Evaluation of the Dispersible Tablet and Capsule Formulations of Mirdametinib in Children With Neurofibromatosis Type 1-Associated Plexiform Neurofibroma (NF1-PN): ReNeu Trial

POSTER #NFS-31

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INTRODUCTION

- Plexiform neurofibromas (PN) are nonmalignant nerve sheath tumors[1] that develop in 30% to 50% of patients with NF1[2,3]
  - PN often cause pain, impaired physical functioning and health-related quality of life, and organ displacement/compression, and they can carry a high relative risk for malignant transformation[4,5]
- There is an unmet need for highly effective and well-tolerated pharmacologic therapies that are available in an alternative formulation for children or adults with NF1-PN with difficulty swallowing[1,5,6]
- Mirdametinib is an investigational, highly selective, CNS-penetrant, small-molecule MEK1/2 inhibitor[7,8] that is orally administered as a dispersible tablet or capsule, with no fasting requirement
- We evaluated the efficacy, safety, and pharmacokinetics (PK) of mirdametinib dispersible tablets (liquid suspension) or capsules in children (≥2 to <18 years of age) and adults with symptomatic inoperable NF1-PN in the pivotal, phase 2b ReNeu trial (NCT03962543)

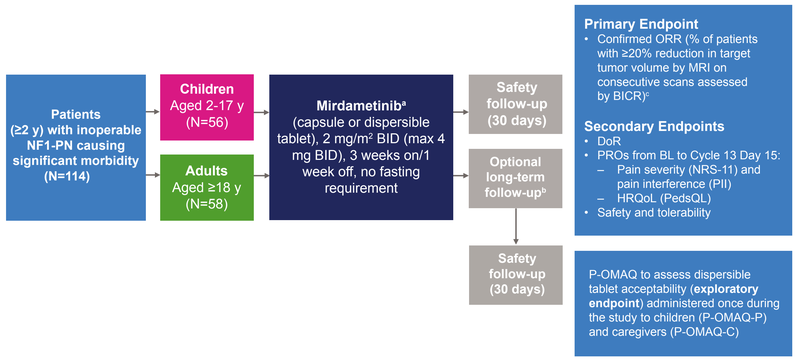
OBJECTIVE

- To report PK parameters and safety of mirdametinib formulations (dispersible tablets and capsules) and acceptability of the dispersible tablet formulation in children treated with mirdametinib in the ReNeu trial

METHODS

- In the open-label, multicenter, pivotal, phase 2b ReNeu trial, patients received either mirdametinib capsules or dispersible tablets at a dose of 2 mg/m^2 BID (maximum 4 mg BID) in 3 weeks on/1 week off 28-day cycles (**Figure 1**)
- For assessment of PK parameters in children, serial PK samples (pre-dose and post-dose at 0.5, 1, 2, 3, and 4 hours) were collected after steady state levels of mirdametinib were achieved (Cycle 1, Day 15)
- Treatment-emergent adverse events (AEs), defined as those that emerged or worsened after the first dose through 30 days after the last dose, were coded per MedDRA version 24.0
- Acceptability of the dispersible tablet was assessed by the Pediatric Oral Medicine Acceptability Questionnaire (P-OMAQ), a content-valid questionnaire for quantifying the acceptability of pediatric oral medicines[9]
  - The 12-item patient self-report version (P-OMAQ-P) for patients 8-17 years of age and the 19-item caregiver version (P-OMAQ-C) for adult caregivers of patients 2 to 17 years of age were both administered once during the study at any time point from Cycle 3 onwards
  - Each questionnaire requested recall of the last 7-day period and utilized a 5-point numerical rating scale for acceptability (1, not at all; 5, very), with higher scores indicating greater acceptability of the dispersible tablet

Figure 1. ReNeu (NCT03962543) Trial Design



[a]Capsules were administered unless a patient requested the use of the dispersible tablet formulation. [b]In the optional long-term follow-up phase, patients continue receiving mirdametinib at the last dose assigned in the treatment phase. [c]Per REiNS criteria. Primary endpoint assessed in 24-cycle treatment phase. BICR, blinded independent centralized review; BID, twice a day; BL, baseline; DoR, duration of response; HRQoL, health-related quality of life; NRS-11, Numeric Rating Scale-11; ORR, objective response rate; PedsQL, Pediatric Quality of Life Inventory; PII, Pain Interference Index; P-OMAQ, Pediatric Oral Medicine Acceptability Questionnaire; PRO, patient-reported outcome; REiNS, Response Evaluation in Neurofibromatosis and Schwannomatosis; y, years of age.

RESULTS

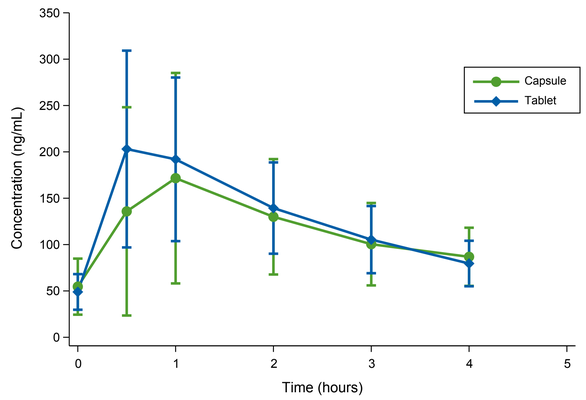
BASELINE DEMOGRAPHICS

- Fifty-six children received either mirdametinib dispersible tablets (n=21) or capsules (n=35) and were included in the safety analysis set; 53 children (n=20 tablets; n=33 capsules) with evaluable PK data were included in the PK population
  - In the adult cohort, 1 patient received dispersible tablets (not included in this analysis), and the remaining 57 patients received capsules
- The median (range) age at time of consent was 6.0 years of age (2-14 years of age) for children receiving tablets and 13.0 years of age (5-17 years of age) for children receiving capsules
- Other patient demographics and baseline characteristics (sex, race, ethnicity, and Karnofsky/Lansky performance status) were generally comparable for children receiving tablets, children receiving capsules, and the overall population of children

PHARMACOKINETICS

- PK parameters of mirdametinib in children receiving dispersible tablets were generally comparable with those in children receiving capsules (**Figure 2, Table 1**)

Figure 2. Mirdametinib Mean Plasma Concentration in Children by Formulation



Concentration-time plot at Cycle 1, Day 15. Error bars are SD. The lower limit of quantification was 1.00 ng/mL.

Table 1. Mirdametinib PK Parameters in Children (Overall and by Formulation) in the PK Population (n=53)

	OVERALL (N=53)	DISPERSIBLE TABLET (N=20)	CAPSULE (N=33)
AUC_{last}, geometric mean (CV%), ng·h/mL	459 (45.6%)	511 (35.7%)	430 (50.2%)
C_{max}, geometric mean (CV%), ng/mL	191 (61.7%)	217 (47.0%)	177 (69.1%)
T_{max}, median (range), h	1.0 (0.0-4.0)	0.9 (0.4-3.0)	1.0 (0.0-4.0)
T_{last}, median (range), h	4.0 (3.8-4.2)	4.0 (3.9-4.1)	4.0 (3.8-4.2)

AUC_{last}, area under the concentration-time curve from time zero to the time of last observed plasma concentration; C_{max}, maximum observed plasma concentration; CV%, percent coefficient of variation; h, hours; PK, pharmacokinetics; T_{last}, time of last observed plasma concentration; T_{max}, time to maximum observed plasma concentration.

SAFETY

- The majority of AEs with each formulation were grade 1 or 2 (**Table 2**)
- Skin AEs were reported by children who received dispersible tablets (81%) and capsules (91%)
- The median age of children receiving the dispersible tablet was 6 years of age, while the median age of children receiving the capsule formulation was 13 years of age. Observed differences between formulations were consistent with the difference in age for patients receiving each formulation (**Table 3**), considering that MEK inhibitor AE presentation varies by age and pubertal status[10,11]
- No new formulation-specific AEs were identified

Table 2. Most Common AEs and TRAEs in Children Treated With Mirdametinib by Formulation and Patient Age (Safety Analysis Set, n=56)

	DISPERSIBLE TABLET (N=21)				CAPSULE (N=35)			
	AE		TRAE		AE		TRAE	
	ANY GRADE	GRADE 3-4	ANY GRADE	GRADE 3-4	ANY GRADE	GRADE 3-4	ANY GRADE	GRADE 3-4
Patient age, median (range)	6.0 (2.0-14.0)				13.0 (5.0-17.0)			
AEs and TRAEs of any grade reported in ≥20% of children, n (%)[a]								
Diarrhea	12 (57)	1 (5)	6 (29)	0 (0)	19 (54)	2 (6)	15 (43)	1 (3)
Cough	7 (33)	0 (0)	0 (0)	0 (0)	5 (14)	0 (0)	0 (0)	0 (0)
COVID-19	7 (33)	0 (0)	0 (0)	0 (0)	7 (20)	0 (0)	0 (0)	0 (0)
Paronychia	7 (33)	0 (0)	7 (33)	0 (0)	11 (31)	0 (0)	10 (29)	0 (0)
Vomiting	7 (33)	0 (0)	1 (5)	0 (0)	15 (43)	0 (0)	7 (20)	0 (0)
Pyrexia	6 (29)	0 (0)	0 (0)	0 (0)	5 (14)	0 (0)	1 (3)	0 (0)
Rash	6 (29)	0 (0)	3 (14)	0 (0)	5 (14)	1 (3)	4 (11)	1 (3)
Abdominal pain	5 (24)	0 (0)	1 (5)	0	10 (29)	2 (6)	7 (20)	2 (6)
Blood creatine phosphokinase increased	5 (24)	3 (14)	5 (24)	3 (14)	7 (20)	1 (3)	6 (17)	1 (3)
Headache	5 (24)	0 (0)	0	0 (0)	14 (40)	1 (3)	6 (17)	0 (0)
Nausea	5 (24)	0 (0)	3 (14)	0 (0)	10 (29)	0 (0)	9 (26)	0 (0)
Pain in extremity	5 (24)	0 (0)	0 (0)	0 (0)	6 (17)	1 (3)	3 (9)	1 (3)
SARS-CoV-2 test positive	5 (24)	0 (0)	0 (0)	0 (0)	6 (17)	0 (0)	0 (0)	0 (0)
Upper respiratory tract infection	5 (24)	0 (0)	0 (0)	0 (0)	8 (23)	0 (0)	1 (3)	0 (0)
Dermatitis acneiform	4 (19)	0 (0)	4 (19)	0 (0)	20 (57)	1 (3)	20 (57)	1 (3)
Ejection fraction decreased	4 (19)	0 (0)	4 (19)	0 (0)	11 (31)	1 (3)	7 (20)	1 (3)

Data are given as number of patients (%), unless otherwise specified. AEs and TRAEs are reported by order of decreasing incidence in the dispersible tablet cohort. AEs were defined as those that started or worsened on or after the first dose of study treatment, including those occurring or increasing in severity up to 30 days after the last dose of study treatment. There was one treatment-related grade 4 blood creatine phosphokinase increase that was asymptomatic. All events of ejection fraction decrease were asymptomatic. [a]Eczema, which occurred in 14% of children overall, was reported in 24% (AE) and 19% (TRAE) of children taking the dispersible tablet and 9% (AE) and 6% (TRAE) of children taking the capsule. AE, adverse event; TRAE, treatment-related adverse event.

Table 3. AEs in Children Treated With Mirdametinib With a ≥15% Difference by Formulation and Patient Age (Safety Analysis Set, n=56)

	DISPERSIBLE TABLET (N=21)	CAPSULE (N=35)
Patient age, median (range)	6.0 (2.0 to 14.0)	13.0 (5.0 to 17.0)
AE with a ≥15% difference by formulation, n (%)		
Cough	7 (33)	5 (14)
Rash	6 (29)	5 (14)
Alopecia	5 (24)	3 (9)
Eczema	5 (24)	3 (9)
Headache	5 (24)	14 (40)
Dermatitis acneiform	4 (19)	20 (57)
Otitis media	4 (19)	0 (0)
Weight increased	1 (5)	8 (23)

Data are number of patients (%) unless otherwise noted. AEs reported by order of decreasing incidence in the dispersible tablet cohort. Each patient is counted only once for each preferred term. AEs (all-cause) were defined as those that started or worsened on or after the first dose of study treatment, including those AEs occurring or increasing in severity up to 30 days after the last dose of study treatment. AE, adverse event.

DISPERSIBLE TABLET ACCEPTABILITY

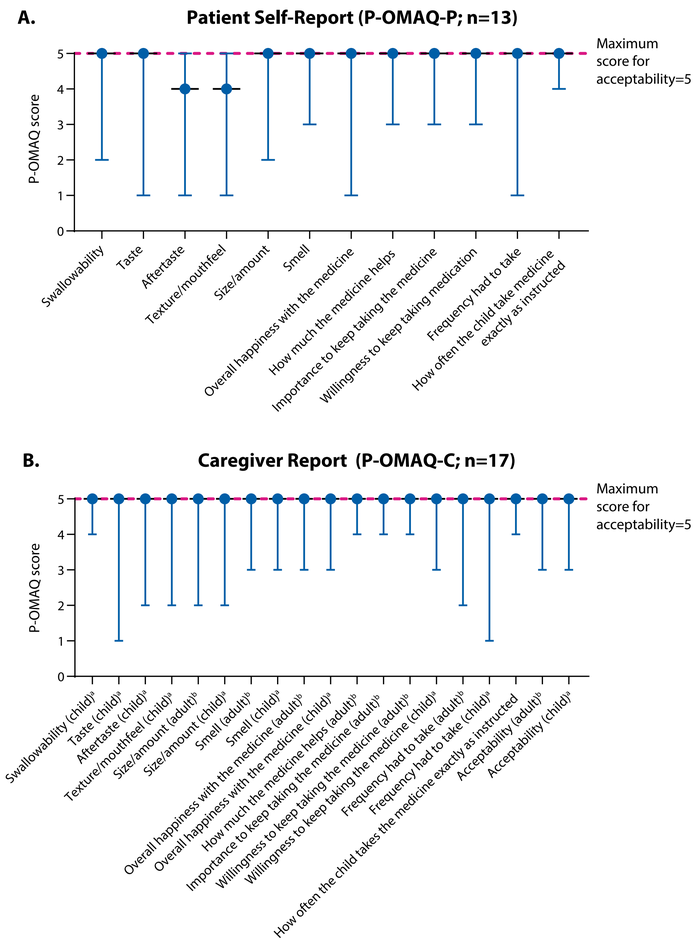
- Median overall P-OMAQ scores demonstrated high overall acceptability of the dispersible tablet by both patients and caregivers (**Table 4**)
- Both patients and caregivers reported high P-OMAQ scores for attributes of the dispersible tablet formulation (median score of 4 or 5 for each item out of a maximum score of 5; **Figure 3**)

Table 4. Overall Acceptability of Dispersible Tablets in Children: P-OMAQ Overall Score by Patient Self-Report and Caregiver Report

CATEGORY	PATIENT SELF-REPORT (P-OMAQ-P, N=13)	CAREGIVER REPORT (P-OMAQ-C, N=17)
P-OMAQ overall score, median (range)[a]	4.7 (3.0-5.0)	4.8 (3.1-5.0)

P-OMAQ-P is a self-report assessment for children 8-17 years of age. P-OMAQ-C is completed by adult caregivers of children 2 to 17 years of age. Both P-OMAQ-P for children taking the dispersible tablet and P-OMAQ-C for their caregivers were administered once during study as appropriate according to the child's age. [a]The overall score is derived as the mean of the individual question scores which range from 1 to 5, with a higher score indicating greater acceptability. P-OMAQ, Pediatric Oral Medicine Acceptability Questionnaire.

Figure 3. Median P-OMAQ Scores by (A) Patient Self-Report and (B) Caregiver Report for Children Taking Mirdametinib Dispersible Tablets



Blue circles represent median scores and vertical bars represent range. P-OMAQ-P is a self-report assessment for children 8-17 years of age. P-OMAQ-C is completed by adult caregivers of children 2-17 years of age. Both P-OMAQ-P for children taking the dispersible tablet and P-OMAQ-C for their caregivers were administered once during study as appropriate according to the child's age. Each questionnaire had a 7-day recall period and used a 5-point numerical rating scale for acceptability (1, not at all; 5, very), with higher scores indicating greater acceptability. [a]Question for adult caregivers about how their child feels about the medicine. [b]Question for adult caregivers regarding how they feel about the medicine. P-OMAQ, Pediatric Oral Medicine Acceptability Questionnaire.

CONCLUSIONS

- In ReNeu, PK profiles were generally comparable for the dispersible tablet and capsule formulations in children with NF1-PN
- The observed differences in AEs between the formulation groups were consistent with the younger age of children receiving tablets compared to those receiving capsules
  - Skin AEs are a known class effect of MEK inhibitors. An age-associated difference in skin AEs was observed between formulation groups (dermatitis acneiform was more common in the capsule group, and rash and eczema were more common in the dispersible tablet group); this difference was expected, given that skin AE presentation varies by age[10,11]
- Patients and caregivers reported high acceptability on all parameters (P-OMAQ scores) for the dispersible tablet formulation
- The dispersible tablet formulation of mirdametinib provides an acceptable dosing option with a tolerable safety profile for children or adults with swallowing difficulties

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