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

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Supplementary Material

Supplementary Methods

The target PN was defined as the clinically most relevant PN, which had to be measurable by volumetric MRI analysis (ie, a PN of at least 3 cm measured in one dimension, which can be seen on at least 3 imaging slices, and has a reasonably well-defined contour).

Visit	N	Missing PAINS-pNF chronic target PN pain score n (%)	Missing PAINS-pNF spike target PN pain score n (%)
Baseline	145	0 (0.0)	0 (0.0)
Cycle 1	144	0 (0.0)	0 (0.0)
Cycle 2	143	0 (0.0)	0 (0.0)
Cycle 4	136	0 (0.0)	0 (0.0)
Cycle 6	135	4 (3.0)	0 (0.0)
Cycle 8	135	5 (3.7)	1 (0.7)
Cycle 10	130	2 (1.5)	0 (0.0)
Cycle 12	125	3 (2.4)	0 (0.0)

Supplementary Table 1. Description of missing PAINS-pNF chronic target PN pain scores and PAINS-pNF spike target PN pain scores from baseline to Cycle 12 (DCO1, N=145)

DCO1, data cut-off 1; PAINS-pNF, PAin INtensity Scale for plexiform neurofibromas; PN, plexiform neurofibromas.

Supplementary Table 2. Test-retest reliability of the PAINS-pNF chronic target PN pain score (DCO1)

	E	aseline to Cycle	Cycle 10 to Cycle 12		
ICC type (95% CI)	FAS N=145	Stable (PGIS)* n=82	Stable (PGIC)* n=78	FAS n=83	Stable (PGIS)* n=42
ICC(1): one-way random, absolute agreement, single rater	0.922 (0.894, 0.943)	0.948 (0.920, 0.966)	0.962 (0.942, 0.976)	0.950 (0.924, 0.968)	0.993 (0.986, 0.996)
ICC(C,1): two-way random, mixed, consistency, single rater	0.932 (0.908, 0.951)	0.952 (0.927, 0.969)	0.963 (0.943, 0.976)	0.951 (0.925, 0.968)	0.993 (0.986, 0.996)
ICC(A,1): two-way random, mixed, absolute agreement, single rater	0.923 (0.874, 0.950)	0.948 (0.915, 0.968)	0.962 (0.942, 0.976)	0.950 (0.925, 0.968)	0.993 (0.986, 0.996)

<0.7 = poor; 0.7–0.8 = modest; 0.8–0.9 = adequate; 0.9–0.95 = good; >0.95 = excellent.²

*PGIS and PGIC for chronic pain.

The high consistency between the ICC(A, 1) and the ICC(C, 1) suggested that there was no systematic error between the two assessments, and that reporting the ICC(1) was acceptable¹

CI, confidence interval; DCO1, data cut-off 1; FAS, full analysis set; ICC, intraclass correlation coefficient; PAINS-pNF, PAin INtensity Scale for plexiform neurofibromas; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PN, plexiform neurofibromas.

Supplementary Table 3. Description of the change in PAINS-pNF chronic target PN pain score from baseline to Cycle 12 across categories of change in PGIS of chronic pain for (a) DCO-PsychA (n=53), and (b) DCO1 (n=46)

(a)

	Change in PGIS of chronic pain from baseline to Cycle 12								
Variable	Three-category improvement n=4	One-category improvement n=14	No change n=31	One-category worsening n=4					
Change in PAINS-pNF chronic	target PN pain score	from baseline to Cy	cle 12						
n (missing)	4 (0)	13 (1)	29 (2)	3 (1)					
Mean (SD)	-3.07 (1.19)	-1.13 (1.90)	-0.41 (0.95)	0.75 (1.15)					
Median	-3.18	-1.27	-0.12	1.32					
Q1, Q3	-3.84, -2.29	-1.71 , 0.12	-0.65, 0.00	-0.58, 1.50					
P10, P90	-4.40, -1.52	-4.39, 0.62	-1.55 , 0.35	-0.58, 1.50					
Min, Max	-4.40, -1.52	-4.67, 1.79	-2.99, 1.81	-0.58, 1.50					

(b)

	Change in PGIS of chronic pain from baseline to Cycle 12									
Variable	Three-category improvement n=1	One-category improvement n=18	No change n=25	One-category worsening n=2						
Change in PAINS-pNF chronic	Change in PAINS-pNF chronic target PN pain score from baseline to Cycle 12									
n (missing)	1 (0)	18 (0)	24 (1)	2 (0)						
Mean (SD)	-7.54 (NE)	-2.66 (1.64)	-0.62 (1.22)	-0.68 (0.71)						
Median	-7.54	-2.16	-0.29	-0.68						
Q1, Q3	-7.54, -7.54	-4.30, -1.21	-1.04, 0.11	-1.18, -0.18						
P10, P90	-7.54, -7.54	-4.73, -1.00	-2.00 , 0.25	-1.18, -0.18						
Min, Max	-7.54, -7.54	-5.56, 0.00	-5.07, 1.27	-1.18, -0.18						

DCO1, data cut-off 1; max, maximum; min, minimum; NE, not estimable; P10, 10th percentile; P90, 90th percentile; PAINS-pNF, PAin INtensity Scale for plexiform neurofibromas; PGIS, Patient Global Impression of Severity; PN, plexiform neurofibromas; Q1, upper quartile; Q3, lower quartile; SD, standard deviation.

Supplementary Table 4. Description of the change in PAINS-pNF chronic target PN pain score from baseline to Cycle 12 across categories of change in PGIC of chronic pain for (a) DCO-PsychA (n=54), and (b) DCO1 (n=46)

(a)

		Change in PGIC of chronic pain from baseline to Cycle 12							
Variable	Much better (n=6)	Moderately better (n=6)	A little better (n=7)	About the same (n=27)	A little worse (n=4)	Moderately worse (n=3)	Much worse (n=1)		
Change in PAINS	S-pNF chronic	target PN pain	score from l	baseline to Cy	cle 12				
n (missing)	6 (0)	6 (0)	7 (0)	24 (3)	4 (0)	2 (1)	1 (0)		
Mean (SD)	-1.93 (1.23)	-1.11 (2.25)	-1.22 (1.69)	-0.49 (1.25)	0.31 (1.09)	0.28 (0.05)	1.32 (NE)		
Median	-1.53	-0.56	-1.52	-0.06	0.20	0.28	1.32		
Q1, Q3	-1.71, -1.27	-3.07, 0.12	-2.83, 0.18	- 0.67 , 0.00	-0.61, 1.24	0.24, 0.31	1.32, 1.32		
P10, P90	-4.40, -1.15	-4.39, 1.81	-2.99, 1.23	-1.29, 0.35	-0.65, 1.50	0.24, 0.31	1.32, 1.32		
Min, Max	-4.40, -1.15	-4.39, 1.81	-2.99, 1.23	-4.67, 1.79	-0.65, 1.50	0.24, 0.31	1.32, 1.32		

(b)

		Change in PGIC of chronic pain from baseline to Cycle 12							
Variable	Much better (n=9)	Moderately better (n=6)	A little better (n=7)	About the same (n=21)	A little worse (n=2)	Moderately worse (n=1)			
Change in PAINS-pNF chronic target PN pain score from baseline to Cycle 12									
n (missing)	9 (0)	6 (0)	7 (0)	20 (1)	2 (0)	1 (0)			
Mean (SD)	-3.57 (2.16)	-3.39 (2.11)	-0.48 (1.12)	-0.90 (1.20)	-0.29 (0.00)	0.00 (NE)			
Median	-3.77	-4.31	-0.67	-0.70	-0.29	0.00			
Q1, Q3	-4.41, -1.74	-4.73, -1.81	-1.18, 0.34	-1.33, -0.11	-0.29, -0.29	0.00, 0.00			
P10, P90	-7.54, -1.00	-5.34, 0.15	-2.09, 1.27	-1.91 , 0.19	-0.29, -0.29	0.00, 0.00			
Min, Max	-7.54, -1.00	-5.34, 0.15	-2.09, 1.27	-5.07, 0.25	-0.29, -0.29	0.00, 0.00			

DCO1, data cut-off 1; max, maximum; min, minimum; NE, not estimable; P10, 10th percentile; P90, 90th percentile; PAINS-pNF, PAin INtensity Scale for plexiform neurofibromas; PGIC, Patient Global Impression of Change; PN, plexiform neurofibromas; Q1, upper quartile; Q3, lower quartile; SD, standard deviation.

	Baseline to Cycle 1			Cycle 10 to Cycle 12		
ICC type (95% CI)	FAS N=145	Stable (PGIS)* n=72	Stable (PGIC)* n=74	FAS n=83	Stable (PGIS)* n=37	
ICC(1): one-way random, absolute agreement, single rater	0.814 (0.752, 0.863)	0.833 (0.746,0.892)	0.863 (0.791, 0.911)	0.894 (0.841, 0.930)	0.973 (0.949, 0.986)	
ICC(C,1): two-way random, mixed, consistency, single rater	0.829 (0.770, 0.874)	0.838 (0.753,0.896)	0.865 (0.795, 0.913)	0.892 (0.838, 0.929)	0.973 (0.948, 0.986)	
ICC(A,1): two-way random, mixed, absolute agreement, single rater	0.816 (0.738, 0.870)	0.833 (0.745,0.893)	0.863 (0.791, 0.912)	0.893 (0.840, 0.930)	0.973 (0.949, 0.986)	

Supplementary Table 5. Test-retest reliability of the PAINS-pNF spike PN pain score (DCO1)

<0.7 = poor; 0.7–0.8 = modest; 0.8–0.9 = adequate; 0.9–0.95 = good; >0.95 = excellent.²

*PGIS and PGIC for spikes of pain.

CI, confidence interval; DCO1, data cut-off one; FAS, full analysis set; ICC, intraclass correlation coefficient; PAINS-pNF, PAin INtensity Scale for plexiform neurofibromas; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PN, plexiform neurofibromas.

Supplementary Figure 1: Distribution of the PAINS-pNF spike target PN pain score at baseline (n=139) and Cycle 12 (n=52) according to the PGIS of spikes of pain (DCO-PsychA)



C, cycle; D, day; DCO, data cut-off; p, p-value for ANOVA, comparing the mean difference across the four groups for PGIS; PAINS-pNF, PAin INtensity Scale for plexiform neurofibromas; PGIS, Patient Global Impression of Severity; PN, plexiform neurofibromas; SD, standard deviation.

Supplementary Figure 2. Effect sizes of the PAINS-pNF spike target PN pain score according to groups defined (a) by the change in PGIS of spikes of pain from baseline to Cycle 12 (n=101) and (b) by the PGIC of spikes of pain at Cycle 12 (DCO1, n=103)



DCO1, data cut-off 1; 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.

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".

Supplementary Table 6. Description of the change in PAINS-pNF spike target PN pain score from baseline to Cycle 12 across categories of change in PGIS of spikes of pain for (a) DCO-PsychA (n=53), and (b) DCO1 (n=46)

(a)

	Change in PGIS of spikes of pain from baseline to Cycle 12								
Variable	Two-category improvement n=4	One-category improvement n=23	No change n=20	One-category worsening n=6					
Change in PAINS-pNF spike ta	rget PN pain score fr	om baseline to Cycle	e 12						
n (missing)	4 (0)	23 (0)	18 (2)	6 (0)					
Mean (SD)	-5.00 (2.83)	-2.04 (2.14)	-1.72 (2.63)	-0.50 (1.22)					
Median	-6.00	-3.00	-1.00	0.00					
Q1, Q3	-7.00, -3.00	-3.00, 0.00	-4.00 , 0.00	-2.00, 0.00					
P10, P90	-7.00, -1.00	-4.00, 1.00	-6.00, 1.00	-2.00, 1.00					
Min, Max	-7.00, -1.00	-6.00, 2.00	-8.00, 1.00	-2.00, 1.00					

(b)

	Change in PGIS of spikes of pain from baseline to Cycle 12							
Variable	Three-category improvement n=1	Two-category improvement n=3	One-category improvement n=21	No change n=20	One-category worsening n=1			
Change in PAINS-pNF spike target PN pain score from baseline to Cycle 12								
n (missing)	1 (0)	3 (0)	21 (0)	20 (0)	1 (0)			
Mean (SD)	-9.00 (NE)	-5.67 (1.15)	-2.33 (2.61)	-1.00 (1.75)	-1.00 (NE)			
Median	-9.00	-5.00	-2.00	-1.00	-1.00			
Q1, Q3	9.00, -9.00	-7.00, -5.00	-3.00 , -1.00	-1.50, 0.00	-1.00, -1.00			
P10, P90	-9.00, -9.00	-7.00, -5.00	4.00, 0.00	-3.00 , 0.00	-1.00, -1.00			
Min, Max	-9.00, -9.00	-7.00, -5.00	-9.00, 2.00	-6.00, 3.00	-1.00, -1.00			

DCO1, data cut-off 1; max, maximum; min, minimum; NE, not estimable; P10, 10th percentile; P90, 90th percentile; PAINS-pNF, PAin INtensity Scale for plexiform neurofibromas; PGIS, Patient Global Impression of Severity; PN, plexiform neurofibromas; Q1, upper quartile; Q3, lower quartile; SD, standard deviation.

Supplementary Table 7. Description of the change in PAINS-pNF spike target PN pain score from baseline to Cycle 12 across categories of change in PGIC in spikes of pain for (a) DCO-PsychA (n=54), and (b) DCO1 (n=46)

(a)

		Change in PGIC in spikes of pain from baseline to Cycle 12							
Variable	Much better (n=6)	Moderately better (n=7)	A little better(n=8)	About the same (n=24)	A little worse (n=6)	Moderately worse (n=2)	Much worse (n=1)		
Change in PAINS	S-pNF spike ta	rget PN pain sco	ore from baseli	ne to Cycle 1	2				
n (missing)	6 (0)	7 (0)	8 (0)	23 (1)	6 (0)	1 (1)	1 (0)		
Mean (SD)	-4.67 (2.80)	-2.57 (2.30)	-2.50 (2.33)	-1.43 (2.04)	-0.33 (2.25)	0.00 (.)	0.00 (NE)		
Median	-5.00	-3.00	-2.00	-1.00	0.50	0.00	0.00		
Q1, Q3	-7.00,-2.00	-5.00, 0.00	-3.50 , -1.50	-3.00,0.00	-2.00, 1.00	0.00, 0.00	0.00, 0.00		
P10, P90	-8.00,-1.00	-5.00, 1.00	-7.00, 1.00	- 4.00 , 1.00	-4.00, 2.00	0.00, 0.00	0.00, 0.00		
Min, Max	-8.00, -1.00	-5.00, 1.00	-7.00, 1.00	-6.00, 1.00	-4.00, 2.00	0.00, 0.00	0.00, 0.00		

(b)

	Change in PGIC in spikes of pain from baseline to Cycle 12								
Variable	Much better (n=8)	Moderately better (n=6)	A little better (n=6)	About the same (n=22)	A little worse (n=2)	Moderately worse (n=2)			
Change in PAINS-pNF spike target PN pain score from baseline to Cycle 12									
n (missing)	8 (0)	6 (0)	6 (0)	22 (0)	2 (0)	2 (0)			
Mean (SD)	-4.63 (2.97)	-2.67 (2.07)	-1.00 (1.67)	-0.91 (1.63)	-3.50 (3.54)	-0.50 (0.71)			
Median	-3.50	-2.50	-1.00	-1.00	-3.50	-0.50			
Q1, Q3	-7.50, -2.50	-5.00, -1.00	2.00, -1.00	-2.00, 0.00	-6.00, -1.00	-1.00, 0.00			
P10, P90	-9.00, -1.00	-5.00, 0.00	-3.00, 2.00	-3.00 , 0.00	-6.00, -1.00	-1.00, 0.00			
Min, Max	-9.00, -1.00	-5.00, 0.00	-3.00, 2.00	-4.00, 3.00	-6.00, -1.00	-1.00, 0.00			

DCO1, data cut-off 1; Max, maximum; min, minimum; P10, 10th percentile; P90, 90th percentile; PAINS-pNF, PAin INtensity Scale for plexiform neurofibromas; PGIC, Patient Global Impression of Change; PN, plexiform neurofibromas; Q1, upper quartile; Q3, lower quartile; SD, standard deviation.



Supplementary Figure 3. eCDF of change in PAINS-pNF chronic target PN pain score from baseline to C12 in groups defined by the change in PGIC (N=54) (DCO-PsychA)

This figure shows the distribution in patients with "much better", "moderately better", "a little better", "about the same", "a little worse", and "moderately worse" pain in the PGIC. The "much worse" category was not presented because it included too few participants to allow an interpretation to be made (n=1).

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



Supplementary Figure 4. eCDF of change in PAINS-pNF spike target PN pain score from baseline to C12 in groups defined by the change in (a) PGIS (n=53), and (b) PGIC (n=54; DCO-PsychA)

Part (b) of this figure shows the distribution in patients with "much better", "moderately better", "a little better", "about the same", and "a little worse" pain in the PGIC. The "moderately worse" and the "much worse" category are not presented because they included too few participants to allow an interpretation to be made (n=1 each).

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

References

1. Nunally et al. *Psychometric Theory* 1994.