Psychometric Validation of the PAINS-pNF Target Plexiform Neurofibroma (PN) Pain Severity Score Using Data from KOMET (NCT04924608)

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OBJECTIVES

- This study aimed to generate quantitative evidence supporting the use of PAINS-pNF target PN pain scores as PRO endpoints relating to chronic pain and spike pain in NF1-PN clinical trials

CONCLUSIONS

- The PAINS-pNF tool allows the separate measurement of chronic and spike pain, which have been identified as distinct relevant concepts in NF1-PN
- PAINS-pNF chronic target PN pain and PAINS-pNF spike target PN pain scores were shown to be reliable, valid, and sensitive to change in the adult NF1-PN patient population, demonstrating suitability for use in clinical trials that enroll patients with NF1-PN
- MSD estimates of a 2-point decrease and a 3-point decrease are reasonable for the chronic and spike target PN pain scores, respectively

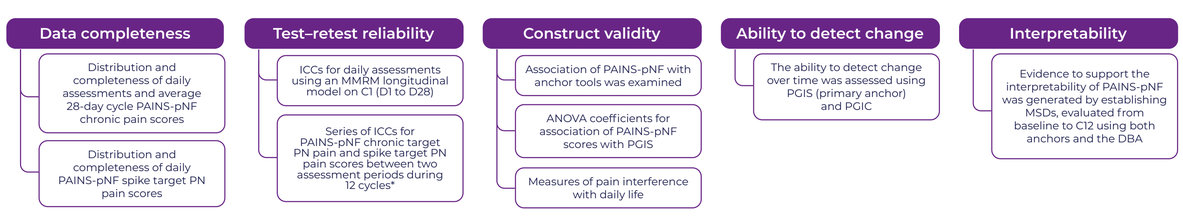
BACKGROUND

- Neurofibromatosis type 1 (NF1) is a genetic disorder that can result in the growth of nerve sheath tumors called plexiform neurofibromas (PN), which can cause pain and disfigurement, and can substantially impact patients' quality of life (QoL)[1,2]
  - Adults with NF1-PN often experience chronic PN-related continuous pain, and spike PN-related pain, which is a sudden burst of tumor pain;[3] therefore, pain-intensity assessment is central to NF1-PN care[4]
- The Numeric Rating Scale-11 (NRS-11), a patient-reported outcome (PRO) measure, is well established for measuring pain intensity in chronic diseases, including NF1;[4] however, it is not specific to the NF1-PN population
  - For the NRS-11 questionnaire, patients are asked to rate their pain on a scale from 'No pain (0)' to 'Worst pain imaginable (10)[4]
- The National Cancer Institute (NCI) developed the PAin INtensity Scale for Plexiform Neurofibromas (PAINS-pNF), an NF1-PN-specific adaptation of the NRS-11
  - Unlike the NRS-11 (a single pain assessment scale), the PAINS-pNF evaluates chronic and spike pain independently
  - The NCI conducted rigorous qualitative research on the content validity of the PAINS-pNF with individuals with NF1-PN;[5] however, a quantitative, psychometric validation of the PAINS-pNF is still pending

METHODS

- In the KOMET study (NCT04924608),[6] adult participants with symptomatic, inoperable NF1-PN (N = 145) completed the PAINS-pNF daily from screening through to Cycle (C) 12
  - Participants reported their worst pain experience for each type of pain since they last went to bed, including overnight, for the target PN selected by the investigator at study entry
    - The target PN was defined as the most clinically relevant PN (**Supplementary Material**)
  - Baseline PAINS-pNF score was defined as the average of the available daily PAINS-pNF scores in the screening period (a minimum of at least four out of seven days for ≥2 non-overlapping 7-day periods)
  - The PAINS-pNF chronic target PN pain score was the average of the daily PAINS-pNF chronic target PN pain assessments over a 28-day period (one cycle)
  - The average cycle PAINS-pNF score was only derived if the participant had four or more daily pain scores in 7 days for at least three non-overlapping 7-day periods in the 28-day cycle of the post-baseline period
  - The PAINS-pNF spike target PN pain score was the maximum daily PAINS-pNF spike target PN pain assessment in the 28-day period, regardless of the number of missing assessments in the 28-day period
  - The measures were rated on a 0–10 scale; the higher the score reported, the greater the pain intensity
- Psychometric validation analyses of PAINS-pNF evaluated cross-sectional and longitudinal psychometric properties for both the PAINS-pNF chronic target PN pain score and the PAINS-pNF spike target PN pain score
- Data completeness, test–retest reliability, construct validity, ability to detect change, and estimation of meaningful score differences (MSDs) were determined (**Figure 1**)
  - The analyses were conducted using two independent datasets from KOMET: the first set was from a data cut-off (DCO) of November 2023 (DCO-PsychA; test data), and the second was from a DCO in April 2024 when all 145 randomized participants had met the opportunity to complete their end of C12 assessment (DCO1; confirmatory data)

Figure 1. Psychometric evaluation process of the PAINS-pNF score



*Test-retest reliability was conducted from baseline to C1, then from C10 to C12.
ANOVA, analysis of variance; C, cycle; D, day; DBA, distribution-based approach; ICC, intraclass correlation coefficient; MMRM, mixed model for repeated measures; MSD, meaningful score difference; PAINS-pNF, PAin INtensity Scale for Plexiform Neurofibromas; PGIC, Patient's Global Impression of Change; PGIS, Patient's Global Impression of Severity.

RESULTS

Study population

- The full analysis set (FAS) comprised 145 patients. The mean (standard deviation [SD]) age was 31 (10.2) years (range: 18–60 years); 52% were male
- Regarding the completeness of the data, <4% of PAINS-pNF scores were missing throughout all 12 cycles (**Supplementary Table 1**)

Baseline assessment

- Mean (SD) PAINS-pNF chronic target PN pain score and PAINS-pNF spike target PN pain score were 4.25 (2.61) and 6.47 (2.82), respectively
- Scores were distributed across the full range of possible values from 0–10, and had good distributional properties (no floor or ceiling effects and good distribution around a mean value)
- In terms of Patient's Global Impression of Severity (PGIS), most participants reported mild or moderate chronic pain (23% and 44%, respectively), and moderate or severe spikes of pain (40% and 26%, respectively)
- Mean (SD) EuroQol-5-dimension-5-level (EQ-5D-5L) visual analogue scale score was 62.9 (20.3) on a scale ranging from 0 ("worst imaginable health state") to 100 ("best imaginable health state"), reflecting a poor overall health state in this sample
- The PAINS-pNF scores for chronic pain and spike pain were strongly correlated throughout the follow-up period, with Spearman's rank correlation coefficients ranging from 0.82 to 0.88

Chronic target PN pain

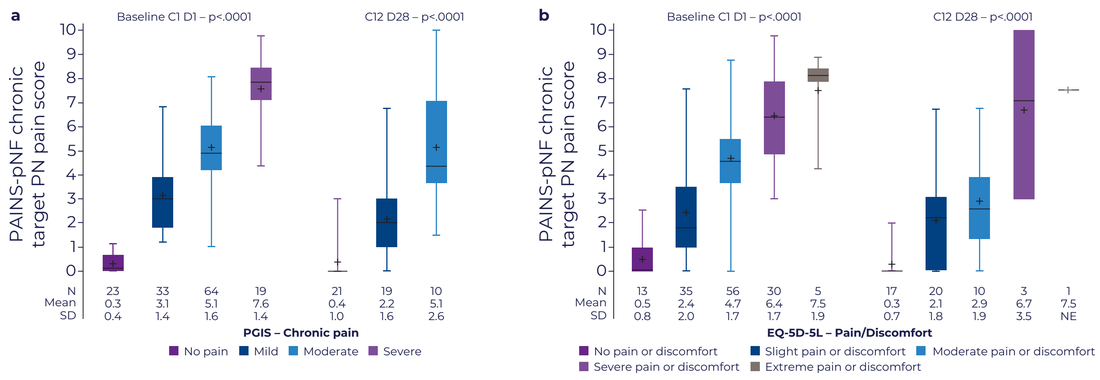
Test–retest reliability

- Longitudinal intraclass correlation coefficients (ICCs) were calculated for daily PAINS-pNF assessments using assessments collected during C1 (Day [D] 1 to D28)
- Analyses of test–retest reliability were conducted between baseline and C1, and between C10 and C12 in the overall FAS, and in the subgroup of the FAS with stable participants (i.e. stable PGIS of chronic pain [change = 0] over the same period)
- All ICC estimates indicated good-to-excellent test–retest reliability of the PAINS-pNF chronic target pain score, with ICC values >0.9[7] (**Supplementary Table 2**)

Construct validity

- Construct validity was supported by examining the association of PAINS-pNF with other relevant parameters
  - PAINS-pNF chronic target PN pain scores were significantly higher in patients reporting high severity of chronic pain (PGIS) and overall pain/discomfort (EQ-5D-5L) (**Figure 2**)
  - PAINS-pNF chronic target PN scores were moderately correlated with other measures of pain (Spearman correlations >0.3)[8]

Figure 2. Distribution of the PAINS-pNF chronic target PN pain score at baseline and C12 according to (a) PGIS of chronic pain and (b) the pain/discomfort item of the EQ-5D-5L (DCO-PsychA)



ANOVA, analysis of variance; C, cycle; D, day; DCO, data cut-off; EQ-5D-5L, EuroQol-5-dimension-5-level; NE, not estimable; p, p-value for ANOVA, comparing the mean difference across the four groups for PGIS and the five groups for EQ-5D-5L; PAINS-pNF, PAin Intensity Scale for plexiform neurofibromas; PGIS, Patient Global Impression of Severity; PN, plexiform neurofibromas; SD, standard deviation.

PLAIN LANGUAGE SUMMARY

Why did we perform this research?

This research aimed to test a new tool, the PAin INtensity Scale for Plexiform Neurofibromas (PAINS-pNF), which was specifically designed by the National Cancer Institute to measure pain in adults with neurofibromatosis type 1 and plexiform neurofibromas (NF1-PN). PN can cause chronic (ongoing) and spike (sudden burst) pain that significantly affect patients' lives. The goal was to validate that the PAINS-pNF tool could reliably assess pain levels due to PN in the clinical trial setting.

How did we perform this research?

In the KOMET study, 145 adults with NF1 and inoperable PN used the PAINS-pNF to report their pain daily, over several 28-day cycles. Data were analyzed for the reliability, validity, and sensitivity of the PAINS-pNF scores to changes in pain. Meaningful score differences were determined, indicating when a change in pain score was significant for patients.

What were the findings of this research and what are the implications?

The results showed that the PAINS-pNF is a reliable and valid tool for measuring chronic and spike pain in patients with NF1-PN. It was sensitive enough to detect changes in pain over time, which makes it suitable for use in clinical trials. The study also established that a 2-point decrease for chronic pain and a 3-point decrease for spike pain were meaningful improvements for patients. These findings suggest that the PAINS-pNF tool could improve how we assess and manage pain in patients with NF1-PN in both clinical practice and research.

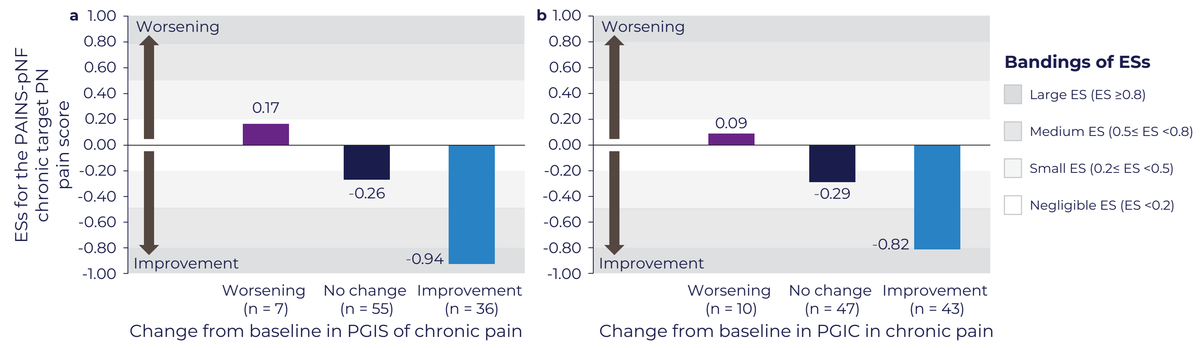
Where can I access more information?

More detailed information and the full results of this study can be accessed through the Supplementary Material (available through the QR code).

Ability to detect change

- The PAINS-pNF chronic target PN pain score showed good ability to capture change between baseline and C12 when using the PGIS and PGIC (**Figure 3**)

Figure 3. Effect sizes of the PAINS-pNF chronic target PN pain score according to groups defined by (a) the change in PGIS of chronic pain from baseline to C12 (n = 98) and (b) the PGIC in chronic pain at C12 (DCO1, n = 100)



Improvement: any negative change in PGIS ratings (e.g. from 4 = "Severe" to 1 = "No pain"), or PGIC as 1 = "Much better", 2 = "Moderately better", 3 = "A little better".
No change: no change in PGIS ratings, or PGIC as 4 = "About the same/No change".
Worsening: any positive change in PGIS ratings (e.g. from 1 = "No pain" to 4 = "Severe"), or PGIC as 5 = "A little worse", 6 = "Moderately worse", 7 = "Much worse".
C, cycle; DCO, data cut-off; ES, effect size; PAINS-pNF, PAin INtensity Scale for plexiform neurofibromas; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PN, plexiform neurofibromas.

- These large ESs (ESs ≥0.8)[9] indicated that the change in the PAINS-pNF chronic target PN pain score was large in participants who reported improvement in the PGIS and PGIC of chronic pain, suggesting a good ability of the PAINS-pNF chronic target PN pain score to detect improvement over time

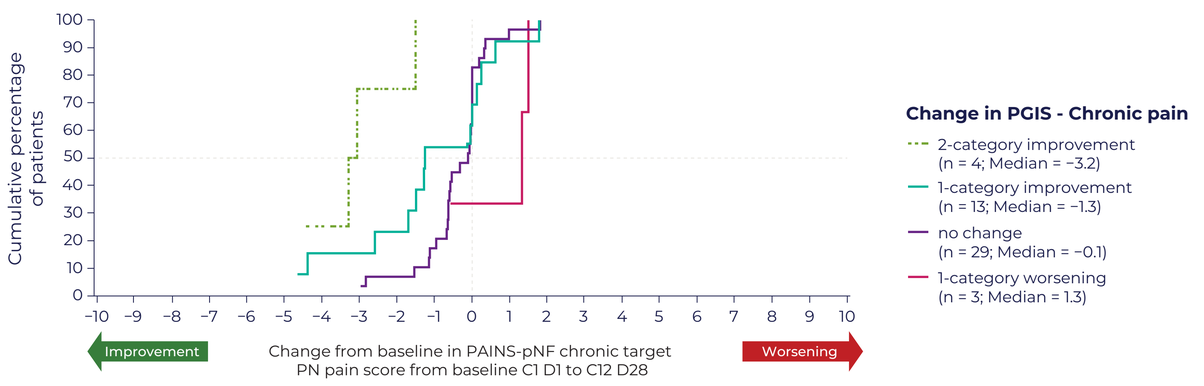
Determination of MSD – Anchor-based approach

- The MSD estimates first determined using DCO-PsychA (test sample) were consistent with new data findings from the confirmatory sample (DCO1), confirming the robustness of estimates
  - The correlations of the change in PAINS-pNF chronic target PN pain score from baseline to C12 with both anchors were slightly higher in the DCO1 than for DCO-PsychA: 0.62 vs 0.41 for the change in PGIS of chronic pain, and 0.52 vs 0.46 for the PGIC in chronic pain
  - These data confirmed the relevance of using PGIC and PGIC as anchors (Spearman's rank correlation coefficients >0.3)[8]
- The distribution of change in PAINS-pNF chronic target PN pain score from baseline to C12 across PGIS (**Figure 4** and **Supplementary Table 3**) and PGIC (**Supplementary Figure 3** and **Supplementary Table 4**) categories was consistent with the 2-point definition of MSD
  - PGIS: The empirical cumulative distribution function (eCDF) showed <10% of the participants with no change in the PGIS of chronic pain, and approximately 25% of those with a one-category improvement; three of the four participants with a two-category improvement had a decrease in PAINS-pNF chronic target PN pain score >2 (**Figure 4**)
  - PGIC: The eCDF showed that <10% of the participants in the "about the same" category had a decrease in PAINS-pNF chronic target PN pain score >2. The percentage of participants with a change in PAINS-pNF chronic target PN pain score >2 in the three PGIC categories corresponding to improvement in chronic pain ranged between 15% and 45% (**Supplementary Figure 3**)

Distribution-based method

- The distribution-based estimates for meaningful change in PAINS-pNF chronic target PN pain score (DCO-PsychA; N = 145) were 1.30 (half SD) and 0.60 (standard error of measurement)

Figure 4. eCDF of change in PAINS-pNF chronic target PN pain score from baseline to C12 in groups defined by the change in PGIS (DCO-PsychA, n = 53)



C, cycle; D, day; DCO, data cut-off; eCDF, empirical cumulative distribution function; PAINS-pNF, PAin INtensity Scale for plexiform neurofibromas; PGIS, Patient Global Impression of Severity; PN, plexiform neurofibroma.

Spike target PN pain

Test–retest reliability

- ICC values for PAINS-pNF spike target PN pain scores were slightly lower than for chronic pain scores, but still showed adequate-to-excellent test–retest reliability[7] (ICC values of 0.81–0.95; **Supplementary Table 5**)

Construct validity

- Construct validity was supported by examination of the association of PAINS-pNF with anchor tools
- PAINS-pNF spike target PN pain scores were significantly higher in participants reporting more severe spikes of pain in PGIS (**Supplementary Figure 1**)

Ability to detect change

- PAINS-pNF spike target PN pain score demonstrated the ability to capture change between baseline and C12 when using the PGIS and PGIC (**Supplementary Figure 2**)
- The correlations of the change in PAINS-pNF spike target PN pain score from baseline to C12 with both anchors were slightly higher in DCO1 than for DCO-PsychA with the change in PGIS of spike pain (0.48 vs 0.33), and similar with the PGIC of spike pain (0.45 vs 0.47)
  - The change in PGIS of spike pain was 0.48 vs 0.33; this was similar with the PGIC of spike pain (0.45 vs 0.47)
- These findings confirmed the relevance of using PGIS and PGIC as anchors (Spearman's rank correlation coefficients >0.3)[8]

Determination of MSD

- The distribution of change in PAINS-pNF spike target PN pain score from baseline to C12 across PGIS (**Supplementary Figure 4a** and **Supplementary Table 6**) and PGIC (**Supplementary Figure 4b** and **Supplementary Table 7**) categories was consistent with the 3-point definition of MSD
  - PGIS: ~30% of both the participants with no change and one-category improvement in the PGIS of spikes of pain had a decrease in PAINS-pNF spike target PN pain score >3, whereas three of the four participants with two-category improvement reached this level of change in score (**Supplementary Figure 4a**)
  - PGIC: ~30% of the participants in the "about the same" and 40% in the "a little better" category had a decrease in PAINS-pNF spike target PN pain score >3, whereas ~70% in the "moderately better" and "much better" groups had a decrease in PAINS-pNF spike target PN pain score >3 (**Supplementary Figure 4b**)

Distribution-based method

- The distribution-based estimates for meaningful change in PAINS-pNF spike target PN pain score (DCO-PsychA; n = 145) were 1.41 (half SD) and 1.15 (standard error of measurement)

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Conflicts of interest

AA is an employee of and has stock/stock options in Alexion, AstraZeneca Rare Disease. AR is an employee of Modus Outcomes. AR declares Alexion, AstraZeneca Rare Disease payment to Modus Outcomes for patient-centered outcomes research services, including analyses presented in the communication. EM declares no conflicts of interest. JN is an employee of and has stock/stock options in Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. JN also provided interpretation of study results and abstract content. JN also declares a leadership role as International Society for Quality of Life Research President. LB declares no conflicts of interest. PLW is a member of the National Institute of Health Intramural Research Program. PLW also received grants/contracts from Neurofibromatosis Therapeutic Acceleration Program. PA is employed by Alexion, AstraZeneca Rare Disease as a consultant. RRR is an employee of and has stock/stock options in Alexion, AstraZeneca Rare Disease. RRR has received payment/honoraria, support for attending meetings/travel, participated on a Data Safety Monitoring or Advisory Board, has a leadership or fiduciary role, and has received drugs, medical writing, gifts, or other services. SM has received support from Intramural Research Program of the National Cancer Institute and has received grants or contracts from Neurofibromatosis Therapeutics Acceleration Program. XY is an employee of and owns stock in Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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Poster | Supplementary material | Plain language summary

Poster presented at ISPOR Europe 2024; Barcelona, Spain; November 17–20, 2024.

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