



Diagnostic Assessment & Prognosis

Assessing quality of life in Alzheimer's disease: Implications for clinical trialsKristin Kahle-Wroblewski^{a,b,*}, Wenyu Ye^a, David Henley^{a,b}, Ann Marie Hake^{a,c}, Eric Siemers^{a,c}, Yun-Fei Chen^a, Hong Liu-Seifert^a^aEli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, USA^bDepartment of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA^cDepartment of Neurology, Indiana University School of Medicine, Indianapolis, IN, USA**Abstract****Introduction:** Characterization of the quality of life (QOL) in Alzheimer's disease (AD) scale within the context of a clinical trial may inform its applicability in future trials.**Methods:** Using data from 1322 patients enrolled in two phase-III studies (EXPEDITION 1 [NCT00905372] and 2 [NCT00904683]) of intravenous solanezumab in outpatients with mild AD dementia, correlations between patient- and caregiver-assessed QOL and between QOL and clinical outcome measures were examined. Longitudinal effects of solanezumab over 80 weeks were explored, controlling for patient and caregiver baseline characteristics.**Results:** Caregivers rated patients' QOL worse than did patients themselves. Patients' QOL was correlated, albeit modestly, with clinical/health measures. Patients' QOL changed minimally over 80 weeks, although a treatment effect of solanezumab on QOL was detected.**Discussion:** Further investigations are needed to determine the optimal measures with which to quantify and qualify QOL of patients with mild AD.© 2016 Eli Lilly and Company. Published by Elsevier Inc. on behalf of the Alzheimer's Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).**Keywords:**

Alzheimer's disease; Quality of life; Solanezumab; Clinical trial; Patient-assessed; Caregiver-assessed

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that is usually characterized by an initial gradual decline in the ability to remember new information, followed by deterioration of additional aspects of memory and other areas of cognition such as language, planning, and organization [1].

Given the wide range of cognitive and functional impairment levels represented across the spectrum of this progressive disease, one of the biggest challenges for clinical trial research in AD is the selection of appropriate measurable outcomes for determining treatment effects. This challenge is exacerbated by the fact that, even early in the disease course, AD is sometimes characterized by decreased insight that impairs the person's

ability to understand the impact of their disease on daily functioning [2], a clinical phenomenon known as anosognosia. Indeed, awareness of memory impairment begins to rapidly decline 2–3 years before the onset of dementia [2], suggesting that patient recall is of limited value in patients with AD. Therefore, caregiver reports and performance-based measures of cognition for patients are used for many clinical trials.

Clinical trials use outcomes designed to track progression of the disease, such as the Mini-Mental State Examination (MMSE) [3] and the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) [4], which measure cognitive function; the Neuropsychiatric Inventory (NPI) [5], which assesses psycho-behavioral symptomatology (and its brief form, the NPI-Q [6]); and measures of activities of daily living (ADL) such as the Alzheimer's Disease Cooperative Study-ADL Inventory (ADCS-ADL) [7].

In addition to clinical measures of disease progression, clinicians and others want to understand the clinical

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meaningfulness of those changes. Measuring quality of life (QOL) is proposed as one method of doing this. QOL is an important consideration in AD because of the devastating impact of this currently incurable disease on patients and caregivers. From the patient's perspective, QOL measures may assist understanding of the magnitude of the impact of treatment intervention, whereas, from a payer perspective, QOL measures can provide a common metric of comparison across disease states. Although the effects of AD on caregiver QOL have been well documented [8–10], until recently, few studies had evaluated the QOL of patients with AD, and data are limited regarding the effects of treatment on patients' QOL [11]. Indeed, whether QOL provides an appropriate reflection of clinical meaningfulness in patients with AD is unclear. In addition, discrepancies between patients' and proxy/caregivers' assessment of patient QOL have been observed in AD [8,12,13].

Currently available treatments have focused on improving symptoms of AD by targeting neurotransmitters; newer treatments aim to slow disease progression by targeting the underlying pathophysiology of AD (e.g., amyloid- β or tau protein) [14–16]. Solanezumab is a monoclonal antibody that binds to the mid-domain of soluble amyloid- β monomers and has been investigated in two completed phase-III clinical trials, EXPEDITION and EXPEDITION 2 [17,18]. In each of these studies, solanezumab and placebo did not differ significantly with respect to their effects on the cognition, functioning, or QOL of patients with mild-to-moderate AD dementia. However, in a pooled secondary analysis of data from both studies, a statistically significant treatment effect of solanezumab was observed on cognitive and functional end points (the 14-point ADAS-Cog [ADAS-Cog 14], MMSE, and instrumental ADCS-ADL [ADCS-iADL]) for patients in the mild dementia subgroup [18].

This study explores the characteristics of the QOL in AD scale (QOL-AD) within the context of the EXPEDITION and EXPEDITION 2 solanezumab trials to inform its applicability in future clinical trials. In a secondary analysis of pooled data from the subgroups of patients with mild AD dementia in these two clinical trials, we examined correlations between patient- and caregiver-assessed QOL and between QOL and clinical outcome measures; we also explored any longitudinal solanezumab treatment effect on QOL over 80 weeks.

2. Methods

Data for these analyses were obtained from two identically designed phase-III multinational, randomized, double-blind, placebo-controlled studies of intravenous solanezumab 400 mg every 4 weeks in outpatients with mild-to-moderate AD dementia (EXPEDITION/EXPEDITION 2) [17,18].

Eligible patients were aged at least 55 years, had probable AD based on National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria [19], had no significant

depression on a screening questionnaire, and were otherwise in good health. Patients were also required to have a consistent caregiver (defined as an individual who knew them well and had contact with them for at least 10 hours each week) to accompany them to study visits and complete caregiver-rated scales. Although patients with MMSE scores of 16–26 were included in these studies, the current analysis was limited to the subset of patients with mild AD dementia (MMSE 20–26) receiving either solanezumab or placebo, given the treatment effect noted in this prespecified subgroup in the previous pooled analysis [18].

The protocols for these two studies were approved by the institutional review board of each participating institution, and all participants provided written informed consent.

2.1. Outcome measure

QOL was measured using the 13-item QOL-AD scale (total score range 13–52; higher scores indicate better QOL) [20–22]. The QOL-AD scale uses a scale of 1–4 (poor, fair, good, or excellent) to rate a variety of life domains, including the patient's physical health, mood, relationships, activities, and ability to complete tasks [21,22]. Both patients (self-assessed) and caregivers (proxy-assessed) completed the QOL-AD. To provide an assessment that may be more balanced than either score alone, a weighted total score was also adopted and calculated ($[\text{patient-assessed total score} \times 2 + \text{caregiver-assessed total score}] / 3$) [20]. Baseline, end point, and change over time from baseline to 80 weeks for patient-assessed QOL, caregiver-assessed QOL, and weighted QOL were calculated. Psychometric properties of the scale have been described in previous work [20–22]. The QOL-AD has been shown to have excellent internal consistency reliability for both patient and caregiver reports ($\alpha = 0.84$ and 0.86 , respectively) at all levels of cognitive functioning and good validity as indicated by correlations with measures of depression, day-to-day functioning, and pleasant events frequency [20,21]. Thorgrimsen and colleagues [22] reported the QOL-AD to have good content validity, construct validity, interrater reliability (all Cohen's kappa values >0.70), test-retest reliability, and internal consistency (Cronbach α coefficient of 0.82).

2.2. Analyses

Baseline characteristics of patients with mild AD dementia and their caregivers were summarized based on nonmissing data and presented as mean (standard deviation [SD]) or as number and percentage of patients/caregivers by treatment group and overall. Categorical variables were compared between treatment groups using chi-squared or Fisher's exact test, and continuous variables were compared using the two-sample t test.

The last observation carried forward (LOCF) data set, with imputations for missing data, was used for analyses at

80 weeks or for change from baseline to 80 weeks for partial correlation analyses and linear regression.

Unadjusted correlation analyses, using Spearman's correlation method, were performed at baseline and end point (80 weeks) to determine correlations between patient- and caregiver-assessed QOL-AD scores. Similar analyses were also performed for the change in these scores from baseline to end point. To estimate the strength of the association between change in QOL-AD from baseline to 80 weeks and change over time in other outcome measures (MMSE, ADAS-Cog 14, ADCS-ADL, ADCS-iADL, NPI total score, NPI caregiver stress score, EuroQol 5-Dimensions [EQ-5D] utility score, and EQ-5D visual analog scale [VAS] score), partial correlation analyses were conducted using Spearman's partial rank-order correlation while controlling for baseline QOL-AD score, baseline of outcome variable examined, patient and caregiver baseline covariates and treatment received at baseline (solanezumab vs. placebo). The baseline covariates included the following patient and caregiver baseline demographics and clinical characteristics: patient age, sex, number of comorbidities, depression (yes/no), and concomitant AD medications (yes/no); whether the patient lived alone (yes/no); duration since AD diagnosis; duration since AD onset; caregiver age, sex, and type; and region.

To assess how a change in one-unit score on other outcome variables predicted change in unit score on the QOL-AD, linear regression models, with change in QOL-AD as the response variable and change in other outcomes as the explanatory variable, were fitted, after controlling for baseline QOL-AD score, patient and caregiver core baseline covariates (see previous paragraph) and treatment received at baseline (solanezumab vs. placebo). The coefficient estimate and standard error-associated *P*-value are reported.

To evaluate the treatment effects of solanezumab versus placebo on QOL over 80 weeks, mixed model repeated measures (MMRM) analyses were conducted for QOL analysis to test the treatment difference between least squares mean at each post-baseline visit from baseline. The dependent variable was the change from baseline in QOL scores. The model included QOL scores at baseline, treatment (solanezumab/placebo), visit, treatment-by-visit interaction, and core baseline covariates (see earlier paragraph), and visit as a repeated measure. The model includes an unstructured covariance matrix.

To further describe the treatment effects on QOL-AD from baseline to 80 weeks, an effect size was calculated in terms of the difference in QOL-AD between two means (solanezumab treated vs. placebo) divided by a pooled baseline SD. Required sample size was estimated using the derived effect size and 80% power to demonstrate statistical difference with significance level set at $\alpha < .05$.

Similar analyses using data from study completers were conducted to verify the results from analyses of LOCF data (data not shown).

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

3. Results

A total of 1322 patients with mild AD dementia were randomized to receive solanezumab ($n = 659$) or placebo ($n = 663$) and are included in the analyses. Table 1 summarizes the baseline characteristics for these patients and their caregivers. Baseline patient and caregiver demographics and characteristics did not differ significantly between treatment groups except for NPI total score, which was lower in patients randomized to solanezumab than in those randomized to placebo ($P = .03$), and EQ-5D VAS, which was higher in patients randomized to solanezumab ($P = .01$).

QOL-AD scores at baseline were numerically higher (better) when assessed by patients compared with caregivers in both treatment groups (Table 2). In the solanezumab group, mean (SD) patient-assessed scores were 37.7 (6.1), and caregiver-assessed scores were 35.2 (6.2). Respective mean (SD) scores in the placebo group were 37.9 (6.0) and 35.2 (6.1). As expected, weighted scores fell between the respective patient- and caregiver-assessed scores.

3.1. Correlations between patient- and caregiver-assessed QOL-AD

Although patient- and caregiver-assessed QOL-AD scores were moderately correlated at baseline ($r = 0.48$) and week 80 ($r = 0.46$), the change in patient-assessed QOL-AD score was only weakly correlated with change in caregiver-assessed QOL-AD score ($r = 0.15$), when considering the pooled patient population with mild AD dementia. Similar findings were obtained when the solanezumab- and placebo-treated populations were considered separately.

3.2. Relationships between QOL and clinical outcomes

Results of the partial correlation analyses indicated that changes in patient-assessed QOL-AD scores had low correlations with changes in other clinical/health end points, whereas small-to-moderate correlations were observed between caregiver-assessed QOL-AD scores and other clinical/health end points (Table 3). The partial correlation coefficient can be squared to provide an estimate of the variance of change in QOL-AD scores accounted for by the change in other clinical outcome measures controlling for all other baseline variables. These calculations suggest that the proportion of variance in change of QOL-AD score accounted for by change in other clinical outcome measures ranged between 0.49% and 12.96%.

Linear regression analysis showed that changes in the clinical/health end points considered showed statistical significance in predicting change in QOL-AD scores (patient-assessed, caregiver-assessed, and weighted), when controlling for baseline QOL-AD score and baseline demographic and clinical characteristics (Table 3). All *P*-values associated with coefficient estimates are $< .05$. The standard errors of the coefficient estimates are small when compared with their coefficients. The coefficients for predicting change

Table 1
Baseline demographics for patients with mild Alzheimer's disease dementia and their caregivers

Demographic	Placebo (n = 663*)	Solanezumab (n = 659*)	Total (N = 1322*)
Patients			
Age, years	73.3 (7.9)	73.9 (8.1)	73.6 (8.0)
Female, n (%)	362 (54.6)	346 (52.5)	708 (53.6)
Years since onset of AD symptoms	4.2 (2.6)	4.3 (2.4)	4.3 (2.5)
Years since AD diagnosis	1.9 (1.9)	1.9 (1.8)	1.9 (1.8)
Number of comorbidities	0.5 (0.9)	0.5 (0.9)	0.5 (0.9)
Previous depression, n (%)	206 (31.1)	189 (28.7)	395 (29.9)
Concomitant AD medicine use, n (%)	587 (88.5)	574 (87.1)	1161 (87.8)
Living alone, n (%)	75 (11.3)	71 (10.8)	146 (11.0)
Region, n (%)			
USA	261 (39.4)	254 (38.5)	515 (39.0)
EU	168 (25.3)	159 (24.1)	327 (24.7)
Other	234 (35.3)	246 (37.3)	480 (36.3)
Baseline clinical measures; possible score range			
MMSE; 0–30	22.5 (2.8)	22.5 (2.8)	22.5 (2.8)
ADAS-Cog 14; 0–90	29.6 (8.8)	30.1 (8.5)	29.9 (8.7)
ADCS-ADL total; 0–78	63.7 (10.8)	63.4 (11.1)	63.6 (11.0)
ADCS-iADL total; 0–56	42.9 (9.5)	42.4 (9.9)	42.6 (9.7)
NPI total; 0–144	9.8 (11.9)	8.4 (11.0) [†]	9.1 (11.5)
NPI caregiver distress; 1–60	5.6 (6.4)	4.9 (6.2)	5.3 (6.3)
EQ-5D utility (using US utility values); –0.11 to 1	0.84 (0.13)	0.84 (0.14)	0.84 (0.14)
EQ-5D VAS; 0–100	70.8 (22.1)	73.7 (18.6) [†]	72.2 (20.4)
Caregivers			
Age, years	63.6 (13.1)	63.6 (13.0)	63.6 (13.0)
Female, n (%)	413 (62.3)	437 (66.3)	850 (64.3)
Relationship to subject, n (%)			
Child	168 (25.3)	178 (27.0)	346 (26.2)
Spouse	417 (62.9)	412 (62.5)	829 (62.7)
Other	75 (11.3)	63 (9.6)	138 (10.4)
Total caregiver time [‡] , median (Q1, Q3), hours	48 (11,120)	60 (12,135)	56 (12,122)

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive subscale (11-item and 14-item); ADCS-ADL, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory; ADCS-iADL, ADCS–instrumental ADL; EQ-5D, EuroQol-5 Dimensions; EU, European Union; MMSE, Mini–Mental State Examination; NPI, Neuropsychiatric Inventory; Q1, Q3, interquartile range; SD, standard deviation; SOC, standard of care; VAS, visual analog scale.

NOTE. Data are presented as mean (SD) unless otherwise indicated.

*Number of randomized subjects. The number of subjects included in each analysis varied based on the number of subjects with a baseline value for that measure.

[†] $P < .05$ for comparisons between solanezumab and placebo using a two-sample t test for continuous measures and chi-squared test for categorical measures, and Wilcoxon rank sum test for median.

[‡]Total caregiver time in the month before the baseline visit.

in the QOL-AD caregiver scores are larger than those for predicting change in QOL-AD patient-assessed scores. Except for the change in EQ-5D utility scores, all coefficients are less than one indicating that for every additional one-unit change in the other clinical outcomes, the change in QOL-AD score would be expected to increase/decrease by less than one unit.

3.3. Change in QOL according to treatment

Results of the MMRM showed a significant least squares mean difference favoring solanezumab versus placebo on patient-assessed QOL-AD scores at 80 weeks (Fig. 1A; $P < .05$). The differences between solanezumab and placebo for caregiver-assessed and weighted QOL-AD at 80 weeks were not statistically significant (Fig. 1B and C).

Mean change of QOL-AD from baseline to 80 weeks, correlation coefficient of QOL-AD between baseline and

80 weeks, effect size of treatment effect on QOL-AD, and required sample size estimations for each group are presented in Table 2. To have 80% power to demonstrate statistical difference ($\alpha < .05$), a sample size of 1092 patients for each group is required to detect a 0.12 effect size relative to placebo on the patient-assessed QOL-AD, 4362 patients for each group on the caregiver-assessed QOL-AD, and 3205 patients for each group for the weighted QOL-AD.

4. Discussion

Results of this study show that patients and caregivers do not report the same level of QOL for patients with mild AD dementia. Patients generally rated their QOL-AD scores to be better than did caregivers. Also, caregivers reported greater decline over time in patients' QOL-AD scores. These results are in agreement with those of other studies conducted using this disease-specific QOL measure in patients with dementia,

Table 2
QOL-AD measure at baseline and 80 weeks and mean change from baseline to end point: placebo and solanezumab

QOL-AD	Mean (SD) at baseline		Mean (SD) at 80 weeks		Mean change (SD) from baseline to 80 weeks		Correlation coefficient (r) between baseline and 80 weeks		Required sample size per group (80% power with $\alpha < 0.05$)
	Placebo	Solanezumab	Placebo	Solanezumab	Placebo	Solanezumab	Placebo	Solanezumab	
	QOL-AD patient-assessed score	37.88 (5.99)	37.71 (6.09)	36.91 (6.20)	37.21 (6.31)	-0.96 (4.55)	-0.48 (4.36)	0.72	
QOL-AD caregiver score	35.18 (6.11)	35.16 (6.22)	33.63 (6.05)	33.48 (6.42)	-1.56 (4.89)	-1.72 (5.04)	0.68	0.69	4362
QOL-AD weighted score	37.00 (5.29)	36.89 (5.40)	35.83 (5.28)	35.98 (5.63)	-1.16 (3.65)	-0.90 (3.59)	0.76	0.79	3205

Abbreviations: QOL-AD, Quality of life in Alzheimer's disease scale; SD, standard deviation.

which also showed that caregivers rate patients' QOL lower than do patients themselves [8,12,23–27]. This pattern appears to hold over the type of setting, with caregivers rating QOL-AD lower than patients in inpatient settings [28] as well as in outpatient interventional studies [23]. Interestingly, this disparity between patient and proxy-reported QOL also seems to occur in other diseases such as end-stage cancer [29], Parkinson disease [30–32], and after stroke [33]. Therefore, it is likely that not all of the discrepancy in patient vs. caregiver QOL ratings is due to features of AD. This suggests there are inherent limitations in using proxy reports generally to elicit subjective information.

In addition to cross-sectional differences between patients and caregivers, changes in caregiver-assessed QOL are greater than those of patient-assessed QOL over time [25–27]. Indeed, patient-assessed QOL typically shows only small changes [26]. When reported, patients enrolled in these studies generally had stages of dementia (mean baseline MMSE scores of 19.5–24.0) [23–26] similar to those of the patients in our study and, most commonly, had baseline mean patient-assessed QOL-AD scores of 25.6–51.7 and caregiver-assessed scores of 24.5–37.9 [8,12,23–26]. Evaluation of patients with mild or very mild AD (Clinical Dementia Rating Scale score of 0.5 or 1) indicates that patient- and caregiver-assessed QOL-AD scores begin to diverge early in the course of dementia, when patients have very mild memory impairment (as determined by a Clinical Dementia Rating Scale–Sum of Boxes score of 4 or MMSE score of 25–30) [8], earlier stages than those of the patients in the present study, and that patient-assessed QOL measures are less sensitive to disease progression than those assessed by caregivers [8,23]. Although starting early in the disease course [8], the divergence between patients' and caregivers' assessments of patient QOL is seen across the range of AD dementia severity (MMSE score range of 0–29; mean score 14.7) [34].

The low-to-moderate correlations between caregiver- and patient-assessed QOL-AD scores seen in this and other studies of patients with AD or other forms of dementia [8,12,23–27,34] as well as the low correlations with other clinical outcomes may reflect a number of factors. Patient QOL has been shown to be impacted by disease-related impaired insight, the number/severity of depressive symptoms, irritability, apathy, ADLs, provision of care at home, and cognitive function [24–26,34]. Clinicians should consider that an AD patient with anosognosia may be reporting QOL accurately to their experience. Caregiver-related factors include differences in the variables affecting the rating of QOL when responding for oneself versus another (e.g., a patient's QOL as assessed by the caregiver may reflect not just the caregiver's assessment of the patient's level of cognition and functioning but also the caregiver's projection of what he would feel like if he were the patient but with unimpaired insight). Caregivers may also be influenced by their emotions for the patient (e.g., resentment, grief for the loss of the patient's identity or the extent of burden they are

Table 3

Partial correlation and linear regression analysis between change in QOL-AD and change in other clinical/health measures after controlling for baseline QOL-AD, baseline clinical/health measures, and patient baseline clinical and demographic characteristics in the pooled population with mild Alzheimer's disease dementia ($N = 1322$)

Clinical/health measure	Change in QOL-AD patient-assessed score		Change in QOL-AD caregiver score		Change in QOL-AD weighted score	
	Partial correlation coefficient*	Coefficient estimate (SE) [†]	Partial correlation coefficient*	Coefficient estimate (SE) [†]	Partial correlation coefficient*	Coefficient estimate (SE) [†]
Change in MMSE score	0.11	0.13 (0.03)	0.23	0.28 (0.03)	0.19	0.18 (0.02)
Change in ADAS-Cog 14 score	-0.08	-0.04 (0.01)	-0.24	-0.12 (0.01)	-0.17	-0.07 (0.01)
Change in ADCS-ADL total score	0.12	0.07 (0.01)	0.36	0.15 (0.01)	0.26	0.10 (0.01)
Change in ADCS-iADL score	0.12	0.08 (0.01)	0.35	0.17 (0.01)	0.25	0.11 (0.01)
Change in NPI total score	-0.1	-0.05 (0.01)	-0.32	-0.17 (0.01)	-0.23	-0.09 (0.01)
Change in NPI stress score	-0.07	-0.07 (0.02)	-0.3	-0.31 (0.02)	-0.19	-0.15 (0.02)
Change in EQ-5D utility (US values)	0.16	4.76 (0.87)	0.29	10.54 (0.91)	0.27	6.54 (0.69)
Change in EQ-5D VAS	0.19	0.05 (0.01)	0.24	0.07 (0.01)	0.26	0.05 (0.01)

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale (14-item); ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; ADCS-iADL, ADCS-instrumental ADL; EQ-5D, EuroQol-5 Dimensions; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; QOL-AD, Quality of life in Alzheimer's disease scale; SE, standard error; SOC, standard of care; VAS, visual analog scale.

NOTE. All P -values associated with the coefficient estimates are $<.05$.

*The partial correlation (Spearman partial rank-order correlation) coefficient reported is the relationship between change in QOL-AD score and change in other outcomes measures (such as MMSE, ADAS-Cog 14, ADCS-ADL total score, ADCS-iADL, NPI total score, NPI stress score, EQ-5D utility, and EQ-5D VAS), while controlling the effect of other variables including baseline QOL-AD score, baseline of outcome variable examined, baseline patient demographic, and clinical characteristics such as age, sex, number of comorbidities, depression (yes/no), and concomitant AD medication (acetylcholinesterase inhibitor or memantine) use (yes/no); caregiver age, sex, and type of caregiver; region; treatment (solanezumab/placebo); whether the patient lived alone (yes/no); duration since AD diagnosis; and duration since AD onset.

[†]Each model evaluated the change in QOL-AD predicted by the change in another clinical/health outcome measure controlled for baseline QOL-AD score, baseline of outcome variable examined, baseline characteristics: age, sex, number of comorbidities, previous depression (yes/no), concomitant AD medication (acetylcholinesterase inhibitor or memantine) use (yes/no), caregiver age, and sex, type of caregiver, region, treatment (solanezumab/placebo), whether patient lives alone, time since AD diagnosis, and time since AD onset.

experiencing) or their own changes in QOL. Additionally, the presence of depression in caregivers has been shown to have a significant effect on the way in which they rate patients' QOL [13]. In one study of patients with AD and their caregivers, patients' QOL evaluations showed a negative relationship with patients' depressive mood and a positive relationship with patients' ADL, whereas caregivers' QOL ratings showed a negative relationship with both patients' depressive mood and behavioral disturbances [12]. In another study, the strongest predictor of patient-assessed QOL-AD scores was their depressive symptoms, whereas functional decline and the presence of neuropsychiatric symptoms in patients predicted poor caregiver ratings of patients' QOL [13]. A recent analysis found caregivers rated patients' QOL better than did the patients themselves when the patient was older, and lower than the patients' assessments when NPI total score and caregiver burden were higher [23]. Further analyses using the current data set may provide additional insights into which patient and caregiver characteristics influence QOL.

The differences between self- and caregiver-reported QOL are part of the challenge in defining a minimally important difference (MID). In the placebo group, the average decline from self-report was less than one point and from caregiver-report was approximately 1.5 points over 80 weeks, whereas in the solanezumab group, the average decline from self-report was about one half of a point and was approximately 1.7 points as reported by caregivers over 80 weeks. With a lack of

consistency in self- and caregiver report, this suggests that different MIDs may be needed depending on who is doing the reporting. However, no set MID is agreed upon in the literature. Prior research suggests a change of three points as a "clinically important difference" or "significant change" [35,36]. The three-point change previously described used an anchor-based approach of moving from poor to excellent health for at least one item on the scale. It is problematic to apply this three-point change when considering a treatment that slows disease progression, as the three points exceed the natural decline of QOL by both self-report and caregiver report as evident in our placebo group. Importantly, this three-point MID was determined as part of interventions meant to improve QOL, whereas the current therapy is intended to slow disease progression. Future research should explore whether a distribution-based approach based on the natural history of QOL decline might therefore be more relevant and how it might be applied to both self- and caregiver-reported scores.

Results of our study also show that the QOL-AD was significantly associated with all the clinical/health outcomes we considered, although these relationships were generally modest and strongest when considering caregiver-assessed QOL (Table 3). Perhaps this is not unexpected, given the same caregiver was also providing the proxy report on a number of other clinical measures. These findings are in agreement with the results of other studies of patients with dementia, which found that caregiver-assessed QOL was

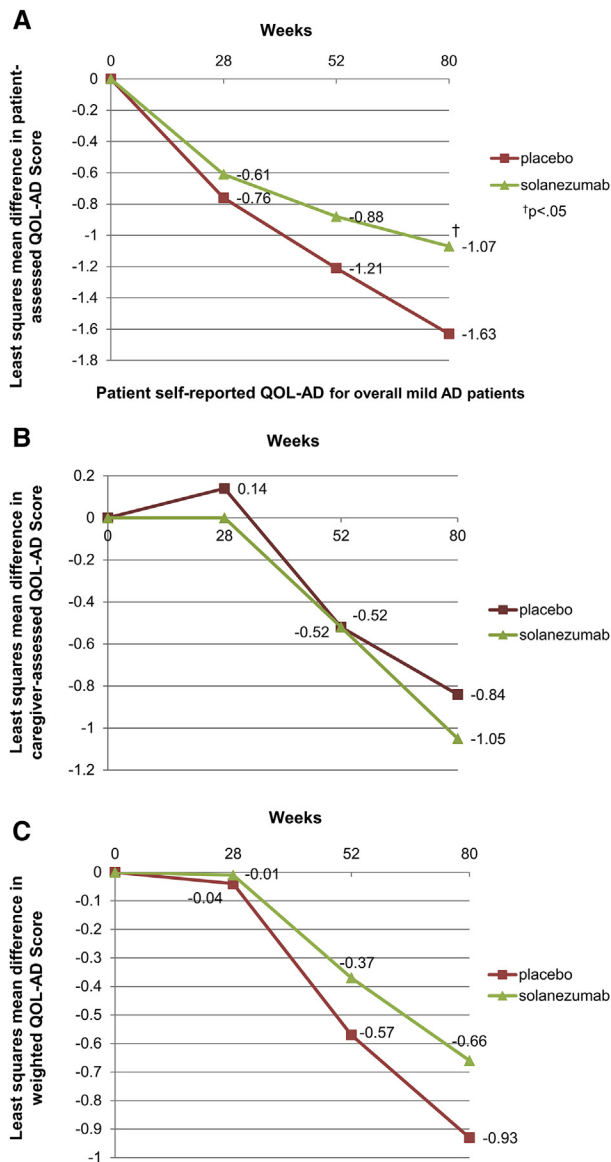


Fig. 1. MMRM analysis* of change from baseline to post-baseline visits in (A) patient-assessed, (B) caregiver-assessed, and (C) weighted (QOL-AD) scores for patients with mild Alzheimer's disease. *The MMRM model evaluated longitudinal treatment effects of solanezumab or placebo on the change from baseline in QOL-AD. The model included QOL scores at baseline, treatment (solanezumab/placebo), visit (as a repeated measure), treatment-by-visit interaction, and the baseline covariates age, sex, number of comorbidities, previous depression (yes/no), concomitant AD medication (acetylcholinesterase inhibitor or memantine) use (yes/no), caregiver age, sex and type, region, whether patient lived alone, time since AD diagnosis, and time since AD onset. † $P < .05$ for statistically significant difference in the solanezumab group versus the placebo group in patient-assessed QOL-AD at 80 weeks. Abbreviations: AD, Alzheimer's disease; MMRM, mixed model repeated measures; QOL-AD, quality of life in Alzheimer's disease scale.

better correlated with clinical outcomes than patient-assessed QOL [24–26,34,37]. In a clinical trial population similar to the one described in this study, a similar modest association between change in patient-reported QOL-AD was reported [25], suggesting that many different types of factors influence change in QOL over time in clinical trial populations.

Prespecified secondary analyses of the phase-III trials (EXPEDITION and EXPEDITION 2) included in the current analyses have suggested a significant benefit of solanezumab on cognition and function in patients with mild AD dementia [18]. Although a significant difference in patient-assessed QOL was detected favoring solanezumab, no statistically significant between-treatment difference was noted in caregiver-assessed QOL. Given the perception that patient-assessed QOL may be less reliable than caregiver-assessed QOL, this inconsistency in treatment effect was somewhat surprising. Several factors should be considered when interpreting these results. It is possible that these results support the suggestion that patients with mild AD dementia do retain enough insight to evaluate their current QOL and discern any impact of treatments (replication in future clinical trials would lend additional support). Because deterioration in cognition has been shown to precede functional decline in patients with mild AD dementia [38], and an obvious functional decline in patients may be necessary before caregivers perceive a change in QOL, caregiver-assessed QOL may be less sensitive to treatment effects over the short term. Somewhat paradoxically, caregiver-assessed QOL-AD was more strongly associated than patient-assessed QOL-AD with other clinical measures, including the key efficacy measures of cognition and iADL that demonstrated a treatment effect in prior analyses [18]. These findings highlight the complexity of AD, particularly when faced with the challenges of obtaining patients' self-assessment of the impact of the disease on their daily lives.

This study has several potential limitations. As discussed, it is possible this study duration was too short to detect a treatment effect on caregiver-assessed QOL in these patients with mild AD dementia. Additionally, although the QOL-AD is validated across a wide range of cognitive levels (MMSE > 10), if the decline in this scale is less than 2 points during a clinical trial, a treatment effect, such as from solanezumab, may not be reliably detected. Even if changes in QOL-AD are associated with changes in clinical outcomes in practice, other factors may also be involved so the relationship may not be a direct one-to-one ratio, or the association may be nonlinear. Another possibility is that QOL may not be associated with cognitive or functional response, as suggested by the results of a small study in 47 patients with probable mild or moderate AD [27]. Finally, as AD progresses and cognition is lost, function becomes impaired. Patient awareness of their cognitive loss also becomes impaired and may interfere with their self-assessment of QOL, so the window for assessing a treatment effect using QOL measures may be limited. As stated previously, neuropsychiatric symptoms, such as depression, that occur early in AD when cognition is less impaired and insight is maintained, may have a profound effect on QOL ratings in mild dementia, whereas QOL may be less affected by these variables during later stages of dementia.

Assessing changes in patients' QOL, due to either disease progression or treatment modification, can be challenging

because of differences between patient and caregiver reporting [8,12,13], the fact that QOL may not decline significantly during a clinical study of typical duration (18–24 months in patients with mild AD dementia) and, as mentioned earlier, the disease itself may compromise patient insight. Future studies to confirm the value of the QOL-AD as a measure of patient QOL in relatively short-term trials of 18–24 months would therefore be of benefit. Consideration of other QOL scales used or new ways to measure QOL in AD would also be useful to help identify the optimal measure for future investigations. Previous studies have shown a moderate and significant correlation between caregiver-assessed QOL-AD and the caregiver-assessed Health Utility Index Mark 3 (HUI-3) [25] and patient- and caregiver-assessed QOL-AD scores and the more generic EQ-5D scale (as rated by both patients and caregivers) [24]. Although the QOL-AD and EQ-5D performed similarly [24], HUI-3 scores were more strongly associated with clinical end points measuring cognition, function, behavior, and dependence than were patient- or caregiver-assessed QOL-AD scores [25].

QOL remains an important consideration when describing the patient experience in AD as well as when considering broader benefits of new therapies and multimodal interventions. However, the current data suggest that very large sample sizes would be needed to detect a treatment effect based on QOL, as compared to a primary outcome like cognition that is central to the disease process, particularly when considering proxy-reported QOL-AD. The practical implications of conducting studies with such high patient numbers are likely to manifest as much longer cycle times for clinical trials as enrollment periods are lengthened. The results of ongoing trials (assuming positive outcomes on primary end points) will, therefore, be of critical importance in determining if a treatment effect on QOL can reasonably be expected within the logistic realities of the current trial design paradigm.

This work is informative for future trials of disease-modifying therapies in AD. Although the present results showed a relatively slow rate of decline in QOL scores in patients with AD, a statistically significant treatment effect with solanezumab was noted. Replication of the observed patient-assessed treatment effects on QOL will provide additional insights into the ability of QOL to be used as a reliable index of clinical meaningfulness. Future studies may also inform whether 80 weeks are sufficient time to detect a treatment effect on patient- or caregiver-assessed QOL.

5. Conclusion

Our study results show that patient- and caregiver-assessed QOL measures reflected different perceptions of QOL, with caregivers rating patient QOL worse than did patients themselves. Although change in caregiver-assessed patient QOL was more highly correlated with the clinical/health measures evaluated than patient-assessed QOL, patient-assessed QOL did show a significant treatment effect in favor of solanezu-

ma. Confirmation of the present findings in future trials and other interventional studies that demonstrate a positive treatment effect on cognition and other clinical outcomes will help those with an interest in AD to better understand how QOL generally, and the QOL-AD in particular, are impacted by interventions that slow disease progression. These insights will be an important part of helping researchers and clinicians understand how to explain the clinical meaningfulness and impact of interventions in AD.

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RESEARCH IN CONTEXT

1. Systematic review: Literature searches indicate that, until recently, few studies have evaluated quality of life (QOL) in patients with Alzheimer's disease (AD) or effects of treatment on patients' QOL. To explore whether QOL reflects clinical meaningfulness in patients with AD, pooled data from patients with mild AD dementia from two phase-III trials of solanezumab were evaluated.
2. Interpretation: Our study confirms that caregivers rate patients' QOL worse than do patients themselves and that patients' QOL is modestly correlated with clinical/health measures. Although caregiver-rated QOL showed a faster rate of decline, a treatment effect on QOL-AD from solanezumab was noted in patient-report only. These results, along with the relatively slow decline in QOL scores of patients with mild AD dementia, suggest that QOL may be an important but complex index of clinical meaningfulness in clinical trials that requires further examination.
3. Future directions: Further studies are needed to confirm whether longer trials will allow demonstration of a treatment effect on QOL and elucidate which subdomains of QOL-AD measures may be most relevant to patients with mild AD dementia.

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