number; **NRS-11**, Numeric Rating Scale-11.

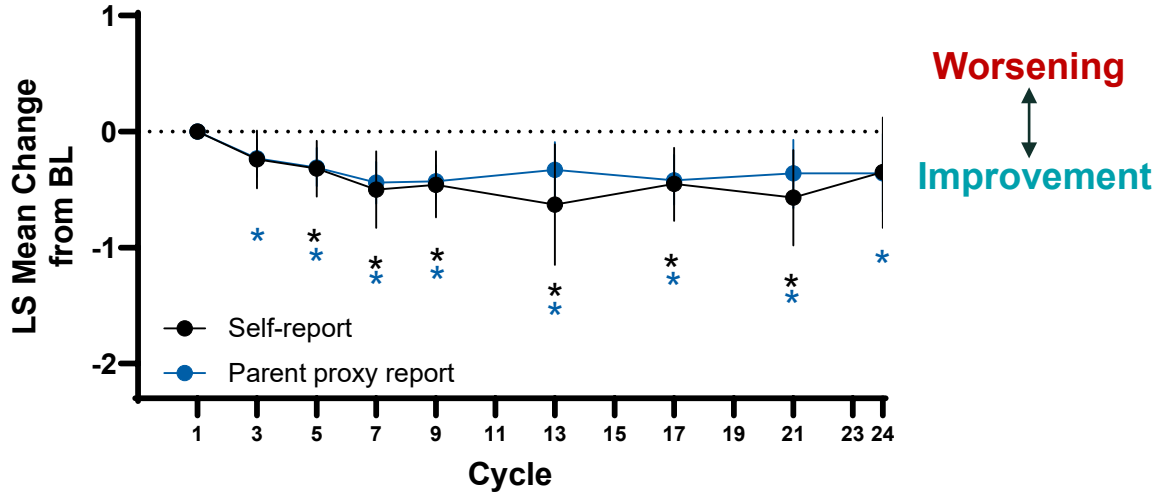
Mirdametinib Demonstrated Early and Sustained Improvement in Pain Interference (PII) Throughout the Treatment Phase

ADULTS



No. patients									
Self-report	52	43	38	37	36	22	21	16	17

CHILDREN

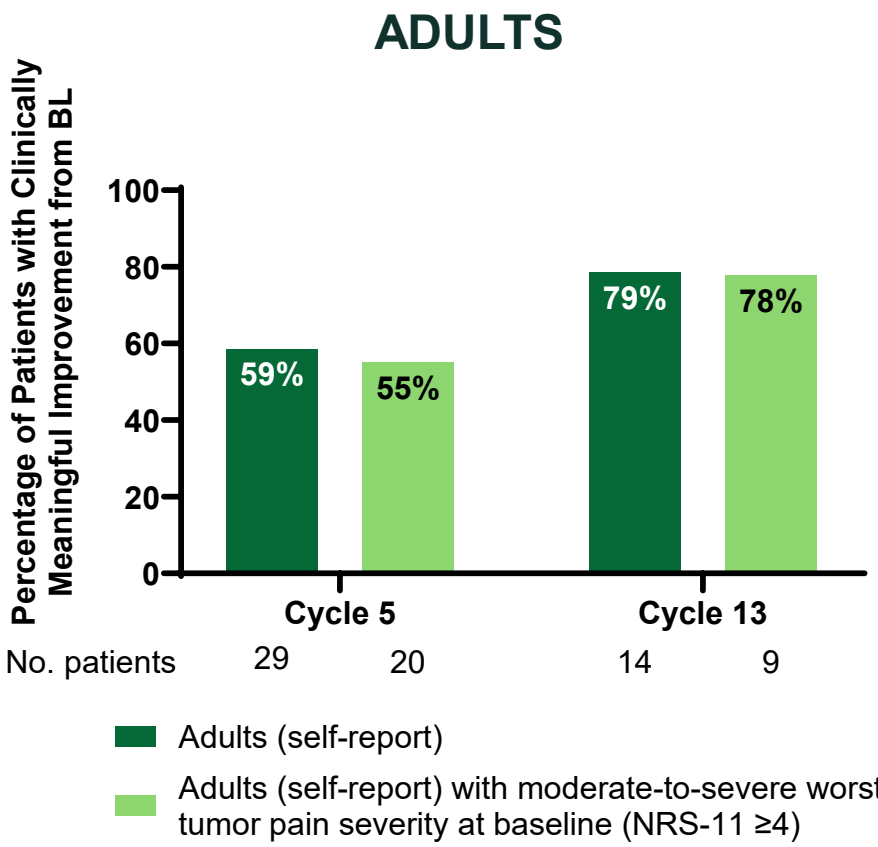


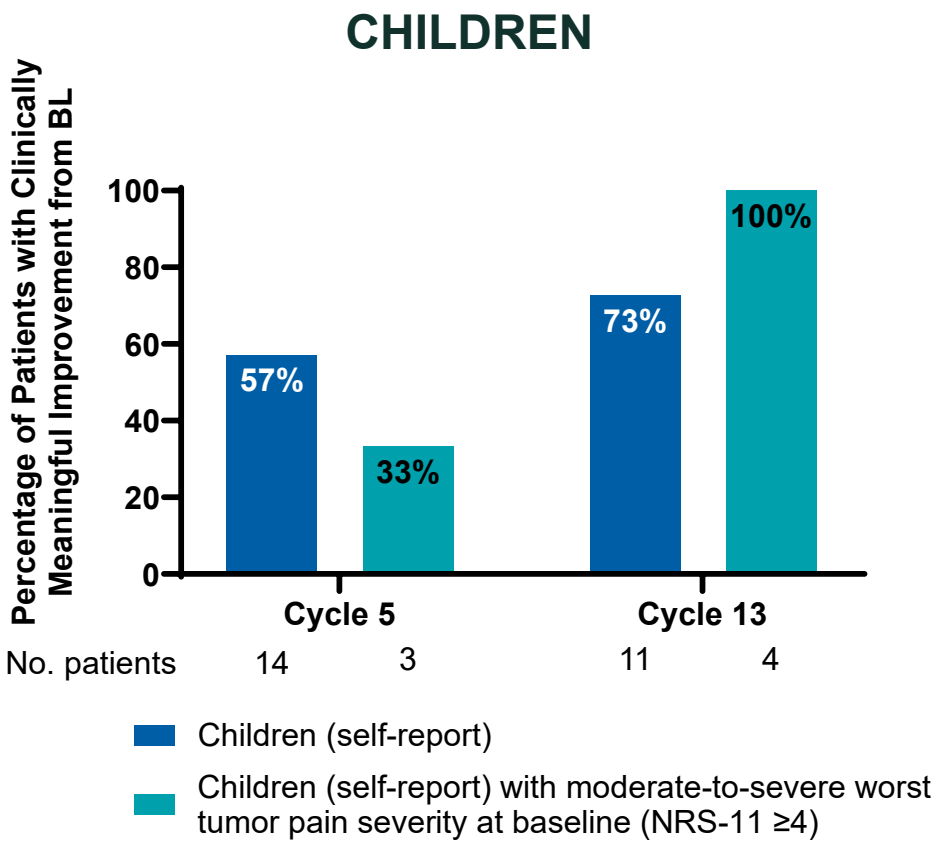
No. patients									
Self-report	45	29	32	33	31	22	25	17	12
Parent proxy report	44	27	26	28	26	20	20	14	16

Significant improvement in **pain interference** began early (Cycle 3, the first on-treatment assessment) and was sustained throughout the 24-cycle treatment phase

Vertical bars indicate 95% CIs. *P<.05 for a statistically significant change from BL. PII scores range from 0 (not at all) to 6 (completely); higher scores indicate greater pain interference (worsening). **BL**, baseline; **LS**, least-squares; **No.,** number; **PII**, Pain Interference Index.

Majority of Patients Achieved Clinically Meaningful Improvement From Baseline in Worst Tumor Pain Severity (NRS-11) With Mirdametinib

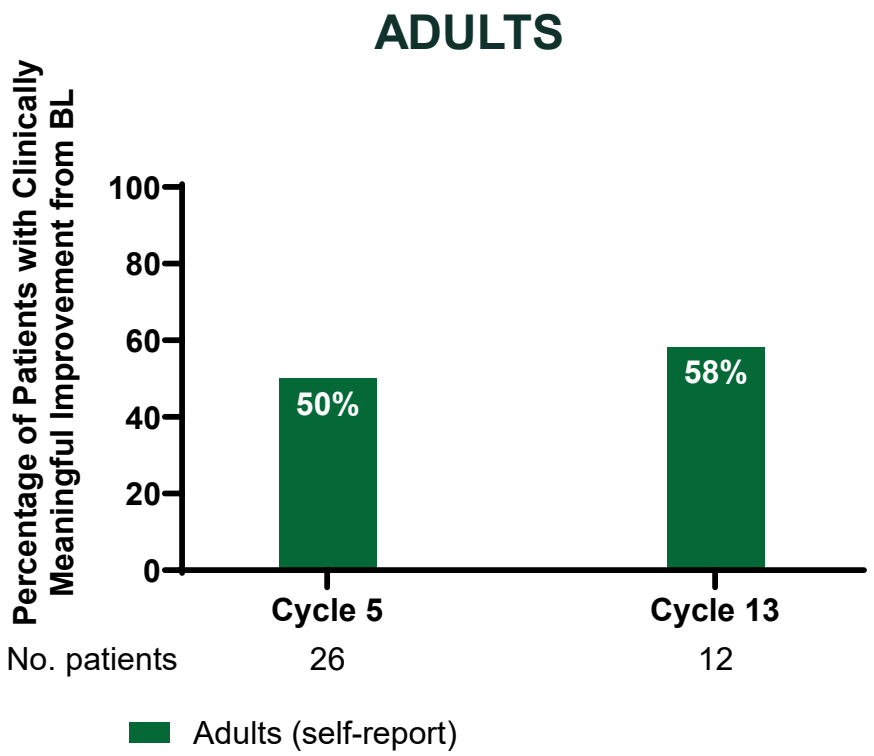


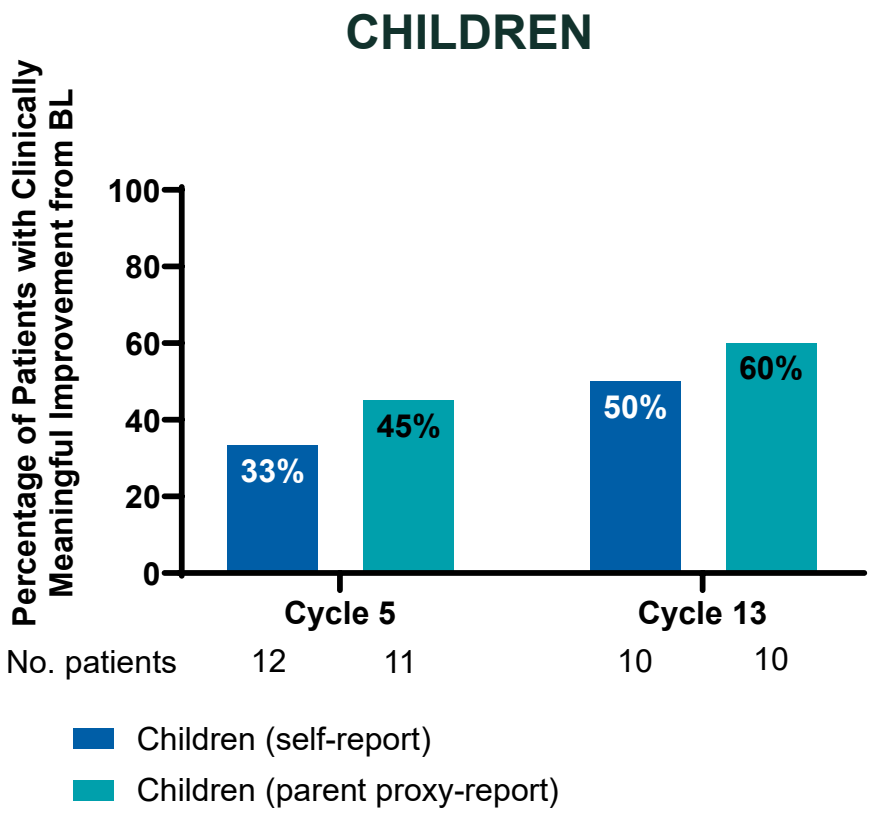


Analysis includes adults and children who could have achieved the clinically meaningful change threshold for the NRS-11[a]

[a]Patients could have attained the clinically meaningful change threshold if their baseline score was ≥1. NRS-11 scores range from 0 (no pain) to 10 (worst pain imaginable); higher scores indicate worse pain. **BL**, baseline; **No.,** number; **NRS-11**, Numeric Rating Scale-11.

Majority of Patients Achieved Clinically Meaningful Improvement From Baseline in Pain Interference (PII) With Mirdametinib





Analysis includes adults and children who could have achieved the clinically meaningful change threshold for the PII[a]

[a]Patients could have attained the clinically meaningful change threshold if their baseline score was >0.8 for adult self-report, and >0.6 for children self-report and parent-proxy report. PII scores: range, 0 [not at all] to 6 [completely]; higher scores indicate worse pain interference. **BL**, baseline; **No.,** number; **PII**, Pain Interference Index.

Summary

In addition to ReNeu meeting its primary endpoint of confirmed ORR, adults and children with NF1-PN in the ReNeu trial reported early, sustained, and clinically meaningful reductions in worst tumor pain severity and pain interference over the course of mirdametinib treatment

- Pain is a common morbidity in NF1-PN and was the most commonly reported BL morbidity in adults and children in the ReNeu trial
- Current clinical practice recommendations indicate that PN-related pain is an important factor in treatment-initiation decisions, and in most cases, the goal of treatment is improvement of PN-associated morbidity[1,2]
- Mirdametinib treatment demonstrated statistically significant and clinically meaningful improvement in worst tumor pain severity and pain interference in adults and children with NF1-PN, including those with moderate-to-severe worst tumor pain severity

NF1, neurofibromas type 1; **ORR**, overall response rate; **PN**, plexiform neurofibroma. **1.** Fisher MJ, et al. *Neuro Oncol*. 2022;24(11):1827-44. **2.** Armstrong AE, et al. *BMC Cancer*. 2023;23(1):553.

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