

Exploring Concurrent Validity of the CLN2 Clinical Rating Scale: Comparison to PedsQL using Mixed Effects Modelling and Data from a Phase 1/2 Single-Arm Trial

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Background

- Neuronal ceroid lipofuscinosis type 2 (CLN2) disease is a rare, autosomal recessive disorder typically manifesting in late-infantile children.
- The disease results in progressive language loss, movement disorders, pain, dementia, vision loss and ultimately death at 8–12 years of age.¹
- The 0–6 point Motor-Language CLN2 Clinical Rating Scale was the primary outcome in the pivotal cerliponase alfa trial (Study 190–201/202) for the treatment of CLN2 disease.

Objectives

- This analysis aimed to concurrently validate the functional CLN2 Clinical Rating Scale by examining its relationship to the Pediatric Quality of Life Inventory 4.0 Generic Core Scales (subsequently referred to as PedsQL) tool for which a minimal clinically important difference (MCID) of 4.5 has been established.²
- A post hoc analysis of clinical trial data using a combination of simple linear regression and mixed effects modelling aimed to provide a robust assessment that overcomes the limitations of using a small dataset with repeated measurements from the same patients.

Methods

- Data from the phase 1/2 single-arm trial (Study 190–201; NCT01907087) and extension study (Study 190–202; NCT02485899) of 23 CLN2 patients treated with cerliponase alfa for a minimum of 96 weeks were used in this analysis (Figure 1).
- CLN2 Clinical Rating Scale data were collected every 8 weeks and PedsQL (Parent Report for Toddlers) data every 12 weeks leading to concurrent data for both measures being available every 24 weeks of the trial (Figure 1).
- To determine the relationship between the clinician-reported CLN2 Clinical Rating Scale total score and the proxy-reported PedsQL score at both the total and domain level, simple linear regression was undertaken using all concurrent data from the trial.
- To further inform and robustly analyse the relationship, mixed effects analyses were then conducted, which accounted for within-patient correlation.

Results

Assessing Relationships Using Simple Linear Regression

- There was strong evidence of a positive correlation between the PedsQL total score and the CLN2 Clinical Rating Scale total score ($p < 0.001$; $\hat{\beta}$ [95% confidence interval (CI)]: 5.47 [3.91, 7.03]; Table 1).
- The CLN2 Clinical Rating Scale total score explained less than 30% of the variance observed in the PedsQL total score (adjusted $R^2 = 0.266$; Table 1).
- The relationship between the total scores of the two scales seemed to be driven by the PedsQL Physical domain ($p < 0.001$; $\hat{\beta}$ [95% CI]: 11.15 [8.91, 13.40]; adjusted $R^2 = 0.424$; Table 1; Figure 2).
- There was also evidence of relationships between the CLN2 Clinical Rating Scale total score and both the Emotional and Social domain scores of the PedsQL ($p = 0.020$ and $p = 0.031$, respectively), however, very little of the variation in these domains was explained by the CLN2 Clinical Rating Scale score (adjusted $R^2 = 0.034$ and 0.028 , respectively; Table 1).

Figure 1. Study 190–201/202 summary diagram

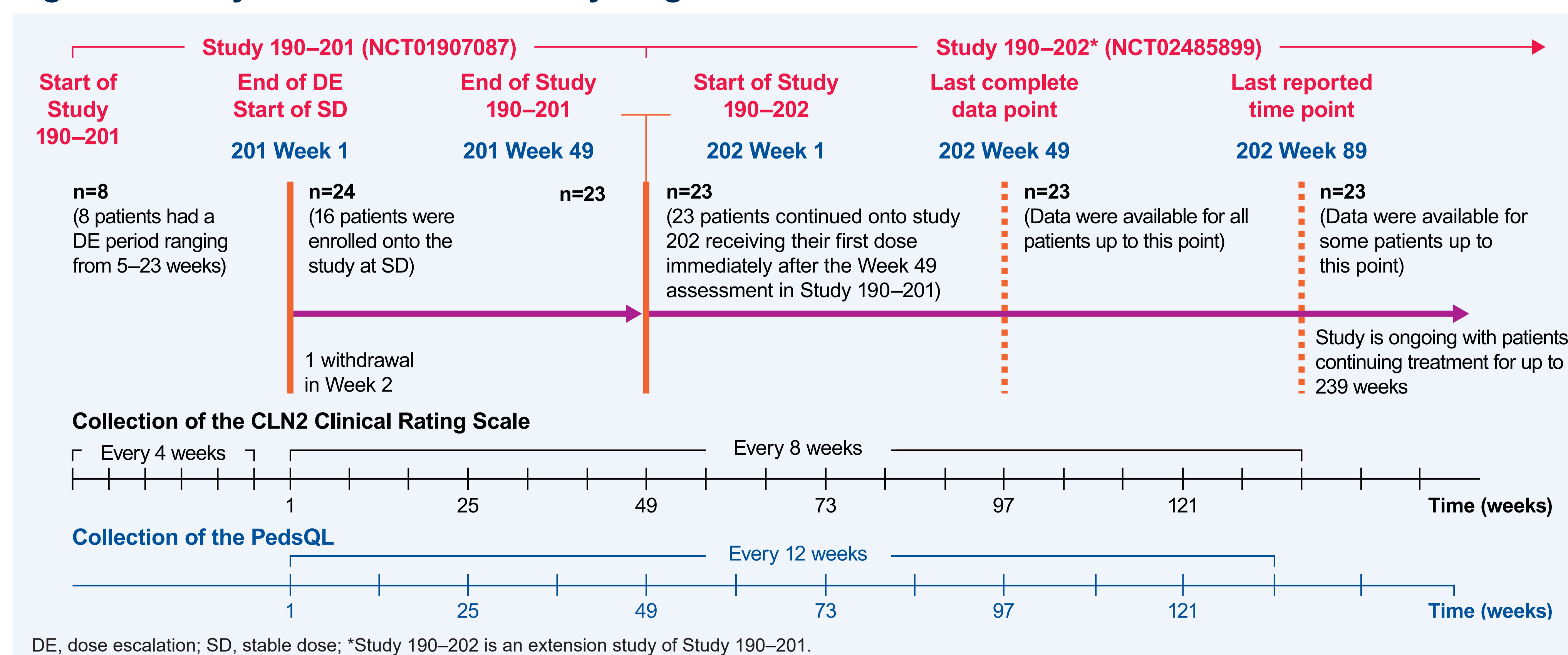


Table 1. Results of simple linear regression models comparing PedsQL with the CLN2 Clinical Rating Scale

Dependent variable (PedsQL)	Independent variable (total score)	Adjusted R ²	$\hat{\beta}$ [†]	95% CI	P-value
Total score	CLN2 Clinical Rating Scale	0.266	5.47	3.91, 7.03	<0.001*
Physical domain score	CLN2 Clinical Rating Scale	0.424	11.15	8.91, 13.40	<0.001*
Emotional domain score	CLN2 Clinical Rating Scale	0.034	2.38	0.38, 4.38	0.020*
Social domain score	CLN2 Clinical Rating Scale	0.028	2.30	0.22, 4.37	0.031*
School domain score	CLN2 Clinical Rating Scale	-0.008	-0.13	-2.71, 2.45	0.921

*p-values <0.05 are considered significant and are highlighted in bold; [†]estimate of the regression parameter for the independent variable of interest. Please see the Methods section for details of the dataset used in this analysis. CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2.

Figure 2. Regression line showing the relationship between the PedsQL Physical domain and the CLN2 Clinical Rating Scale

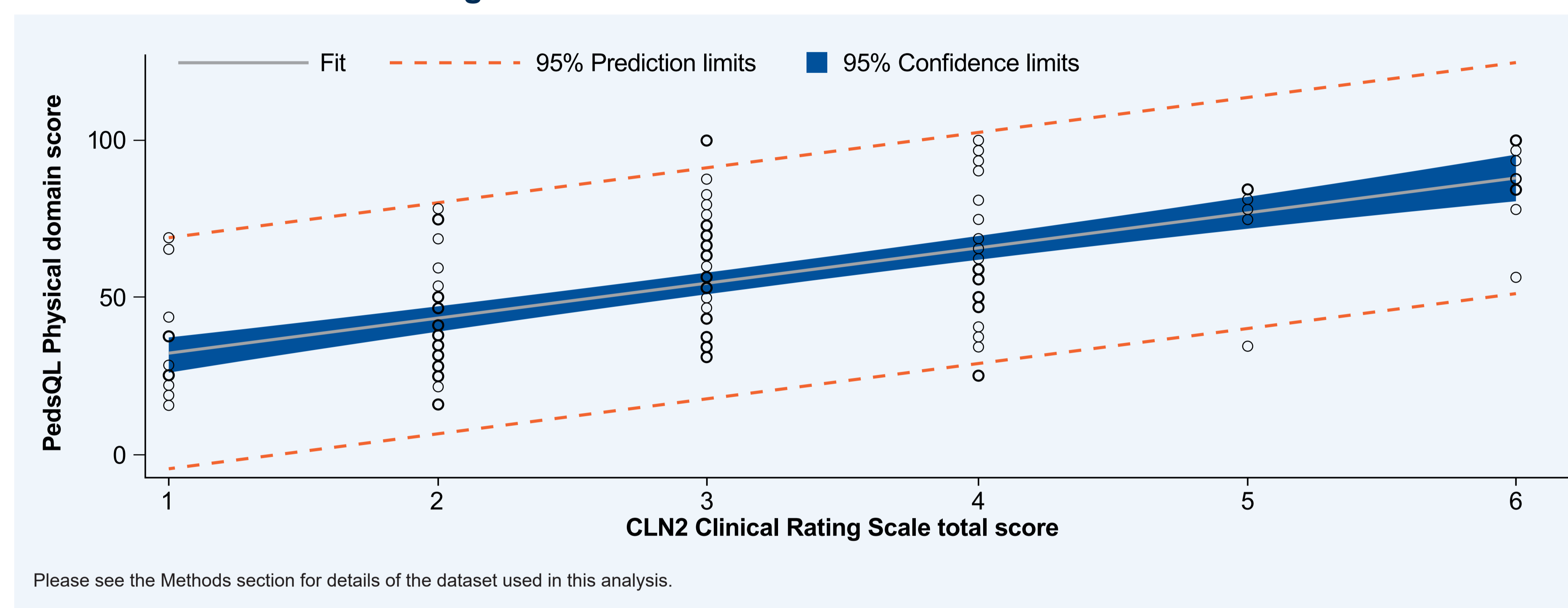


Table 2. Results of mixed effects regression models comparing PedsQL with the CLN2 Clinical Rating Scale

Dependent variable (PedsQL)	Independent variable (total score)	AIC		$\hat{\beta}$ [†]	95% CI	P-value
		Full model	Null model			
Total score	CLN2 Clinical Rating Scale	1022.1	1037.4	5.06	2.66, 7.44	<0.001*
Physical domain score	CLN2 Clinical Rating Scale	1118.3	1148.8	10.41	7.21, 13.54	<0.001*
Emotional domain score	CLN2 Clinical Rating Scale	1088.0	1090.8	2.12	-0.57, 4.74	0.138
Social domain score	CLN2 Clinical Rating Scale	1100.7	1102.8	1.86	-1.39, 5.06	0.266
School domain score	CLN2 Clinical Rating Scale	1078.0	1078.4	-0.13	-2.73, 2.50	0.918

*p-values <0.05 are considered significant and are highlighted in bold; [†]estimate of the regression parameter for the independent variable of interest. Please see the Methods section for details of the dataset used in this analysis. AIC, Akaike information criterion; CI, confidence interval; CLN2, neuronal ceroid lipofuscinosis type 2.

Confirming the Relationships Using a Mixed Modelling Approach

- Using a mixed effects regression model, there was strong evidence of a positive correlation between the PedsQL total score and the CLN2 Clinical Rating Scale total score ($p < 0.001$; $\hat{\beta}$ [95% CI]: 5.06 [2.66, 7.44]; Table 2).
- Similar to the simple linear regression results, the PedsQL Physical domain score still appeared to drive this relationship ($p < 0.001$), with the model predicting that a 1-point increase in the CLN2 clinical rating scale translates to a 10.4-point increase in the Physical domain score ($\hat{\beta}$ [95% CI]: 10.41 [7.21, 13.54]; Table 2).

- Estimates of the regression parameter ($\hat{\beta}$) for both the PedsQL total score and Physical domain score were larger than the 4.5 point MCID for the PedsQL, suggesting that a 1-point change in the CLN2 Clinical Rating Scale has a patient-relevant impact on quality of life (QoL).
- There was no longer evidence of a relationship between CLN2 Clinical Rating Scale total score and either the Emotional or Social domain scores of the PedsQL (Table 2).

Conclusions

- Both simple linear regression and mixed effects analysis provided evidence of concurrent validity between the CLN2 Clinical Rating Scale and PedsQL, with results suggesting that the Physical domain of the PedsQL drives this relationship.
- This relationship could suggest that a 1-point change on the CLN2 Clinical Rating Scale provided a MCID in the PedsQL total score and Physical domain score.
- Adjusted R^2 values from the simple linear regression analysis may suggest that although the Motor and Language domains are a key driver of patient QoL, they may not capture fully the impact of this disease on patients' QoL.
- A key limitation of this analysis was the small sample size. It was also assumed that the relationship between both scales remained constant over the duration of treatment.

References

- Steinfeld R, et al. Am J Med Genet. 2002;112(4):347–354; 2. Varni J, et al. Expert Rev Pharmacoecon Outcomes Res 2005;5(6):705–719.

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