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Health-related quality of life in patients with prominent negative symptoms: results from a multicenter randomized Phase II trial on bitopertin

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Abstract
Purpose Symptoms of schizophrenia fall into three categories (positive, negative and cognitive symptoms), which probably impact differently on patient's health-related quality of life (HRQoL). The present study aimed to explore HRQoL in patients with prominent negative symptoms.
Methods In the 323 patients with prominent negative symptoms included in a multicenter Phase II trial investigating the safety and efficacy of bitopertin, HRQoL was assessed using the Schizophrenia Quality of Life Scale (SQLS), symptoms severity using the Positive and Negative Syndrome Scale and functioning using the Personal and Social Performance Scale. SQLS measurement properties were assessed; HRQoL was compared between treatment arms, and relationships between HRQoL, symptoms and functioning at baseline were explored.
Results Both SQLS scores (Vitality/Cognition and Psychosocial Feelings) demonstrated good test–retest (ICC = 0.77 and 0.74) and internal consistency reliability (Cronbach's $\alpha = 0.86$ and 0.93). Clinical validity with regard to schizophrenia severity and ability to detect change in severity of symptoms of schizophrenia were satisfactory. The SQLS structure was not formally disconfirmed. No statistically significant difference was observed between treatment arms. Negative symptoms were more strongly associated with functioning than positive symptoms. Functioning and Anxiety/Depression were strongly related to both SQLS domains.
Conclusion Overall, SQLS measurement properties were supported in these patients with prominent negative symptoms of schizophrenia. The impact of negative symptoms on functioning and HRQoL suggests that improving these symptoms will be a meaningful benefit in this population of patients.

Keywords Quality of life · Schizophrenia · Negative symptoms · Bitopertin

Introduction

Health-related quality of life (HRQoL) is a multidomain concept that represents the patient's perception of the effect of illness and treatment on physical, psychological and social aspects of life [1]. Assessing HRQoL is critical in capturing which health aspects are meaningful for the patients themselves. This is particularly true in schizophrenia where many symptoms are difficult for an external observer to evaluate [2]. Several studies have shown that individuals with schizophrenia are able to describe their experience, reporting difficulties functioning in society, reduced contacts with others and worries about what others may think about them [3].

Symptoms of schizophrenia fall into three categories: positive, negative and cognitive [4]. The different ways in which these symptoms impact patients' HRQoL remain largely unexplored. While generic measures of HRQoL can be used in patients with schizophrenia [5], instruments

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specifically developed for use in schizophrenia, such as the Schizophrenia Quality of Life Scale (SQLS; J&J) [6], may be preferable. The SQLS has been used to show improved HRQoL in schizophrenia patients treated with a range of treatments [7, 8].

Schizophrenia is currently treated with typical and atypical antipsychotics (also known as neuroleptics and second-generation antipsychotics). Typical antipsychotics are high-affinity D2 receptor antagonists, whereas atypical antipsychotics have lower-affinity D2 receptor antagonism but combine this with activity at a broad range of other neurotransmitter receptors targeting dopamine, serotonin and norepinephrine amongst others [9]. While antipsychotic drugs have been demonstrated to treat positive symptoms of schizophrenia, their effect on negative symptoms and cognitive impairment remains unclear [10–12]. It has been previously observed that the administration of an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, a glutamate receptor, led to a symptomatic pattern in healthy subjects similar to that of individuals with schizophrenia [13]. Therefore, targeting the glutamatergic signaling pathway may treat all three symptom categories. Related new treatment developments include inhibitors of the glycine transporter and activators of the metabotropic glutamate receptors [14]; bitopertin is a glycine transporter 1 inhibitor [15].

A Phase II study (NCT00616798) demonstrated that bitopertin was effective as an adjunctive therapy in schizophrenia patients ($N = 323$) with prominent negative and cognitive/disorganized symptoms [defined according to the Positive and Negative Syndrome Scale (PANSS)] who were stable on atypical antipsychotics. After 8 weeks of treatment, patients who had received 10 or 30 mg/day bitopertin exhibited a larger reduction (−6.50 and −6.65, respectively) in the PANSS Negative Symptom Factor Score (NSFS) than those who received placebo (−4.86; $p < 0.05$) [16]. The present secondary analysis of the Phase II study aimed to investigate the appropriateness of the SQLS to measure the impact of therapeutic intervention on HRQoL in this population of patients with prominent negative symptoms, to evaluate the benefit of bitopertin in terms of HRQoL and to investigate relationships between functioning, HRQoL and symptoms of schizophrenia.

Materials and methods

Study design

This work was a secondary analysis of data collected in trial NCT00616798, a randomized, double-blind, placebo-controlled, add-on trial of the safety and efficacy of bitopertin in patients with prominent negative or disorganized thought symptoms [16]. Study participants were aged 18–60 years, diagnosed with schizophrenia according to the DSM-IV TR, medically stable on current atypical antipsychotic treatment over the prior 1 month and psychiatrically stable without symptom exacerbation over the prior 3 months. Key inclusion criteria were a total score of ≥40 on the sum of the 14 items constituting the PANSS Negative symptoms and disorganized thought/cognition factors [17]; a score of ≤28 on the sum of the 8 items of the PANSS positive symptoms factor and a score of 4 on 2 or fewer of the items P1 (delusions), P3 (hallucinatory behavior), P6 (suspiciousness) and G9 (unusual thought) and none with a score of 5; and taking 2 or fewer antipsychotics, with the primary antipsychotic being an SGA and the total dose of all antipsychotics not exceeding 6 mg of risperidone equivalents. Key exclusion criteria were a score of 4 or more on the PANSS item G6 (depression); any movement disorder due to antipsychotic treatment not currently controlled with anti-EPS treatment; and clozapine treatment within the last 3 months. More details on the study design are given elsewhere [16].

Following a one-month, run-in period to confirm symptom stability, patients were randomized to bitopertin 10, 30 or 60 mg given orally once a day for 8 weeks, or to placebo. The primary objective was to evaluate the effect of bitopertin on the mean change in the PANSS NSFS from baseline to week 8. Analysis of HRQoL measured with the SQLS was a secondary endpoint. The study was conducted in compliance with the principles of the Declaration of Helsinki or with the laws and regulations of the country in which the research was conducted. Signed informed consent was obtained for each patient prior to participating in this study. The study was conducted at 66 sites in Brazil, France, Germany, Hungary, Japan, Mexico, Poland, Russia and the USA, following International Conference on Harmonization Guidelines for Good Clinical Practice. The protocol was approved by the health authorities of each country and respective ethics committees of each site.

Assessments

All assessments were done at baseline (randomization) and repeated at week 8. Patients' HRQoL was assessed with the fourth revision of the self-reported SQLS [6, 18], which is composed of 33 items across two domains: Psychosocial Feelings (20 items) and Cognition/Vitality (13 items). Items are scored on a 5-point Likert-type scale assessing frequency (never to always). Scores were computed according to the rules defined by the developers, including the management of the missing items. Domain scores range from 0 to 100 with a higher score associated with worse quality of life.

Severity of schizophrenia symptoms experienced by patients was assessed using the PANSS, a 30-item

clinician-administered scale with each symptom rated on a 7-point scale (from absent to extreme) [19]. Further classification of symptoms using a factor analysis of the PANSS was calculated for five factors: negative symptoms, positive symptoms, disorganized thought, uncontrolled hostility/excitement and Anxiety/Depression [17]. A higher factor score is associated with greater symptom severity.

Patient functioning was evaluated using the Personal and Social Performance Scale (PSP), a clinician-reported measure of personal and social dysfunction in patients with acute symptoms of schizophrenia [20]. The PSP includes four items of personal and social functioning, graded using a 6-point severity scale (from absent to very severe). A single overall rating score is obtained ranging from 0 to 100 with a higher score associated with better personal and social functioning.

Clinicians also completed the Clinical Global Impression of Severity (CGI-S) scale rating overall severity of illness on a 7-point scale (from normal/not ill, to among the most severely ill patients) and the Clinical Global Impression of Improvement (CGI-I) scale, a 7-point scale rating improvement or worsening in severity of illness over the study (from very much improved to very much worse). Two other global impression scales focusing on negative symptoms only, CGI-S negative and CGI-I negative, were also completed by clinicians.

Data analysis

Demographics and baseline assessments (SQLS, PANSS and PSP) were described in the study population.

Confirmatory factor analysis (CFA) was performed to confirm the construct validity of the SQLS. The prespecified model included the two SQLS domains as defined in the scoring of the questionnaire. The quality of this model was assessed according to the root-mean-square error of approximation (RMSEA), standardized root-mean-square residual (SRMSR), goodness-of-fit index (GFI), adjusted GFI (AGFI), normed (NFI) and comparative fit index (CFI) [21]. Clinical validity [22] was assessed by comparing SQLS scores at baseline across severity subgroups defined by the CGI-S and CGI-S negative. Cross-cultural validity was determined by investigating differential item functioning (DIF) across cultural groups using logistic regressions [23]: for each item, a logistic regression in which the response to the item is the explained variable and the domain score and the culture are explanatory variables. Hence, this approach allows detecting whether respondents from different cultures who are comparable from the measured concept perspective (since the analysis is adjusted on the observed score) respond differently to the item of interest, which is the very definition of differential item functioning. The magnitude of DIF was classified based on effect sizes (DIF-ES) obtained from logistic regression pseudo-R^2 [24, 25]: DIF-ES > 0.035 was considered as moderate DIF and >0.070 large DIF. For this analysis, patients were gathered into homogeneous cultural groups based on geography and family of language spoken, which are complementary components of a proxy used for "culture": European Germanic, Uralic, European Romance, American Romance, North American English, Slavic and Japanese. Internal consistency reliability of SQLS scores was estimated using Cronbach's alpha at baseline. Test–retest reliability of SQLS scores was evaluated by calculating intraclass correlation coefficients (ICC) between baseline and week 8 in patients with unchanged rating on the CGI-S [26, 27]. Ability to detect changes over time [28] was assessed by comparing changes in SQLS scores between patients considered "Improved" (patients minimally to very much improved), with "No change" and "Worsened" (patients minimally to very much worsened), as defined by the CGI-I and CGI-I negative at week 8. Magnitude of change in these groups was quantified by effect sizes (ES). ES around 0.20, 0.50 and 0.80 were considered small, moderate and large, respectively [29]. All analyses pertaining to measurement properties of the SLQS were done independently of treatment (i.e., on the pooled data of the four treatment groups).

Changes in SQLS scores from baseline to week 8 were compared between treatment groups, using analyses of covariance (ANCOVA) models: ANCOVA models included baseline value of the explained SQLS score and global region (North America, Latin America, Eastern Europe, Western Europe, Japan) as covariates. When scores were missing at week 8, the last observation carried forward principle was applied: The latest available assessment was imputed using the score at baseline or time of discontinuation whichever was last. The percentage of patients reaching a meaningful improvement of their SQLS score ("HRQoL responders") between baseline and week 8 was obtained for each treatment arm. HRQoL responder thresholds were defined using anchor-based methods based on the CGI-I and CGI-I negative and distribution-based methods based on ES and standard error of measurement.

Relationships between HRQoL, symptoms of schizophrenia and functioning assessed by the SQLS, PANSS and PSP, respectively, were studied by univariate linear regressions at baseline. Path modeling [30] was then used to explore relationships between symptoms, functioning and HRQoL. The initial path model, based on the Wilson and Cleary model [31], assumed that symptoms impact functioning, which impacts HRQoL. However, a direct relationship between symptoms and HRQoL was also tested.

The analyses were performed using SAS® software version 9.2 for Windows (SAS Institute, Cary, NC, USA).

Results

Patients

Of 323 recruited patients, 312 completed at least one SQLS item at baseline and were included in the analyses. Among those, 271 also had SQLS data at the end-of-trial visit at 8 weeks. Baseline characteristics, PANSS factor scores, PSP score and SQLS scores are presented in Table 1. Most patients were rated by clinicians as mildly or moderately ill in terms of overall and negative symptoms of schizophrenia. The large majority of patients were minimally or much improved over the course of the trial as rated by clinicians using the CGI-I and CGI-I negative (Fig. 1).

Measurement properties of SQLS

CFA results supporting the construct validity of SQLS are presented in Fig. 2. Correlations were only added to the initial model between some measurement error terms to reflect the unique association between items (i.e., the common information shared by the items which is not captured by the other items of the domain). Their addition was justified by statistical improvement of the model and shared item content. Five items had factor loadings below 0.5 (four in Cognition/Vitality and one in the Psychosocial Feeling). The fit of the model was acceptable.

The SQLS demonstrated good clinical validity (Table 2): Patients with symptoms rated as more severe had significantly worse SQLS scores. However, this was not found when SQLS scores were compared between groups of patients with different severity of negative symptoms.

In the cultural validity analyses, eight items of the Psychosocial Feeling domain had moderate DIF and one had large DIF—item 15 "My feelings swung from high to low." In the Cognition/Vitality domain, three items had moderate DIF and one showed large DIF—item 28 "I felt drowsy" (Table 3). Differences were often observed in Uralic, Slavic and Japanese cultures when compared to patients from the other cultural groups.

Both SQLS scores showed good reliability coefficients (Table 2): Cronbach's α was 0.93 for Psychosocial Feeling and 0.86 for Cognition/Validity, and ICC was 0.74 for Psychosocial Feeling and 0.77 for Cognition/Validity.

The pattern of change in SQLS scores in patients classified as improved and stable in terms of overall and negative symptoms of schizophrenia showed moderate improvement in patients classified as improved and stability in stable patients. Very few patients were classified in the "worsened" groups preventing any meaningful interpretation.

HRQoL response thresholds defined by the anchor-based and distribution-based methods ranged between

Table 1 Demographic characteristics of the study population and scores at baseline

Characteristics	Patients ($n = 312$)
Age (years), mean (SD)	39.9 (10.1)
Sex [n (%)]	
Male	200 (64.1)
Cultural subgroup [n (%)]	
European Germanic	16 (5.1)
Uralic	49 (15.7)
European Romance	12 (3.9)
American Romance	39 (12.5)
North American English	88 (28.2)
Slavic	70 (22.4)
Japanese	38 (12.2)
BMI, Mean (SD)	28.0 (5.8)
Smoking status [n (%)]	
Current smoker	130 (41.7)
Never smoked	140 (44.9)
Past smoker	42 (13.5)
Duration of illness, mean (SD)	11.6 (9.0)
Age at first diagnosis, mean (SD)	28.3 (9.3)
Primary antipsychotic treatment [n (%)]	
Aripiprazole	35 (11.2)
Olanzapine	87 (27.9)
Paliperidone	27 (8.7)
Quetiapine	43 (13.8)
Risperidone	92 (29.5)
Risperidone (long acting)	21 (2.2)
SQLS, Mean (SD)	
Psychosocial Feelings	39.6 (18.2)
Cognition/Vitality	45.6 (16.8)
PSP, Mean (SD)	
Global score	50.2 (12.6)
PANSS, Mean (SD)	
Negative symptoms	26.2 (3.8)
Positive symptoms	17.7 (3.6)
Disorganized thought	20.7 (3.5)
Uncontrolled hostility/excitement	6.4 (2.2)
Anxiety/Depression	8.2 (2.6)
Total	79.2 (9.2)
CGI-S [n (%)]	
Normal	0 (0.0)
Borderline mentally ill	3 (1.0)
Mildly ill	67 (21.5)
Moderately ill	196 (62.8)
Markedly ill	43 (13.8)
Severely ill	3 (1.0)
Extremely ill	0 (0.0)
CGI-S negative [n (%)]	
Normal	0 (0.0)

Table 1 continued

Characteristics	Patients ($n = 312$)
Borderline mentally ill	0 (0.0)
Mildly ill	12 (3.8)
Moderately ill	169 (54.2)
Markedly ill	110 (35.3)
Severely ill	21 (6.7)
Extremely ill	0 (0.0)

SD standard deviation, *BMI* body mass index, *SQLS* Schizophrenia Quality of Life Scale, *PSP* Personal and Social Performance Scale, *PANSS* Positive and Negative Syndrome Scale, *CGI-S* Clinical Global Impression-Severity

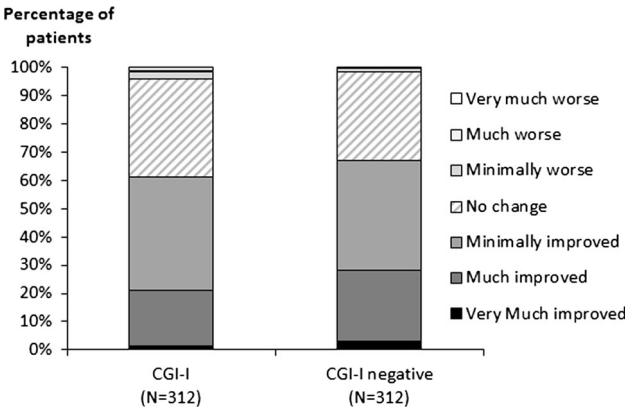


Fig. 1 Description of patients' improvement during the trial according to clinician-rated CGI-I and CGI-I negative at week 8 ($N = 312$)

−3.61 and −9.03 for the Psychosocial Feelings score and between −3.26 and −8.15 for the Cognition/Vitality score (Table 2).

Investigation of the effect of bitopertin on HRQoL

The change in SQLS scores over the trial was not statistically different between bitopertin and placebo groups. Mean changes in SQLS scores were consistently slightly greater (indicating greater improvement) in the bitopertin groups than in the placebo group (adjusted mean difference from placebo ranging from −0.01 to −1.50). In the responder analysis, the percentage of responders was consistently greater in the bitopertin arms than in the placebo arm for both the higher and lower bounds of the HRQoL response thresholds (Table 4).

Relationships between HRQoL, symptoms and functioning

The cross-sectional regressions at baseline showed that the PANSS NSFS was associated with the SQLS Cognition/Vitality domain but not with the SQLS Psychosocial domain, while the PANSS Positive Factor Score was associated with the SQLS Psychosocial domain but not with the SQLS Cognition/Vitality score. A strong association was also found between the PANSS Anxiety/Depression score and both SQLS domains (Table 5).

The initial hypothesized path model linking PANSS factor scores to PSP score and SQLS scores was modified to include only significant relationships. The goodness of fit of the final path model was very good (Fig. 3).

In this model, the PANSS Positive and Negative Symptom Factor Scores were related to functioning. The effect of negative symptoms on functioning was about three times as strong as the effect of the positive symptoms (standardized parameter estimate −0.459 vs. −0.160). PANSS Negative and Positive Factor Scores also had a direct effect on the Cognition/Vitality score but not on the Psychosocial Feelings. Both SQLS domains were also strongly associated with functioning and Anxiety/Depression.

Discussion

The objective of this study was to investigate the HRQoL of patients with negative symptoms of schizophrenia using data from a Phase II clinical trial. The objectives of these secondary analyses were to assess the appropriateness of using the SQLS in this population and to explore the benefit in terms of HRQoL of bitopertin as well as the relationship of HRQoL with symptoms and functioning. For the consideration of the second objective of our analyses (i.e., exploration of the benefit of bitopertin in terms of HRQoL), it is important to note that, since we performed these analyses, two Phase III studies of bitopertin in negative symptoms were recently reported as not meeting their primary endpoints [32, 33].

The SQLS was developed and validated in schizophrenia, without specific characterization of the types of symptoms experienced [18, 34, 35]. In this study, most measurement properties of the SQLS were supported in patients with prominent negative symptoms of schizophrenia. The reliability of SQLS scores was good, as shown by both internal consistency and test–retest, and its two-domain structure was not disconfirmed by the CFA. Clinical validity based on the overall assessment of schizophrenia severity was very good: Patients with more severe symptoms had poorer HRQoL according to SQLS scores. The SQLS also showed good ability to detect improvement in overall and negative symptoms of schizophrenia. Cross-cultural differences were identified in two SQLS items in particular, but this may be due to semantic differences and the small number of items affected suggests minimal impact on HRQoL measurement.

The SQLS was not developed specifically for individuals with negative symptoms of schizophrenia. Hence, it may not capture accurately the specific domains of HRQoL

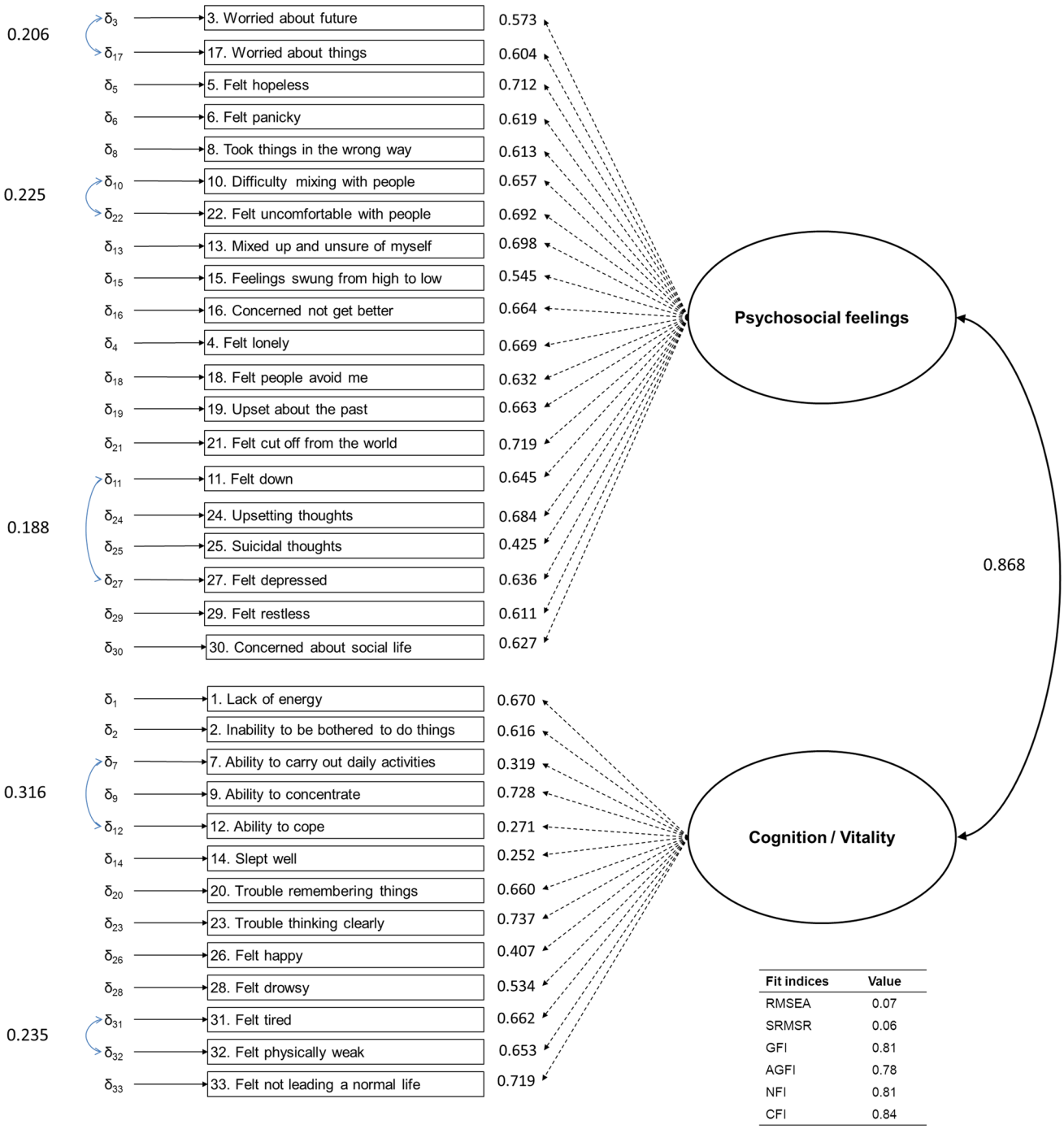


Fig. 2 Confirmatory factor analysis (CFA) on the hypothesized measurement model of the SQLS at baseline ($N = 312$). Parameter estimates are provided as standardized estimates. *RMSEA* root-mean-square error of approximation, *SRMSR* standardized root-mean-square residuals, *GFI* goodness-of-fit index, *AGFI* adjusted goodness-of-fit index, *NFI* normed fixed index, *CFI* comparative fit index

that are impacted by these symptoms. This may explain why patients with more severe negative symptoms at baseline were found not to have poorer SQLS scores and the potential room for improvement of the structure identified by the CFA in our sample. A more specific measure may have allowed finer changes in HRQoL to be detected in this patient population. Such an instrument might be obtained by modifying marginally the SQLS, for example, by adding items or domains. This would require further qualitative research in particular to identify HRQoL aspects specific to patients with prominent negative symptoms. Nonetheless, the SQLS was still shown in this study to allow a proper measure of HRQoL in this population.

Table 2 Measurement properties of the SQLS: clinical validity, reliability, ability to detect change and responder thresholds based on anchor-based and distribution-based approaches

Psychometric properties	SQLS domains	
	Psychosocial Feelings	Cognition/Vitality
Clinical validity		
CGI-S ($n = 312$)		
Mean score (SD)		
Mildly ill or less ($n = 70$)	35.6 (17.8)	40.2 (16.2)
Moderately ill ($n = 196$)	39.6 (18.1)	45.8 (16.5)
Markedly ill or more ($n = 46$)	45.6 (17.6)	52.4 (16.1)
p value[a]	0.0148	0.0005
CGI-S negative ($n = 312$)		
Mean score (SD)		
Mildly ill or less ($n = 12$)	39.3 (16.5)	46.3 (15.1)
Moderately ill ($n = 169$)	39.6 (18.3)	44.1 (16.8)
Markedly ill or more ($n = 131$)	39.7 (18.3)	47.3 (16.8)
p value[a]	0.9957	0.2624
Reliability		
Internal consistency reliability ($n = 312$)		
Cronbach's α[b]	0.93	0.86
Test–retest reliability ($n = 146$)		
ICC[b]	0.74	0.77
Ability to detect change		
Based on CGI-I ($n = 271$)		
Effect size[c]		
Improved ($n = 174$)	−0.45	−0.50
No change ($n = 92$)	−0.03	−0.05
Worsened ($n = 5$)	0.51	−0.36
Based on CGI-I negative ($n = 271$)		
Effect size[c]		
Improved ($n = 193$)	−0.44	−0.48
No change ($n = 76$)	0.03	−0.03
Worsened ($n = 2$)	0.28	0.22
Responder threshold definition		
Anchor-based approaches		
CGI-I-based[d]	−6.36	−6.05
CGI-I-negative-based[d]	−4.64	−3.50
Distribution-based approaches		
$0.2 \times SD_{BL}$	−3.61	−3.26
$0.5 \times SD_{BL}$	−9.03	−8.15
SEM	−4.74	−6.27

SD standard deviation, *SQLS* Schizophrenia Quality of Life Scale, *CGI-S/I* Clinical Global Impression-Severity/Improvement, *ICC* intraclass correlation coefficient, SD_{BL} standard deviation at baseline, *SEM* standard error measurement

[a] p value from Tukey test

[b] Recommended satisfactory threshold: Cronbach's $\alpha > 0.7$ and ICC > 0.7

[c] ES around 0.20, 0.50 and 0.80 considered small, moderate and large, respectively

[d] Responder thresholds defined as mean change from baseline to week 8 in SQLS scores of patients whose change was rated as "Minimal improvement" on the CGI-I/CGI-I negative

SQLS may therefore be used to evaluate treatment benefit in terms of HRQoL in patients with negative symptoms of schizophrenia. In this Phase II trial, the small differences in HRQoL were systematically in favor of bitopertin over placebo but did not reach statistical significance. It is important to note that the trial was not

Table 3 Differential item functioning analyses of the SQLS across cultural groups at baseline using logistic regression ($N = 312$)

Domains	Items	DIF-ES[a]
Psychosocial Feelings	3. I was worried about my future	0.021
	4. I felt lonely	0.031
	5. I felt hopeless	0.044
	6. I felt panicky	0.043
	8. I took things people said the wrong way	0.022
	10. I found it difficult to mix with people	0.024
	11. I felt down	0.029
	13. I felt very mixed up and unsure of myself	0.045
	15. My feelings swung from high to low	0.119
	16. I felt concerned that I would not get better	0.019
	17. I worried about things	0.036
	18. I felt that people tended to avoid me	0.016
	19. I got upset thinking about the past	0.027
	21. I felt cut off from the world	0.044
	22. I felt uncomfortable with people	0.021
	24. I had upsetting thoughts	0.042
	25. I had suicidal thoughts	0.020
	27. I felt depressed	0.039
	29. I felt restless	0.052
	30. I was concerned about my social life	0.013
Cognition/Vitality	1. I lacked the energy to do things	0.018
	2. I could not be bothered to do things	0.017
	7. I was able to carry out my day-to-day activities	0.034
	9. I found it hard to concentrate	0.006
	12. I felt that I could cope	0.029
	14. I slept well	0.049
	20. I had trouble remembering things	0.017
	23. I had trouble thinking clearly	0.049
	26. I felt happy	0.060
	28. I felt drowsy	0.075
	31. I felt tired	0.013
	32. I felt physically weak	0.008
	33. I felt like I was not leading a normal life	0.019

DIF differential item functioning

[a] DIF-ES lower than 0.035, between 0.035 and 0.070, and greater than 0.070 indicate negligible, moderate and large DIF-ES, respectively

perfectly designed to detect HRQoL improvements. The impact of a treatment on patients' HRQoL is likely not to be observed on a short term, and many confounders may intervene. For an initial biological benefit to translate into improved HRQoL, several steps may be required (alleviating symptoms, enhancing functioning and being perceived as a daily benefit by the patient), and this may be also affected by individual characteristics and environmental factors [31]. Demonstrating a symptomatic benefit over only 8 weeks is, therefore, challenging. While there is no clear evidence on the time needed to be able to detect improvement in the HRQoL of patients with schizophrenia further to the introduction of a new treatment, a period of at least 3 months could be reasonably hypothesized. The consistent better results in the bitopertin groups in terms of HRQoL may be seen as a potential signal regarding the HRQoL-related benefit of bitopertin.

While it is accepted that patients with more severe symptoms of schizophrenia have worse HRQoL [36], the impact in particular of negative versus positive symptoms, on functioning and quality of life, is less documented [37]. In this study, the complex relationships linking HRQoL and symptoms and functioning were investigated. It was shown that only three types of symptoms play a role in the model linking the different patient-centered outcomes: negative symptoms, positive symptoms and Anxiety/

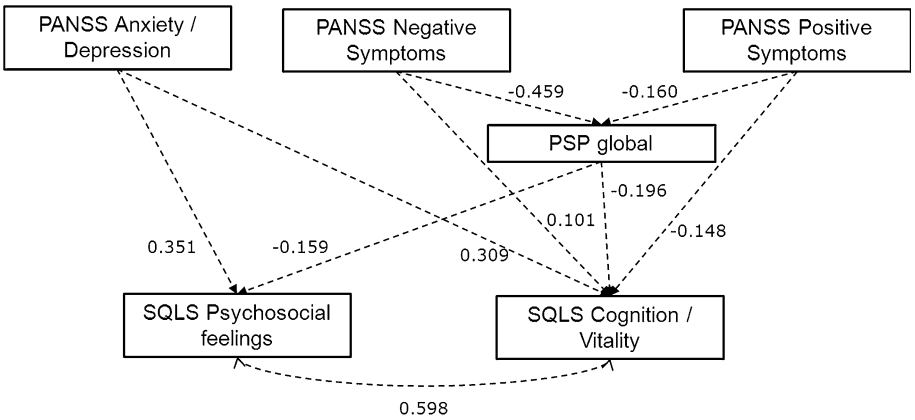
Table 4 Comparison of treatment arms: ANCOVA comparing change in SQLS score over the trial between treatment arms and responder analysis

SQLS scores	Methods	Placebo ($N = 77$) (%)	Bitopertin 10 mg ($N = 81$)	Bitopertin 30 mg ($N = 77$)	Bitopertin 60 mg ($N = 77$)
Psychosocial Feelings	Adjusted mean difference from Placebo[a]		−0.48	−0.63	−0.01
	p value		0.82	0.77	1.00
	Percentage of patient reaching lower responder threshold (−4.64)	39.1	47.9 %	53.0 %	46.2 %
	Percentage of patient reaching upper responder threshold (−9.03)	24.6	33.8 %	31.8 %	29.2 %
Cognition/ Vitality	Adjusted mean difference from placebo[a]		−1.12	−0.65	−1.50
	p value		0.56	0.74	0.44
	Percentage of patient reaching lower responder threshold (−3.50)	50.6	69.1 %	61.0 %	70.1 %
	Percentage of patient reaching upper responder threshold (−8.15)	34.8	35.2 %	39.4 %	43.1 %

[a] Adjusted mean difference in change from baseline obtained by ANCOVA models of change in score from baseline with baseline value of the SQLS score and global region (North America, Latin America, Eastern Europe, Western Europe, Japan) as covariates

Table 5 Univariate linear regression of baseline SQLS scores on baseline PANSS scores ($N = 312$)—parameter estimates

	Baseline score			
	Psychosocial Feeling		Cognition/Vitality	
	Estimate	*p* value	Estimate	*p* value
PANSS negative factor score	0.43	0.11	0.71	<0.01
PANSS positive factor score	1.22	<.0001	0.05	0.86
PANSS disorganized thought factor score	0.67	0.02	0.42	0.13
PANSS uncontrolled hostility/excitement factor score	1.33	<0.01	0.61	0.16
PANSS Anxiety/Depression factor score	2.35	<0.001	1.42	<0.001



Fit indices	Value
RMSEA	0.06
SRMSR	0.03
GFI	0.99
AGFI	0.97
NFI	0.99
CFI	0.99

Fig. 3 Path model linking PANSS factor scores, PSP score and SQLS scores at baseline—standardized parameter estimates ($N = 312$). *RMSEA* root–mean-square error of approximation, *SRMSR* standardized root-mean-square residuals, *GFI* goodness-of-fit index, *AGFI* adjusted goodness-of-fit index, *NFI* normed fixed index, *CFI* comparative fit index

Depression. Both negative and positive symptoms were associated with functioning, but the deleterious effect of negative symptoms on functioning was much stronger than the impact of positive symptoms. This is in line with a recent analysis of the CATIE study that showed that in patients with chronic schizophrenia, functioning assessed using a subset of items from the Heinrich's and Lehman's Quality of Life Scales was much more strongly correlated with the PANSS Negative factor than the Positive factor [38]. The impact of functioning on both domains of HRQoL was also confirmed in our data, validating the hypothesis that the symptomatic impact on HRQoL is achieved mainly through functioning. Finally, the role of Anxiety/Depression on the HRQoL of patients with negative symptoms of schizophrenia also appeared to be central; however, it was not achieved through functioning but had a direct impact on HRQoL.

These findings, in particular those on the relationships between schizophrenia symptoms and HRQoL, should be interpreted in light of the composition of the sample of patients used for these analyses. These patients had prominent negative and cognitive/disorganized symptoms; it would be extremely interesting to investigate whether these findings are replicated in other groups of patients with schizophrenia, for example, in patients who have a concomitant positive and negative symptoms. The patients of this study were also all stable on atypical antipsychotics. This concomitant treatment, with potential side effects, may have affected the assessment of the association between HRQoL and schizophrenia symptoms or of the benefit of bitopertin. Further analyses extending our analyses in other populations of patients with schizophrenia, maybe in more naturalistic settings, or exploring further the relative direct and indirect impacts of symptoms and functioning on HRQoL, using for instance proper mediation analysis, would certainly be of great interest to enhance the knowledge on HRQoL of patients with schizophrenia.

In conclusion, even though the SQLS may not be ideal for assessment of HRQoL in patients with negative symptoms of schizophrenia, its measurement properties were overall supported in this sample of patients. No statistically significant benefit of bitopertin on the HRQoL in these patients was observed. However, it was shown that the patients' negative symptoms had a substantial impact on their functioning and HRQoL, and that functioning and Anxiety/Depression played a central role in the experience of these patients.

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Compliance with Ethical Standards

Funding This study was funded by Hoffmann-La Roche.

Conflict of interest DR and SS are employees of Roche Products LTD, and CGB and DU are employees of F Hoffmann-La Roche. AR, employee of Mapi, was paid consultant to Roche Products LTD. RF was paid consultant to Roche Products LTD.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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