Indirect Treatment Comparison (ITC) of Mirdametinib and Selumetinib for the Treatment of Children With Neurofibromatosis Type 1 (NF1)-Associated Plexiform Neurofibroma (PN)

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BACKGROUND

- Neurofibromatosis type 1 (NF1) is an autosomal-dominant genetic condition with a birth incidence of approximately 1/2500[1]
- Plexiform neurofibromas (PNs) are nonmalignant nerve sheath tumors reported in 30% to 50% of people with NF1[2-4]
  - PNs often cause morbidities including pain, impaired health-related quality of life, disfigurement, and increased risk of malignant transformation[5]
- The goal of treatment is to reduce PN-related morbidity by reducing tumor volume, although current treatment options are limited[5]
- Mirdametinib is a US Food and Drug Administration (FDA)-approved MEK1/2 inhibitor for both adults and children (≥2 years of age) with NF1 who have symptomatic PN not amenable to complete resection (ReNeu, NCT03962543)[6]
- Selumetinib is an FDA-approved MEK1/2 inhibitor for children (≥2 to <18 years of age) with symptomatic, inoperable NF1-PNs (SPRINT, NCT01362803)[7]
- ReNeu is a pivotal, phase 2b trial of mirdametinib in patients with NF1-PN, which met the primary endpoint of confirmed objective response rate (ORR; 41% of adults and 52% of children)[8]
- No head-to-head trials assessing the relative efficacy and safety of mirdametinib and selumetinib have been conducted to date

OBJECTIVE

- In the absence of comparative head-to-head trials, an indirect treatment comparison (ITC) was conducted to assess the relative efficacy and safety of mirdametinib and selumetinib in pediatric patients with NF1-PNs using data from the ReNeu and SPRINT trials, respectively

MATERIALS AND METHODS

- A feasibility assessment showed that ReNeu and SPRINT were comparable in terms of study design, treatment characteristics, and endpoint definitions; however, imbalances were observed in the patient characteristics, indicating potential baseline differences between the 2 trial populations[8,9]
- Considering the lack of a common arm and the availability of the individual patient-level data from the ReNeu trial, unanchored population-adjusted indirect comparison (PAIC) approaches were deemed feasible to assess the relative efficacy and safety of mirdametinib and selumetinib
- Matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) are commonly used PAIC methods recommended in Technical Support Document (TSD) 18 from the National Institute for Health and Care Excellence Decision Support Unit[10]
- In the MAIC approach, patients in the ReNeu trial were weighted to match the published aggregate baseline characteristics of SPRINT; in the STC, an outcome regression model was fit to data of ReNeu, which was used to predict outcomes for the SPRINT population
- Prognostic variables (PVs) and effect modifiers (EMs) need to be adjusted for in unanchored MAIC and STC per the TSD[10]; because of the single-arm design of ReNeu, only PVs were tested
- In the base-case analysis, PVs identified as significant in univariate logistic regression for confirmed ORR and generalized linear models for mean best percent reduction from baseline in target PN volume (*P* value <.1) were adjusted in the ITC analysis; if no significant PV was identified for an endpoint, clinically important variables identified by NF1 clinical experts were adjusted in the ITC analysis instead
  - Few PVs reached statistical significance based on the ReNeu clinical trial data, necessitating this approach
- An analysis to determine which PVs were statistically significant for each treatment-related adverse event (TRAE) was not conducted because of the large number of TRAEs included in this analysis and low incidence rates for the reported TRAEs; therefore, only the PVs identified by the NF1 clinical experts were considered for the base case
- A comparison of commonly reported baseline characteristics adjusted in the ITC analysis is shown in **Table 1**

Table 1. Comparison of Baseline Characteristics Adjusted in the ITCs

	MIRDAMETINIB (n=56) ReNeu – Pediatric Cohort	SELUMETINIB (n=50) SPRINT
Age, years, mean (SD)[a]	10.60 (4.45)	10.30 (3.92)
Volume of target PN, mL[a]		
Mean (SD)	255.01 (559.13)	837.11 (925.01)
Median (range)	98.89 (5.17, 3630.34)	487.50 (5.60, 3820.00)
Body surface area[a]		
Mean (SD)	1.19 (0.39)	1.13 (0.34)
Median (range)	1.13 (0.50, 1.90)	1.04 (0.67, 1.93)
Location of the target PN, n (%)[b,c]		
Trunk only	13 (23.21)	5 (10.00)
Trunk with limbs; limbs only	11 (19.64)	16 (32.00)
Head and neck/neck with trunk	28 (50.00)	29 (58.00)

[a]SPRINT data from European Medicines Agency.[11] [b]For location of the target PN, the percentages for mirdametinib do not sum up to 100% as some categories could not be matched to the selumetinib data. [c]SPRINT data from Gross et al.[9] ITC, indirect treatment comparison; PN, plexiform neurofibroma; SD, standard deviation.

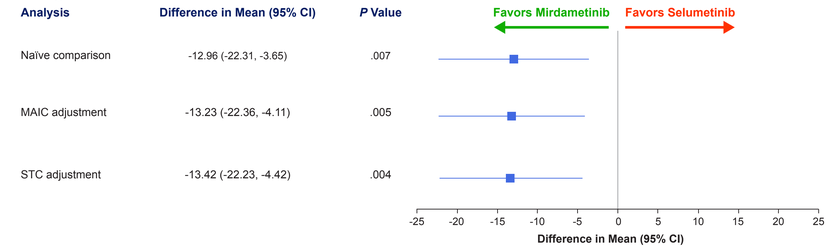
- The following efficacy endpoints were assessed: mean best percent reduction from baseline in target PN volume and confirmed ORR
  - Mean best percent reduction from baseline in target PN volume and confirmed ORR were the only commonly reported efficacy endpoints in ReNeu and SPRINT with similar definitions; although mean time to response (TTR) was also considered, a comparison of this endpoint was not feasible as there were no published patient data for mean TTR for SPRINT
    - For best percent reduction from baseline in target PN volume, mean was used instead of median to facilitate the ITC; in the STC, the outcome regression model was based on the reported means
    - Data for best percent reduction from baseline in target PN volume for SPRINT was sourced from the selumetinib independent central review with 2 blinded independent central reviewers (BICRs)[11]; in the ITC analyses, only age was adjusted, as it was the sole PV that reached statistical significance
  - For confirmed ORR, data were sourced from the US prescribing information for selumetinib (independent central review) to align with ORR data reported in ReNeu (central radiologic review with two blinded independent reviewers)[11]
    - In the MAIC and STC, adjustments were made for age, body surface area, target PN localization, and target PN size based on NF1 clinical expert input, as no PVs reached statistical significance
- Safety endpoints included TRAE rates reported in both the SPRINT trial publication[9] for selumetinib and the pediatric cohort of ReNeu[8] for mirdametinib; for the TRAE endpoints, age was adjusted in the ITCs based on clinical expert opinion
- Continuous outcomes (eg, mean best percent reduction from baseline in target PN volume) were calculated using the differences in mean values with 95% confidence interval (CI)
- Binary outcomes (eg, confirmed ORR and TRAEs) were estimated using odds ratios (OR) with 95% CIs

EFFICACY RESULTS

MEAN BEST PERCENT REDUCTION FROM BASELINE IN TARGET PN VOLUME

- The mean best percent reduction from baseline in target PN volume by BICR was significantly greater with mirdametinib vs selumetinib (**Figure 1**)
- In both the MAIC and STC base case, mirdametinib showed a significantly greater mean best percent reduction from baseline in target PN volume compared with selumetinib

Figure 1. Results of ITC of Mirdametinib vs Selumetinib: Mean Best Percent Reduction From Baseline in Target PN Volume

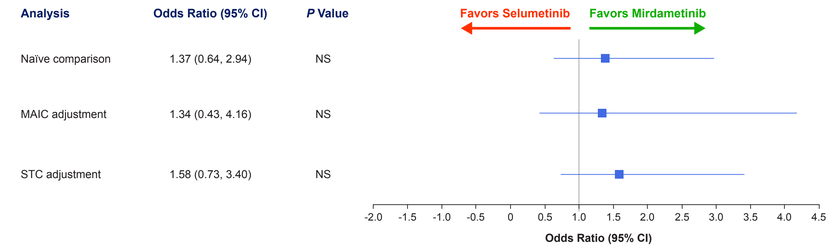


Mean best percent reduction from baseline in target PN volume was estimated in 54 patients in ReNeu. CI, confidence interval; MAIC, matching-adjusted indirect comparison; PN, plexiform neurofibroma; STC, simulated treatment comparison.

CONFIRMED ORR

- In the naïve comparison of mirdametinib and selumetinib (ie, without adjustments for population differences), mirdametinib showed a numerically higher confirmed ORR; however, significance was not reached
- In both ITC analyses, mirdametinib demonstrated a numerically higher confirmed ORR compared with selumetinib, but the results of the ITC analyses were not significant (**Figure 2**)

Figure 2. Results of ITC Comparison of Mirdametinib and Selumetinib for Confirmed ORR

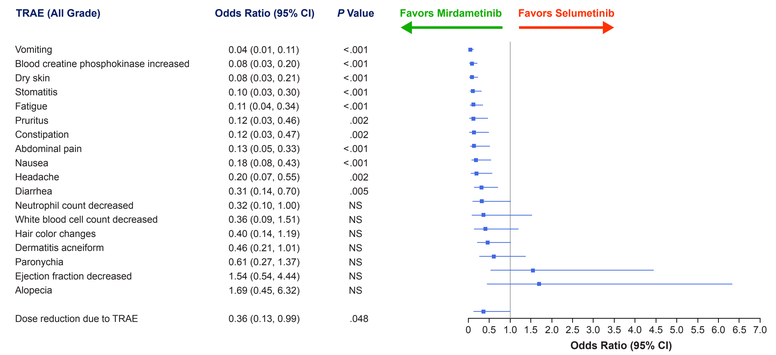


Confirmed ORR as defined by independent central review. CI, confidence interval; MAIC, matching-adjusted indirect comparison; NS, not significant; ORR, overall response rate; STC, simulated treatment comparison.

SAFETY RESULTS

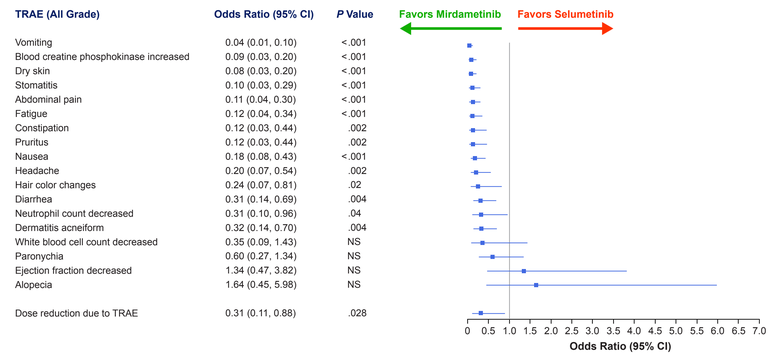
- In the MAIC and/or STC, all-grade TRAE odds ratios were significantly lower with mirdametinib vs selumetinib for dermatitis acneiform, diarrhea, nausea, vomiting, fatigue, blood creatine phosphokinase increased, dry skin, pruritus, constipation, abdominal pain, stomatitis, hair color change, headache, and neutrophil count decreased (*P*<.05; **Figures 3** and **4**)
- The odds ratio of dose reductions due to TRAEs was significantly lower with mirdametinib vs selumetinib (*P*<.05; **Figures 3** and **4**)
- The odds ratios of all-grade paronychia, white blood cell count decreased, alopecia, and ejection fraction decreased were not significantly different between mirdametinib and selumetinib

Figure 3. Safety Results: MAIC



CI, confidence interval; NS, not significant; TRAE, treatment-related adverse event.

Figure 4. Safety Results: STC



CI, confidence interval; NS, not significant; TRAE, treatment-related adverse event.

LIMITATIONS

- Although head-to-head comparisons are the gold-standard approach, ITCs represent a statistical method used to address the limitations of naïve comparisons; however, ITC results should be interpreted in the context of the following limitations:
  - Effective sample size was small in all analyses, which limited statistical power, but the sample size was relatively large[12] in the context of trials investigating rare diseases
  - A small number of PVs were adjusted in the base case and sensitivity analyses; unmeasured treatment PVs may have resulted in confounding
  - The SPRINT trial reported a longer follow-up time compared with the ReNeu trial, which can introduce bias when assessing the efficacy and safety of mirdametinib; an updated analysis with longer follow-up data from ReNeu would help to address this limitation
  - There were some differences in the endpoint definitions, such as that confirmed ORR was captured for ReNeu only during the 24-cycle treatment phase, whereas for SPRINT, it was for the entire trial duration
  - For TRAE endpoints, because the ReNeu trial classified TRAEs based on Common Terminology Criteria for Adverse Events (CTCAE) version 5 and SPRINT was based on version 4, any limits based on classification were considered to be small

CONCLUSION

- **On the basis of this ITC analysis, mirdametinib demonstrated a significantly greater mean best percent reduction from baseline in target PN volume, significantly lower rate of dose reductions due to TRAEs, and significantly lower rates of most of the commonly reported TRAEs vs selumetinib in children with NF1-PN**

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DISCLOSURES

IM, YH, and HM: Employment: Cytel, Inc, which received funding from SpringWorks Therapeutics, Inc, to conduct this study.
TB, MDW, and AL: Employment: SpringWorks Therapeutics, Inc; stock and ownership interest: SpringWorks Therapeutics, Inc.

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