Demonstrating Fitness-for-Purpose of a Single-Item Ordinal Satisfaction Endpoint in the IRAKLIA Study of Isatuximab Using Complementary Psychometric, Regression, Structural Equation Modelling, and Network Analysis Methods

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Background

- IRAKLIA (NCT05405166) was a randomised, open-label, non-inferiority Phase 3 study that evaluated subcutaneous (SC) versus intravenous (IV) administration of isatuximab (Isa) combined with pomalidomide and dexamethasone in adult patients with relapsed and/or refractory multiple myeloma.[1]
- The 9-item Patient Experience and Satisfaction Follow-up Questionnaire (PESQ-FU) was developed in accordance with the Food and Drug Administration guidance to focus in part on patient satisfaction with the method of administration (Item 8).
- The PESQ-FU was incorporated into the IRAKLIA study, with the key secondary objective of assessing patient satisfaction with Isa SC compared to IV endpoint at Cycle 5 Day 15 (C5D15), in a 28-day cycle. Item 8 asks patients to rate their satisfaction with their injection method using a 5-point Likert scale (Very satisfied to Very dissatisfied).
- Single-item ordinal endpoints cannot support dimensionality analyses or internal-consistency reliability, and their small number of ordered response categories can constrain traditional psychometric analyses.
- Complementary evidence was therefore needed to determine whether Item 8 responses meaningfully reflected patient-reported satisfaction with the injection method.

Objective

To evaluate whether PESQ-FU Item 8 functions as an interpretable, experience-driven measure of satisfaction with the injection method, and to illustrate how complementary quantitative methods can strengthen the validity argument for a single-item ordinal patient-reported outcome (PRO) endpoint.

Methods

- Evidence was developed sequentially across traditional psychometric, multivariable regression, latent-variable, and exploratory network approaches to provide complementary perspectives on the interpretability of the endpoint.
- Traditional psychometric analyses evaluated the Item 8 response distribution, item-to-item correlations, known-groups validity, and test-retest reliability.
- Ordinal logistic regression modelled higher satisfaction (collapsed into three categories: Very Satisfied, Satisfied, Neutral or Less) as a function of injection discomfort, pain, injection-method side effects, time saved, baseline expectations (captured with the Patient Expectation Questionnaire at Baseline [PEQ-BL], assessing pre-treatment expectations of discomfort, pain, side effects, and time saved), and demographic/clinical covariates.
- Structural equation modelling (SEM) specified discomfort, pain, and injection-method side effects as indicators of a latent Injection Experience construct and evaluated the independent relationships of Injection Experience and perceived time saved with satisfaction.
- Partial-correlation network analysis estimated the direct conditional associations of satisfaction with the PESQ-FU variables and broader health-related quality of life (HRQoL) variables, after accounting for the other variables in the network.

Results

Analysis population and response distribution

- PESQ-FU responses were available for 392 intent-to-treat participants in the pooled study arms at C5D15.
- Overall, 33.2% of participants were very satisfied and 50.3% were satisfied with the injection method, resulting in a strongly favourable response distribution.

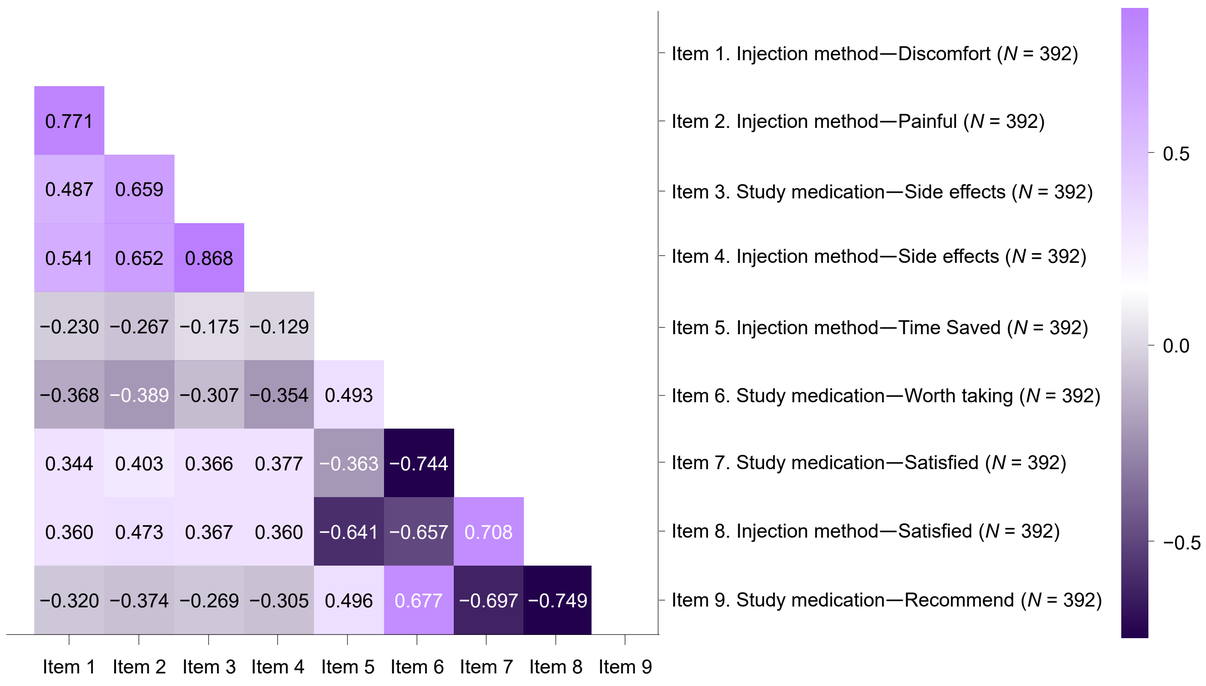
Known-groups validity and test-retest reliability

- Item 8 differed across groups defined by injection discomfort, pain, and perceived time saved (all omnibus $p < 0.001$). Satisfaction generally increased with more favourable injection experiences, although the ordering was less consistent among the smaller groups reporting unfavourable experiences.
- Test-retest reliability between C5D15 and C6D15 was below the expected threshold of 0.70 (intraclass correlation coefficient (ICC) = 0.611; 95% confidence intervals (CI): 0.538–0.676; n = 319). However, the average difference was close to zero, and most individual differences were no greater than one response category.

Item-to-item correlations

- As depicted in **Figure 1**, Item 8 was associated with conceptually relevant PESQ-FU items in the expected directions. The largest polychoric correlations were with willingness to recommend the medication (Item 9; r = −0.749), medication satisfaction (Item 7; r = 0.708), perceiving the medication as worth taking (Item 6; r = −0.657), and time saved (Item 5; r = −0.641).
- A moderate correlation was observed with injection pain (Item 2; r = 0.473), with more modest correlations with medication side effects (Item 3; r = 0.367), injection discomfort (Item 1; r = 0.360), and injection-method side effects (Item 4; r = 0.360).

Figure 1. Item-to-item correlations at C5D15 for the PESQ-FU



Note(s): Polychoric correlation coefficients are reported for each pair of items. Negative correlations reflect opposite scoring directions: lower item scores indicate better outcomes for item 5 (saved time), higher scores indicate better outcomes for items 1 (discomfort), 2 (pain), 4 (injection side effects) and 8 (injection satisfaction). All items were scored on a 1-to-5 response scale.
C5D15, Cycle 5 Day 15; N = number of participants; PESQ-FU, Patient Experience and Satisfaction Follow-up Questionnaire.

Ordinal logistic multivariable regression

- The regression included 340 participants with C5D15 PESQ-FU data and baseline PEQ-BL data. Satisfaction responses were grouped as Very Satisfied (n = 118), Satisfied (n = 170), and Neutral or Less (n = 52). Results represent adjusted statistical associations and should not be interpreted as causal.
- Perceived time saved showed the largest adjusted association with higher satisfaction (odds ratio [OR] = 2.80), followed by less pain (OR = 1.96) and fewer injection-method side effects (OR = 1.53) (**Table 1**).
- Baseline expectation of time saved was also associated with higher satisfaction (OR = 1.36); demographic/clinical covariates were not associated after adjustment.

Table 1. Ordinal logistic regression for injection satisfaction with the injection method (PESQ-FU Item 8) at C5D15

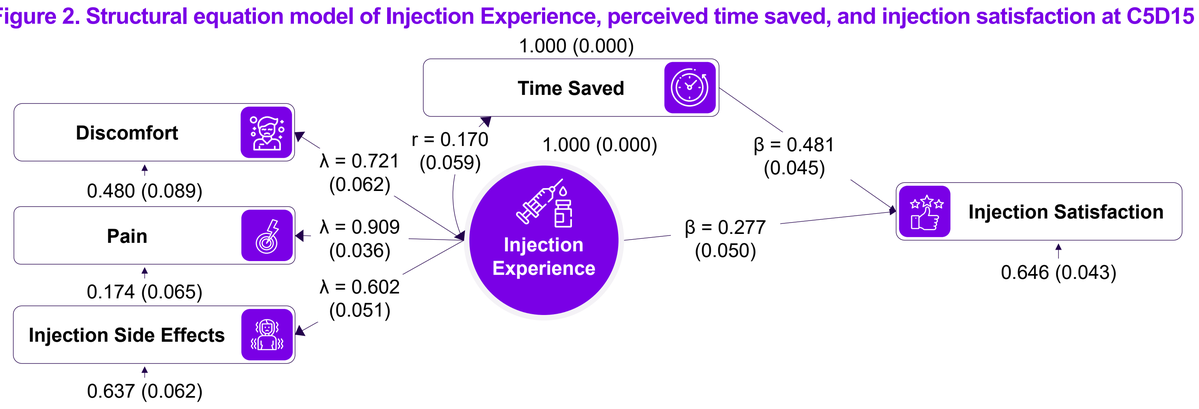
Predictor/covariate	OR	95% CI	p-value
Primary injection-experience predictors			
PESQ-FU Item 1: Injection method—Discomfort	0.93	0.68–1.26	0.631
PESQ-FU Item 2: Injection method—Painful	**1.96**	**1.34–2.91**	**<0.001**
PESQ-FU Item 4: Injection method—Side effects	**1.53**	**1.12–2.08**	**0.006**
PESQ-FU Item 5: Injection method—Time saved	**2.80**	**2.15–3.69**	**<0.001**
Demographic and clinical covariates			
Age (mean-centred at 65 years)	0.98	0.96–1.01	0.130
Male	0.65	0.38–1.09	0.103
Weight >85 kg (reference: <65 kg)	1.13	0.56–2.27	0.737
Weight 65–≤85 kg (reference: <65 kg)	1.52	0.86–2.69	0.153
ORR status (responder)	1.04	0.57–1.89	0.909
Baseline expectations			
PEQ-BL Item 1: Injection method—Discomfort	0.86	0.61–1.21	0.377
PEQ-BL Item 2: Injection method—Painful	0.99	0.68–1.44	0.948
PEQ-BL Item 4: Injection method—Side effects	1.17	0.83–1.64	0.376
PEQ-BL Item 5: Injection method—Time saved	**1.36**	**1.04–1.78**	**0.027**

Note(s): ORs represent the change in odds of higher satisfaction per one-category improvement, holding the other variables constant. Higher scores indicate better outcomes (less pain, fewer side effects, and more time saved). Firth's penalised maximum likelihood was applied. Proportional-odds assumption: χ^2 (13) = 10.39, p = 0.662. Predicted probabilities were strongly associated with observed responses: c = 0.82 (Somers' D = 0.65).
C5D15, Cycle 5 Day 15; CI, confidence interval; OR, odds ratio; ORR, overall response rate; PEQ-BL, Patient Expectation Questionnaire at baseline; PESQ-FU, Patient Experience and Satisfaction Follow-up Questionnaire.

Structural Equation Modelling

- The SEM analysis showed excellent model fit (comparative fit index = 0.998; Tucker-Lewis fit index = 0.994; root mean-square error of approximation = 0.020; standardised root-mean square residual = 0.014).
- Standardised factor loadings supported the Injection Experience construct: discomfort = 0.721, pain = 0.909, and injection side effects = 0.602 (**Figure 2**).
- Modelling these three correlated items as indicators of a common latent factor captured their shared variance and addressed the multicollinearity concerns raised by estimating them separately in the regression model.
- Standardised path coefficients (β) showed that time saved and Injection Experience were each independently associated with injection satisfaction (β = 0.481 and β = 0.277, respectively), with time saved showing the larger association.
- Time saved and Injection Experience were weakly correlated (r = 0.170), supporting their interpretation as related but distinct aspects of the patient experience. Together, they explained 35% of the variance in injection satisfaction.

Figure 2. Structural equation model of Injection Experience, perceived time saved, and injection satisfaction at C5D15

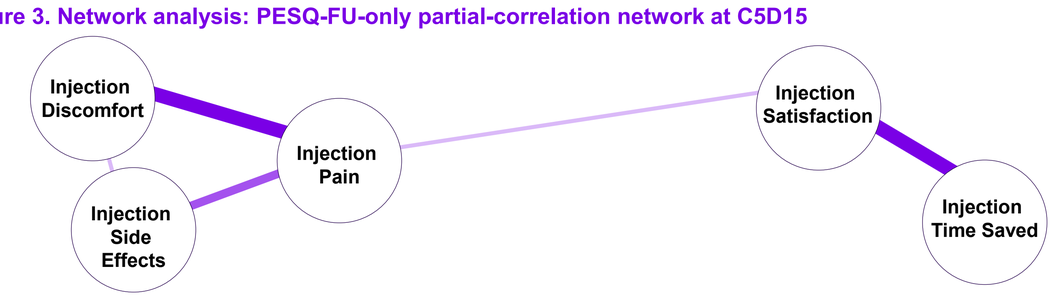


Values are standardised estimates; standard errors are shown in parentheses.
N, number of participants; PESQ-FU, Patient Experience and Satisfaction Follow-up Questionnaire; SEM, structural equation modelling.

Network analysis

- The broader network examined satisfaction in relation to injection-related PESQ-FU items and selected HRQoL variables among 379 complete cases. A sensitivity network restricted to the five injection-related PESQ-FU items included all 392 participants and provided a more stable and interpretable item-level model.
- In the PESQ-FU-only network, Injection satisfaction (Item 8) had a moderate direct association with perceived time saved (Item 5; partial r = 0.501) and a small direct association with pain (Item 2; partial r = 0.204), after accounting for the other items in the network. No additional direct associations with satisfaction were identified. (**Figure 3**)
- Consistent with the regression and SEM findings, the network results indicated that injection-method satisfaction primarily reflected the reported experience of time savings, with pain providing additional information. This convergence supports the interpretation of PESQ-FU Item 8 as an experience-driven satisfaction endpoint.

Figure 3. Network analysis: PESQ-FU-only partial-correlation network at C5D15



Note: The analysis used only complete cases (N = 392). A GGM was applied to remove spurious correlations. Edge width/opacity = association strength; edge colour = positive (purple).
C5D15, Cycle 5 Day 15; GGM, Gaussian graphical model; N, number of participants; PESQ-FU, Patient Experience and Satisfaction Follow-up Questionnaire.

Limitations

- The analyses were primarily cross-sectional and observational at C5D15; regression, SEM, and network relationships should not be interpreted as causal.
- As a single-item endpoint, Item 8 cannot be evaluated using dimensionality or internal-consistency analyses; its validity argument therefore relies on convergence across complementary evidence.
- The strongly favourable response distribution restricted variability, which may have attenuated correlations and reliability estimates and limited differentiation among highly satisfied participants.

Conclusions

- Evidence across traditional psychometric, regression, SEM, and network analyses converged on a coherent interpretation of PESQ-FU Item 8 as an experience-driven measure of satisfaction with the injection method.
- Logistic regression estimated the adjusted associations of individual injection experiences with satisfaction; SEM modelled their shared and structural relationships; and network analysis evaluated direct conditional associations without imposing the hypothesised SEM structure.
- Satisfaction was most strongly associated with perceived time saved, with Injection Experience, particularly pain and injection-method side effects, providing additional information.
- These findings support PESQ-FU Item 8 as a clinically informative endpoint in comparative administration settings and illustrate how complementary quantitative methods can strengthen a validity argument for a conceptually meaningful single-item PRO endpoint when the evidence available for multi-item scales cannot be generated.

References
1. Ailawadhi S, *et al., J Clin Oncol*. 2025; 43: 2527–2537.

Conflicts of Interest
AT, **PG**, **JM**, **MSU**, and **BA** are employees of Sanofi and may hold stock or stock options.
JCM, **DS**, **EB**, and **SR** are employees of IQVIA, and **MK** is an employee of Aixial Group, both of which received funding from Sanofi for this research.

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