Health-Related Quality of Life (HRQoL) in Adults and Children With Neurofibromatosis Type 1-Associated Plexiform Neurofibroma (NF1-PN) Treated With Mirdametinib in the Pivotal Phase 2b ReNeu Trial

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Disclosures

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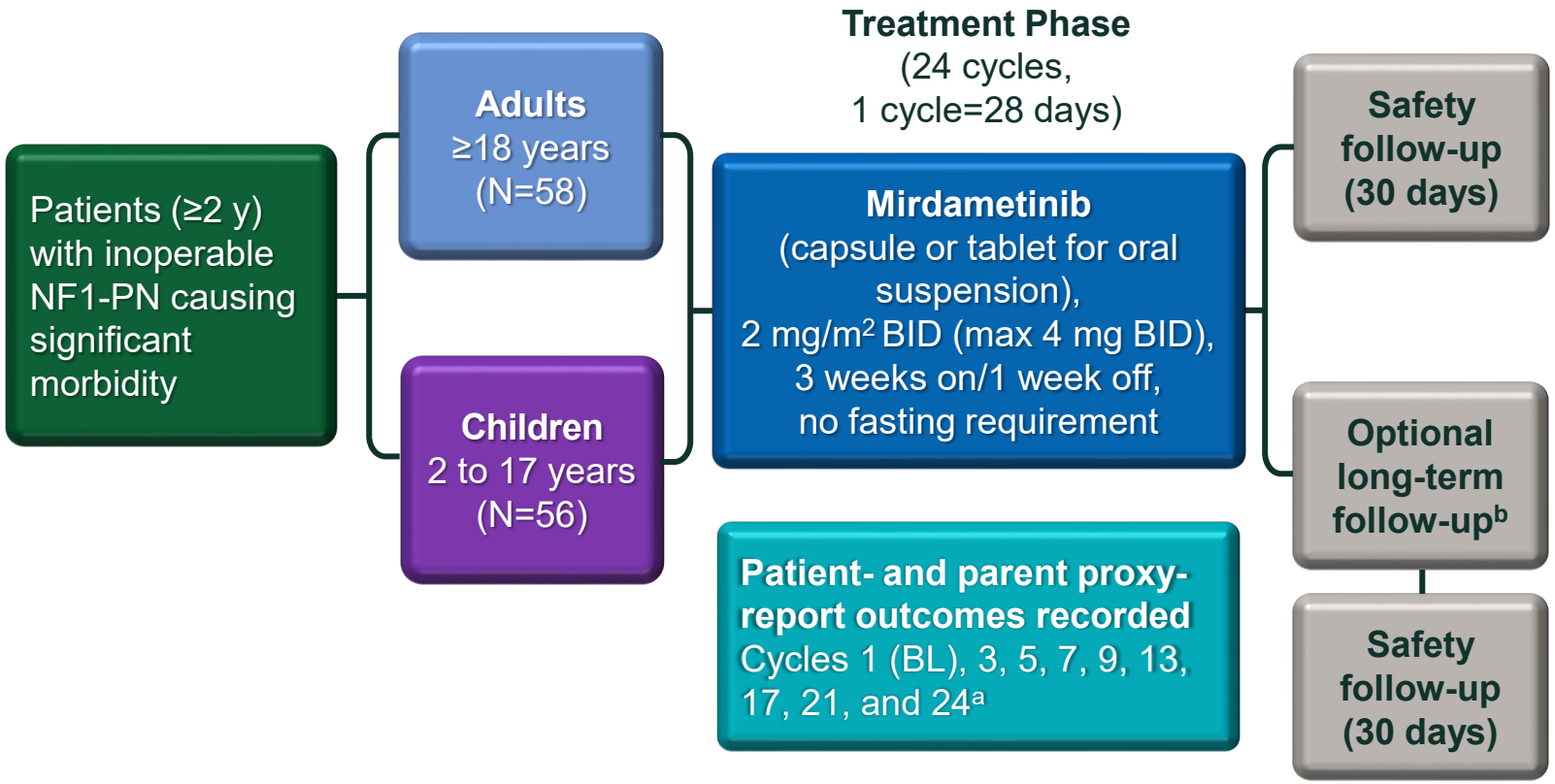
Introduction

- Plexiform neurofibromas (PNs) are nonmalignant peripheral nerve sheath tumors that develop in 30% to 50% of patients with neurofibromatosis type 1 (NF1)[1,2]
- Patients with NF1-PN can often experience pain, disfigurement, impaired physical functioning, and substantial deterioration in HRQoL[3,4]
- No pharmacologic therapies have been approved for adults; one MEK inhibitor is US FDA-approved for children (≥2 years of age)[5]
  - There is a need for effective and tolerable NF1-PN treatment options that improve HRQoL in adults and children
- Mirdametinib is an investigational, oral, highly selective, potent, allosteric, CNS-penetrant, small-molecule MEK1/2 inhibitor[6-9,a]

[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**, Food and Drug Administration; **HRQoL**, health-related quality of life; **MEK**, mitogen-activated protein kinase kinase; **NF1**, neurofibromatosis type 1; **NF1-PN**, neurofibromatosis type 1-associated plexiform neurofibroma; **PN**, plexiform neurofibroma.

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;24:1827-44. **5.** KOSELUGO [Prescribing Information]. AstraZeneca Pharmaceuticals LP; 2024. **6**. Weiss BD, et al. *J Clin Oncol*. 2021;39(7):797-806. **7.** LoRusso PM, et al. *Clin Cancer Res*. 2010;16(6):1924-37. **8.** Jousma E, et al. *Pediatr Blood Cancer*. 2015;62(10):1709-16. **9.** de Gooijer MC, et al. *Int J Cancer*. 2018;142(2):381-91.

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
- Patient/parent proxy-reported outcomes from BL at Cycle 13:
  - **Worst tumor pain severity (NRS-11)**
  - **Pain interference (PII)**
  - **HRQoL (PedsQL)**
- Safety and tolerability

[a]Patient- and parent proxy-reported outcomes were recorded at Cycle 1 Day 1 (Baseline) and at Day 15 of subsequent cycles, and Cycle 13 was the prespecified endpoint. [b]During 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. Confirmed ORR was compared with the null hypothesis (minimum clinically relevant response rate of 23% for adults and 20% for children). 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; **MRI**, magnetic resonance imaging; **NRS-11**, Numeric Rating Scale-11; **ORR**, objective response rate; **PedsQL**, Pediatric Quality of Life Inventory; **PII**, Pain Interference Index; **REiNS**, Response Evaluation in Neurofibromatosis and Schwannomatosis.

ClinicalTrials.gov. https://www.clinicaltrials.gov/study/NCT03962543. Accessed May 9, 2024.

Primary Results From the ReNeu Trial[1]

- Primary endpoint met, with confirmed ORR of 41% in adults (*P*<.001) and 52% in children (*P*<.001) during the treatment phase[a]
  - An additional 2 adults and 1 child achieved confirmed responses in the LTFU phase
- Median best target PN volume reduction from baseline was >40% in adults and children
- More than 50% of patients with a confirmed response achieved a deep response (>50% best PN volume reduction from baseline)
- In both adults and children, median duration of treatment was 22 months and median DoR was not reached
- Manageable safety profile with majority of TRAEs grade 1 or 2[b]

Objective: To report patient- and parent proxy-reported outcomes of HRQoL in adults and children with NF1-PN treated with mirdametinib from the ReNeu trial

[a]Confirmed ORR was compared with the null hypothesis (minimum clinically relevant response rate of 23% for adults and 20% for children). [b]The most commonly reported TRAEs were dermatitis acneiform, diarrhea, and nausea in adults and dermatitis acneiform, diarrhea, and paronychia in children. One treatment-related SAE in adult cohort, grade 3 RVO with confounding factors (hormonal contraception and COVID-19 vaccination). No treatment-related SAEs or RVO in pediatric cohort. **RVO**, retinal vein occlusion; **SAE**, serious adverse event; **TRAE**, treatment-related adverse event.

1. Moertel CL, et al. ASCO Annual Meeting, May 31-Jun 4, 2024.

Change in HRQoL (PedsQL) From Baseline Through Cycle 13

HRQoL – PedsQL 4.0 Generic Core Scales
Questionnaire Validated for Adults and Children[1,2,a]

Total Score
(Mean of all item scores)

Four Functioning Subscales

- **Physical Functioning**
- **Emotional Functioning**
- **Social Functioning**
- **School/Work Functioning**

Prespecified Analysis
LS mean MMRM analysis of change from BL by visit in PedsQL Total Score and Subscale Scores

- **Secondary endpoint**
  Change from BL at Cycle 13

Post hoc Analyses
Percentage of adults and children with a clinically meaningful improvement in PedsQL Total Score and Subscale Scores from BL at Cycle 13, among patients who could have attained a clinically meaningful improvement[b]

[a]Patient-reported by all patients ≥5 years of age and parent proxy-reported for all patients 2 to 17 years of age and patients with cognitive impairment ≥18 years of age. Items on the PedsQL are assessed on a Likert scale from 0 to 4. These are then reverse scored and linearly transformed to a 0-to-100 scale, with higher scores indicating better HRQoL. [b]Within-patient clinically meaningful thresholds of improvement for adults and children calculated as an increase from BL of >0.5 × SD, using SD from BL. Analyses were conducted among patients who could have attained a clinically meaningful improvement from baseline, defined as those with a baseline score lower than the difference between the maximum PedsQL score (100 points) and the MCT for improvement for PedsQL (ie, 100 – MCT). The MCT was calculated separately for PedsQL Total Score and each subscale.

LS, least squares; **MCT**, meaningful change threshold; **MMRM**, mixed model repeated measures; **SD**, standard deviation.

1. Varni JW, et al. *Expert Rev Pharmacoecon Outcomes Res*. 2005;5(6):705-19. **2**. Varni JW, Limbers CA. *J Health Psychol*. 2009 May;14(4):611-22.

Baseline Demographics, Morbidities, and HRQoL Scores

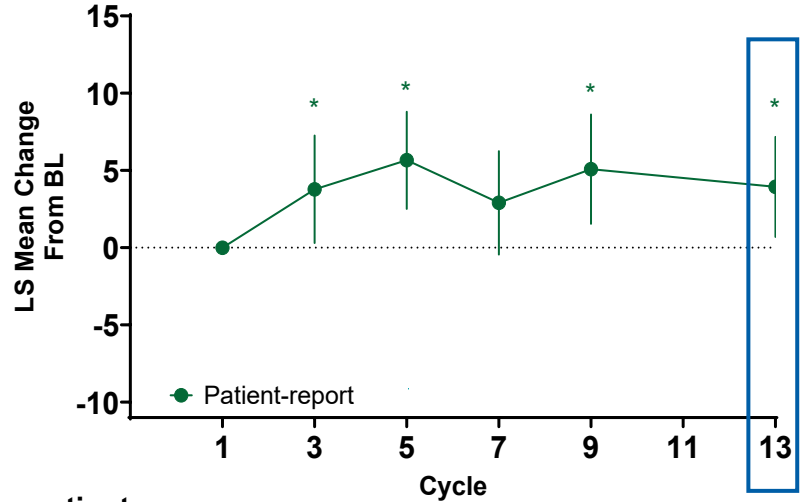
	Adults (N=58)	Children (N=56)	
Age, median (range), y	34 (18-69)	10 (2-17)	
Sex, n (%)			
Female	37 (64)	30 (54)	
Male	21 (36)	26 (46)	
Type of PN-related morbidity, n (%)			
Pain	52 (90)	39 (70)	
Disfigurement or major deformity	30 (52)	28 (50)	
Motor dysfunction or weakness	23 (40)	15 (27)	
Airway dysfunction	3 (5)	7 (12)	
Other	10 (17)	12 (21)	
PedsQL Scores at BL,[a] mean (range)	Patient-report (n=55)	Patient-report (n=50)	Parent proxy-report (n=55)
Total Score	67 (24-100)	76 (18-100)	72 (23-99)
Functioning Subscales			
➢ Physical	58 (0-100)	78 (12-100)	74 (0-100)
➢ Emotional	68 (5-100)	75 (5-100)	73 (35-100)
➢ Social	80 (10-100)	81 (20-100)	73 (5-100)
➢ School/Work	67 (15-100)	70 (15-100)	66 (0-100)[b]

[a]PedsQL items are assessed on a Likert scale from 0 (never a problem) to 4 (almost always a problem); these are reverse scored and linearly transformed to a 0-to-100 scale (0=100; 1=75; 2=50; 3=25; 4=0). PedsQL Total Score is the mean of all item scores; higher scores indicate better HRQoL. [b]n=54.

Prespecified Secondary Endpoint: Mirdametinib Treatment Demonstrated Improvement in HRQoL (PedsQL Total Score) From Baseline at Cycle 13

ADULTS

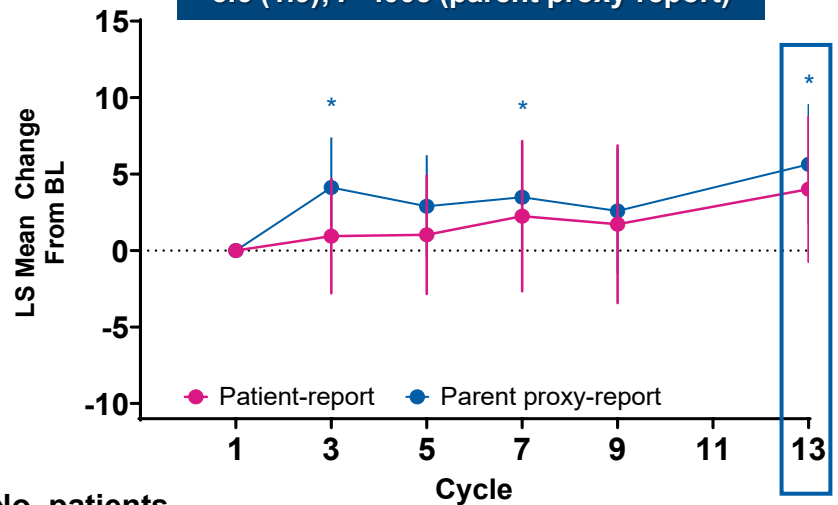
LS mean (SE) change from BL[a] at C13
3.9 (1.6); *P*=.018



No. patients						
Patient-report	55	48	46	44	44	34

CHILDREN

LS mean (SE) change from BL[a] at C13
4.0 (2.4); *P*=.096 (patient-report)
5.6 (1.9); *P*=.005 (parent proxy-report)



No. patients						
Patient-report	50	48	47	41	42	38
Parent proxy-report	55	52	52	48	47	43

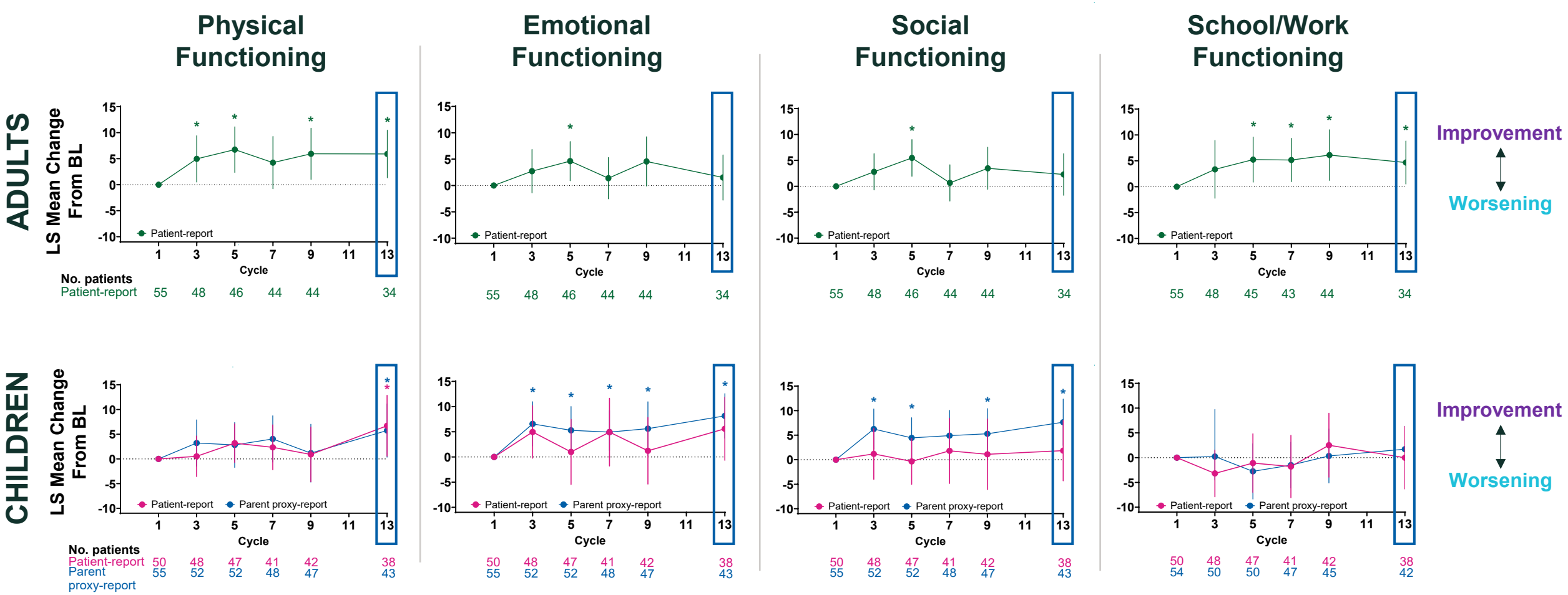
Improvement

Worsening

Improvement in **PedsQL Total Score** began early (Cycle 3, the first on-treatment assessment) and was sustained at most timepoints through Cycle 13 for adults and children by parent proxy-report

**P*<.05 for a statistically significant change from BL. [a]BL was Cycle 1, Day 1.
Error bars indicate 95% CIs. PedsQL items are assessed on a Likert scale from 0 (never a problem) to 4 (almost always a problem); these are reverse scored and linearly transformed to a 0-to-100 scale (0=100; 1=75; 2=50; 3=25; 4=0). PedsQL Total Score is the mean of all item scores; higher scores indicate better HRQoL. **No.**, number; **SE**, standard error.

Prespecified Secondary Endpoint: Mirdametinib Treatment Demonstrated Improvements in Several PedsQL Subscales From Baseline at Cycle 13

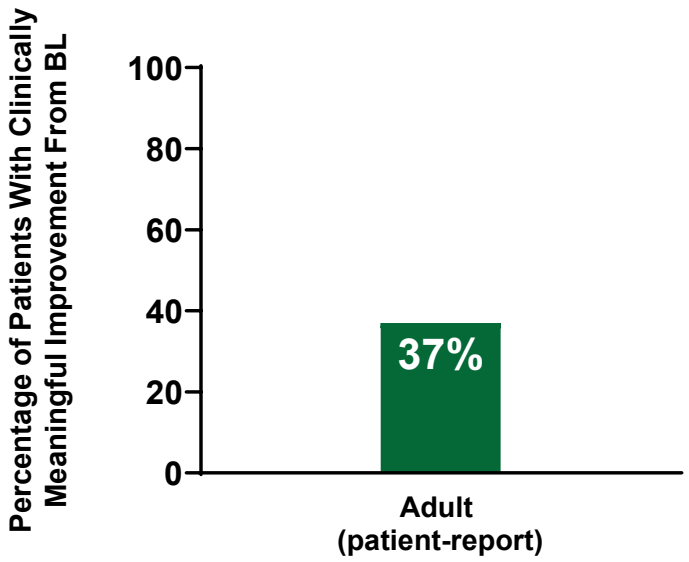


Improvement from BL at Cycle 13 was statistically significant for **Physical Functioning** (adult patient-report, child patient-report, and parent proxy-report), **Emotional Functioning** and **Social Functioning** (parent proxy-report), and **School/Work Functioning** (adult patient-report)

*P<.05 for a statistically significant change from BL. BL was Cycle 1, Day 1. Error bars indicate 95% CIs. PedsQL items are assessed on a Likert scale from 0 (never a problem) to 4 (almost always a problem); these are reverse scored and linearly transformed to a 0-to-100 scale (0=100; 1=75; 2=50; 3=25; 4=0). Higher scores indicate better HRQoL. **CI**, confidence interval.

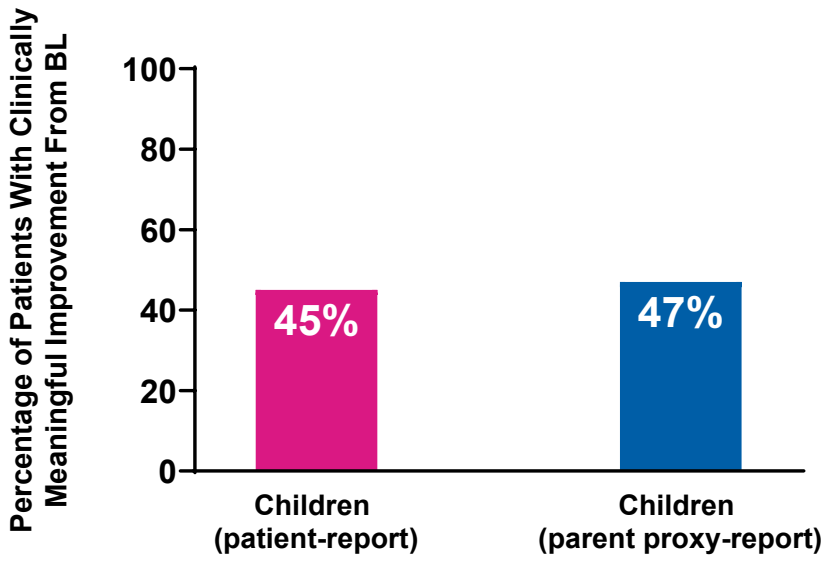
Adults and Children Achieved Clinically Meaningful Improvement at Cycle 13 From Baseline in HRQoL (PedsQL Total Score) With Mirdametinib

ADULTS



	Adult (patient-report)
No. patients	27

CHILDREN

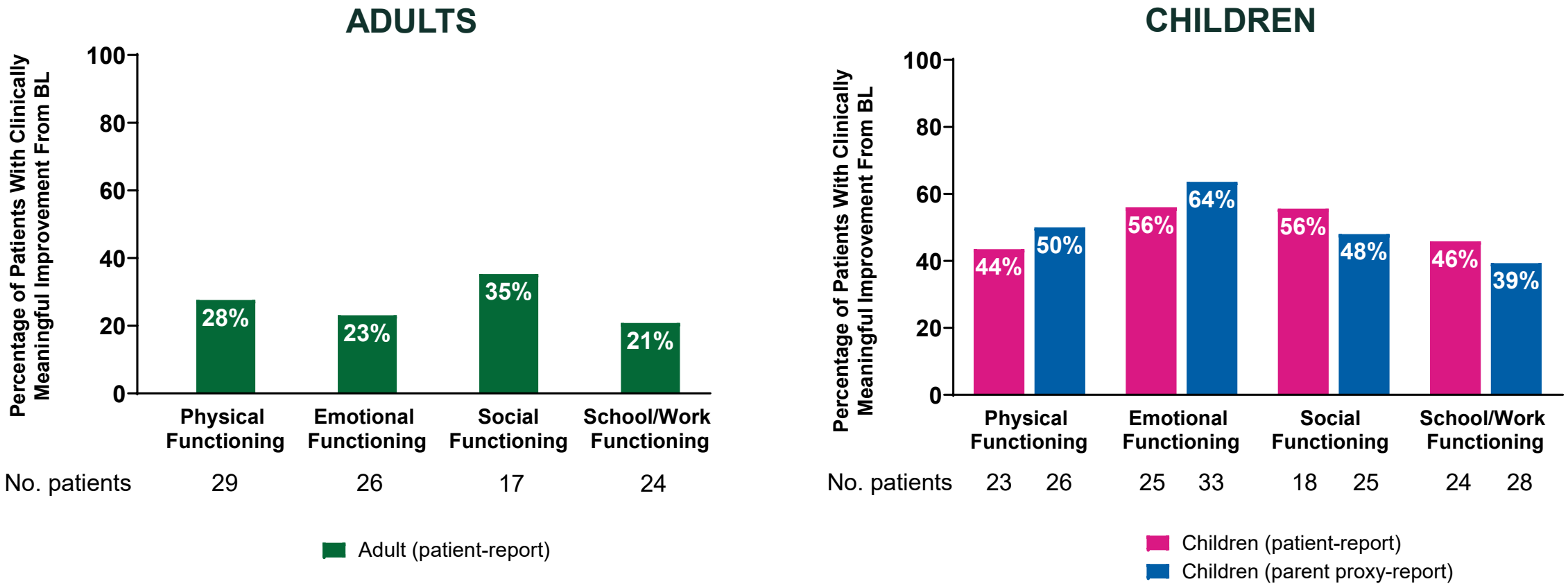


	Children (patient-report)	Children (parent proxy-report)
No. patients	29	32

Analysis included patients who could have achieved a clinically meaningful improvement in PedsQL Total Score[a,b]

[a]Patients could have attained a clinically meaningful improvement from baseline if their baseline score was lower than the difference between the maximum PedsQL score (100 points) and the MCT for improvement (ie, 100 – MCT).
[b]Within-patient clinically meaningful thresholds of improvement for adults and children calculated as an increase from BL of >0.5 × SD, using SD from BL. PedsQL items are assessed on a Likert scale from 0 (never a problem) to 4 (almost always a problem); these are reverse scored and linearly transformed to a 0-to-100 scale (0=100; 1=75; 2=50; 3=25; 4=0). PedsQL Total Score is the mean of all item scores; higher scores indicate better HRQoL.

Adults and Children Achieved Clinically Meaningful Improvement at Cycle 13 From Baseline in HRQoL (PedsQL Subscale Scores) With Mirdametinib



Analysis included patients who could have achieved a clinically meaningful improvement in PedsQL Subscale Score[a,b]

[a]Patients could have attained a clinically meaningful improvement from baseline if their baseline score was lower than the difference between the maximum PedsQL score (100 points) and the MCT for improvement (ie, 100 – MCT).
[b]Within-patient clinically meaningful thresholds of improvement for adults and children calculated as an increase from BL of >0.5 × SD, using SD from BL. PedsQL items are assessed on a Likert scale from 0 (never a problem) to 4 (almost always a problem); these are reverse scored and linearly transformed to a 0-to-100 scale (0=100; 1=75; 2=50; 3=25; 4=0). MCT for improvement calculated separately for each subscale score.

Summary

ReNeu trial: In addition to meeting the primary endpoint of confirmed ORR, early, sustained, and clinically meaningful improvements in HRQoL (PedsQL Total Score) were also observed during mirdametinib treatment

- Patients treated with mirdametinib had a significant improvement in PedsQL Total Score from BL at Cycle 13 as reported by adults and parents of children with NF1-PN (prespecified secondary endpoint)
- Clinically meaningful improvement was achieved from BL at Cycle 13 in the PedsQL Total Score and Subscales in adults and children
- These results, together with the significant ORR, deep and durable PN volume reductions, significant reductions in pain, manageable safety profile,[1] and availability as a tablet for oral suspension support the potential for mirdametinib to be a new and important treatment option for adults and children with NF1-PN

1. Moertel CL, et al. ASCO Annual Meeting, May 31-Jun 4, 2024.

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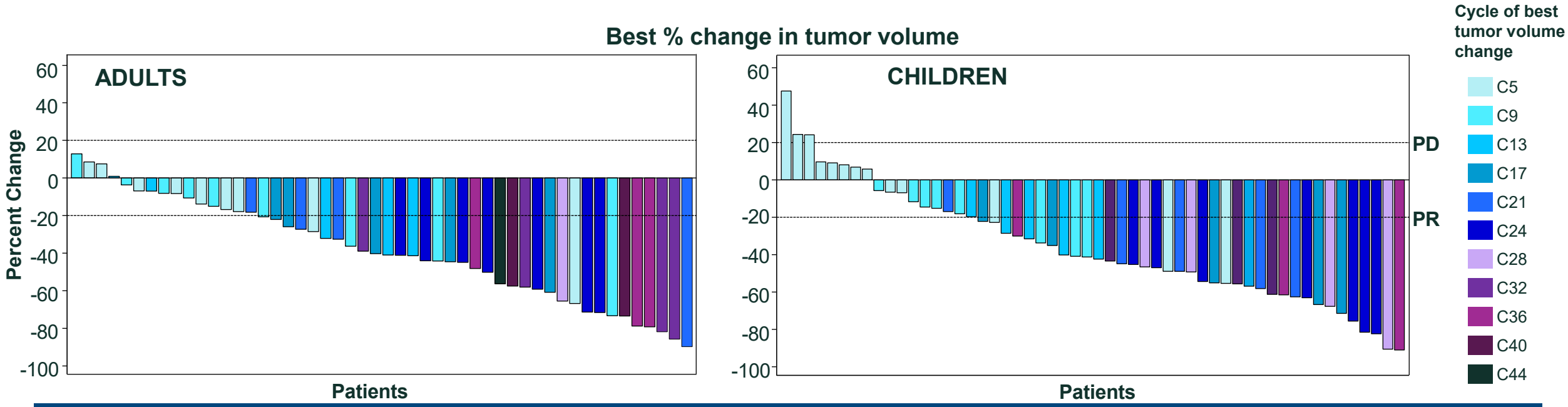
Mirdametinib Demonstrated Significant Confirmed ORR by BICR and Deep and Durable Tumor Volume Reductions in Adults and Children



	Adults	Children
Confirmed ORR during treatment phase (primary endpoint)[a,b]	41% (24/58; *P*<.001[c])	52%[a] (29/56; *P*<.001[c])
Confirmed ORR (treatment phase + LTFU phase)[b,d]	45% (26/58)	54% (30/56)
Median best change in tumor volume (range)	–41% (–90 to 13)	–42% (–91 to 48)
Percentage of patients with confirmed objective response who achieved a deep response (>50% tumor volume reduction from baseline)	62%	52%
Median DoR	Not reached	Not reached
Median DoT	22 months	22 months
Median time to onset of response (range)	7.8 months (4 to 19)	7.9 months (4 to 19)

[a]Confirmed ORR defined as proportion of patients with ≥20% reduction of target PN volume from baseline assessed by BICR on ≥2 consecutive scans within 2 to 6 months during the treatment phase. [b]Data cutoff: September 20, 2023. [c]The minimum clinically relevant ORR (null) was defined as 23% for adults and 20% for children. [d]84% of adults and 85% of children who completed the treatment phase chose to continue in the LTFU.
DoT, duration of treatment.

Mirdametinib Safety Profile

Treatment-related adverse events (TRAEs)	Adults (N=58)[a]		Children (N=56)	
Safety population, n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TRAE	**57 (98)**	**9 (16)**	**53 (95)**	**14 (25)**
TRAEs of any grade reported in ≥20% of patients in either cohort				
Dermatitis acneiform	45 (78)	5 (9)	24 (43)	1 (2)
Diarrhea	28 (48)	0 (0)	21 (38)	1 (2)
Nausea	21 (36)	0 (0)	12 (21)	0 (0)
Vomiting	16 (28)	0 (0)	8 (14)	0 (0)
Fatigue	12 (21)	1 (2)	5 (9)	0 (0)
Ejection fraction decreased	7 (12)	0 (0)	11 (20)	1 (2)
Blood creatinine phosphokinase increased	6 (10)	1 (2)	11 (20)	4 (7)
Paronychia	1 (2)	0 (0)	17 (30)	0 (0)
Serious TRAEs[b]	1 (2)		0 (0)	
Interruptions due to TRAEs	5 (9)		8 (14)	
Dose reductions due to TRAEs	10 (17)		7 (12)	
Discontinuations due to TRAEs[c]	12 (21)		5 (9)	

[a]There was one death due to COVID-19 in an adult (not considered to be treatment-related). [b]One treatment-related SAE in adult cohort, grade 3 RVO with confounding factors (hormonal contraception and COVID-19 vaccination). No treatment-related SAEs or RVO in pediatric cohort. [c]TRAEs leading to treatment discontinuation in >1 patient included dermatitis acneiform (4 adults, 1 child), diarrhea (4 adults, 1 child), nausea (4 adults), rash (1 adult, 1 child), and urticaria (2 children). The presence of more than 1 AE may have led to treatment discontinuation in a patient.