Zanubrutinib vs Ibrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL): Impact on Health-Related Quality of Life (HRQoL)

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Background

- Symptoms that patients with CLL and SLL experience have a negative impact on patients' HRQoL[1,2]
- The ALPINE trial (NCT03734016), a randomized, open-label, multi-country phase 3 study, compared zanubrutinib with ibrutinib in patients with R/R CLL/SLL[3]
- The final PFS analysis (August 8, 2022 cutoff date), at a median follow-up of 29.6 months, showed that zanubrutinib demonstrated superior PFS to ibrutinib and continued to show improved ORR[4]
  - ORR: 86.2 vs 75.7%; nominal 2-sided *P*=.0007
  - PFS: HR: 0.65 (95% CI, 0.49–0.86); 2-sided *P*=.0024

Objective: To assess HRQoL, as a secondary objective, in patients treated with zanubrutinib or ibrutinib in the ALPINE trial

1. Eichhorst B, et al. *Ann Oncol.* 2021;32(1):23-33; 2. Holtzer-Goor KM, et al. *Qual Life Res.* 2015;24(12):2895-2906; 3. Hillmen P, et al. *Future Oncol.* 2020;16(10):517-523; 4. Brown JR, et al. *N Engl J Med.* 2023;388(4):319-332.
CLL, chronic lymphocytic leukemia; HR, hazard ratio; HRQoL, health-related quality of life; ORR, overall response rate; PFS, progression free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

Study Design

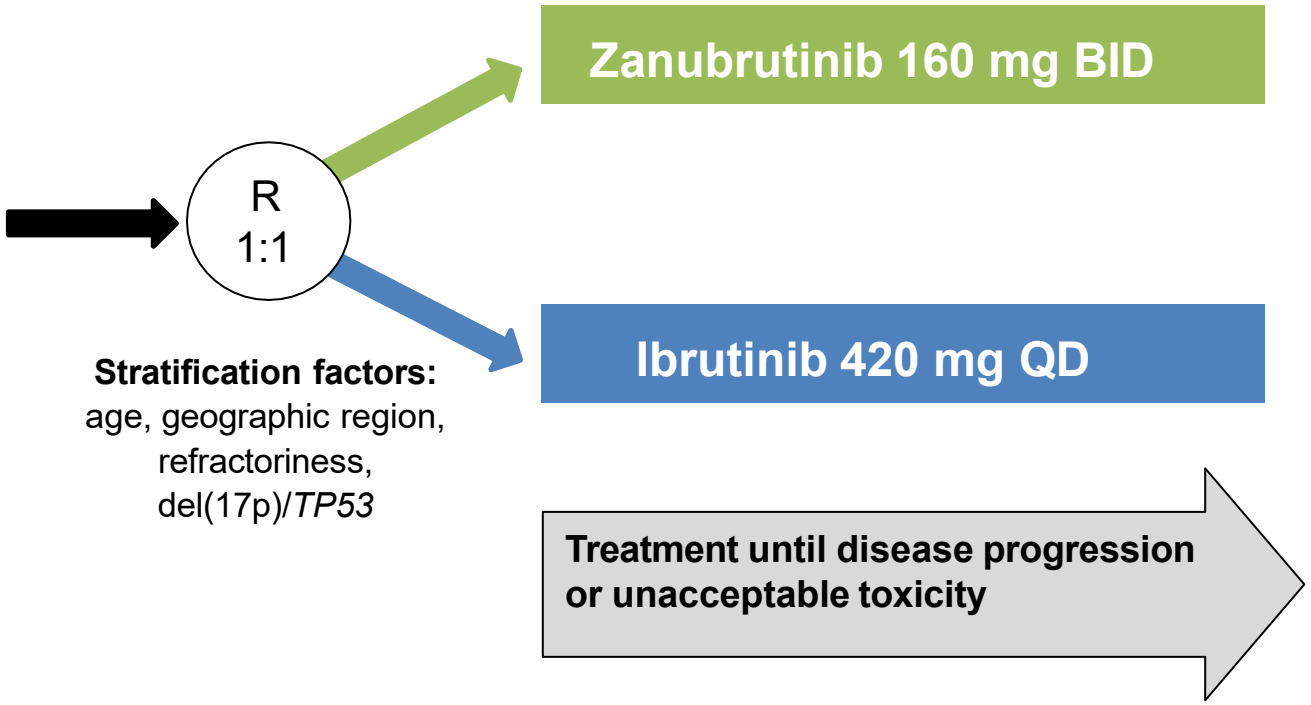
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI
- ECOG PS ≤2

Key Exclusion Criteria

- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists



BID, twice a day; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; mg, milligram; QD, daily; R, randomized; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

HRQoL Assessments and Endpoints

- Key clinical cycles were cycles 7 (6 months) and 13 (12 months)
- Key PRO endpoints, i.e., the most relevant disease and treatment scales, measured by EORTC QLQ-C30 were:
    - Global health status (GHS)
    - Physical functioning
    - Role functioning
    - Four symptoms: fatigue, pain, nausea/vomiting, and diarrhea
        - GHS and functioning scales: higher scores indicate better HRQoL; higher scores on the symptom scales indicate worsening HRQoL

GHS, global health status; HRQoL, health-related quality of life; PRO, patient-reported outcome; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30.

Statistical Analyses

- Changes from baseline for all the EORTC QLQ-C30 scales and EQ-5D-5L's VAS scores were analyzed descriptively using means and SDs
- A mixed model for repeated measures (MMRM) compared changes in the PRO endpoints from baseline between the treatment groups at cycles 7 and 13
  - MMRM analyses were conducted only for the predefined key PRO endpoints, in accordance with FDA/EMA requirements
- Clinically meaningful change was defined as a ≥5-point mean difference from baseline

EMA, European Medicines Agency; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L, European Quality of Life 5-Dimensions 5-Levels questionnaire; FDA, United States of America (USA) Food and Drug Administration; MMRM, mixed model for repeated measures; PRO, patient-reported outcome; SD, standard deviation; VAS, visual analog scale.

Patient Demographic and Clinical Characteristics

	Zanubrutinib (n=327)	Ibrutinib (n=325)
Age, median (range)	67 (35-90)	68 (35-89)
≥65 years, n (%)	201 (61.5)	200 (61.5)
Male, n (%)	213 (65.1)	232 (71.4)
ECOG PS ≥1, n (%)	198 (60.6)	203 (62.5)
Prior lines of systemic therapy, median (range)	1 (1-6)	1 (1-12)
>3 prior lines, n (%)	24 (7.3)	30 (9.2)
del(17p) and/or *TP53*mut, n (%)	75 (22.9)	75 (23.1)
del(17p)	45 (13.8)	50 (15.4)
*TP53*mut without del(17p)	30 (9.2)	25 (7.7)
del(11q), n (%)	91 (27.8)	88 (27.1)
IGHV mutational status, n (%)		
Mutated	79 (24.2)	70 (21.5)
Unmutated	239 (73.1)	239 (73.5)
Complex karyotype[a]	56 (17.1)	70 (21.5)
Bulky disease (≥5 cm), n (%)	145 (44.3)	149 (45.8)

Demographics and baseline characteristics were generally balanced across arms

[a]Complex karyotype is defined as having ≥3 abnormalities.
ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain.

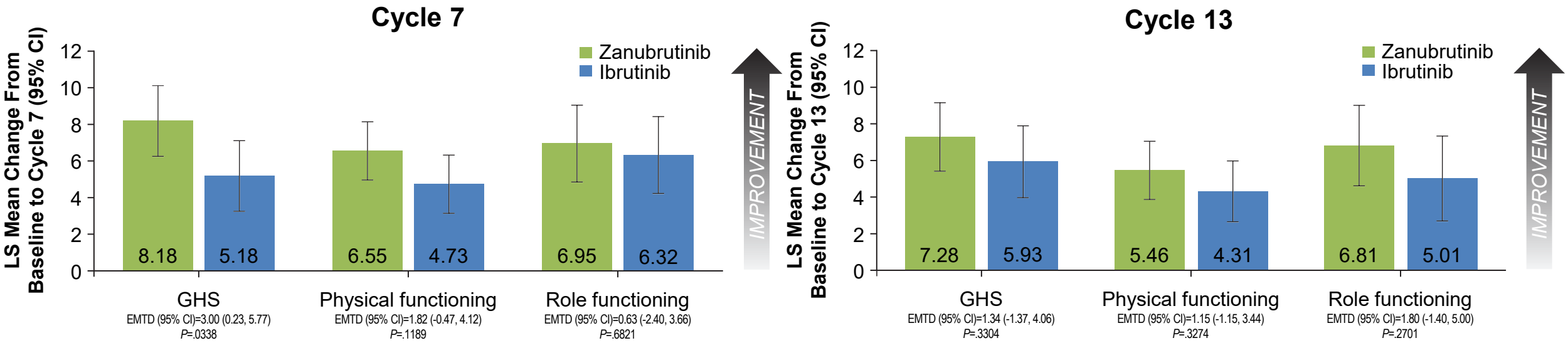
Adjusted Completion Rates

		Zanubrutinib (n=327)	Ibrutinib (n=325)
Baseline	Number of patients	327	325
	Number of completed questionnaires	315	312
	Completion rate (%)[a]	315 (96.3)	312 (96.0)
	Adjusted completion rate (%)[b]	315 (96.3)	312 (96.0)
Cycle 7	Number of patients	307	292
	Number of completed questionnaires	275	256
	Completion rate (%)[a]	275 (84.1)	256 (78.8)
	Adjusted completion rate (%)[b]	275 (89.6)	256 (87.7)
Cycle 13	Number of patients	296	271
	Number of completed questionnaires	279	250
	Completion rate (%)[a]	279 (85.3)	250 (76.9)
	Adjusted completion rate (%)[b]	279 (94.3)	250 (92.3)

The adjusted completion rates were high (>87%) in both treatment groups at each assessment timepoint

[a]Completion rate: number of patients completed questionnaire/total number of patients in relevant treatment arm. [b]Adjusted completion rate: number of patients completed questionnaire/total number of patients in study at relevant visits in relevant treatment arm.

LS Mean Change From Baseline for EORTC QLQ-C30 in GHS and Functioning Scales

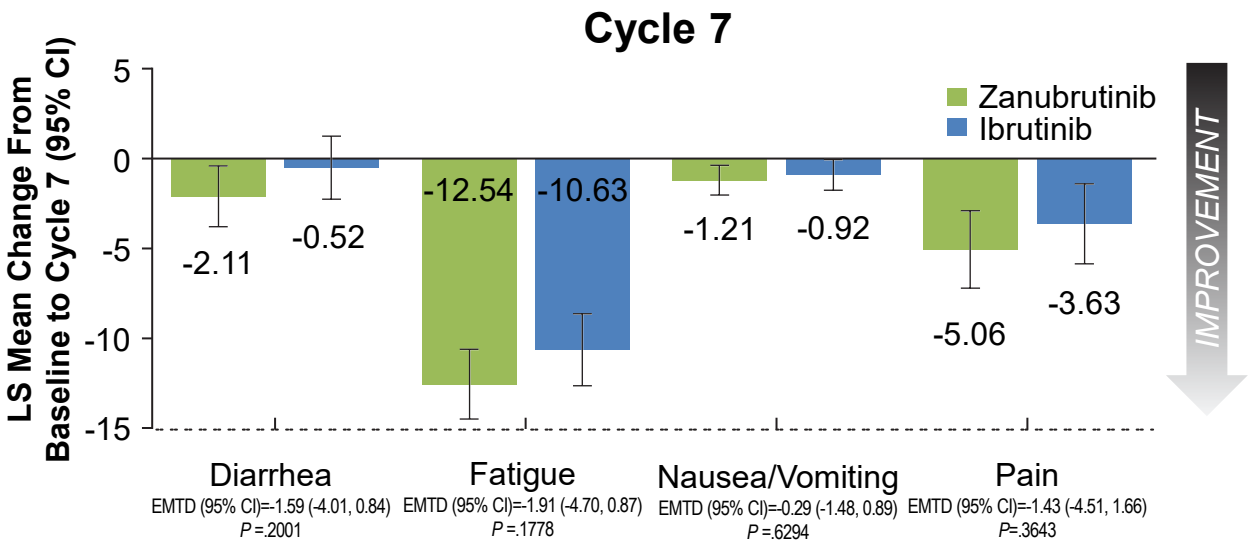


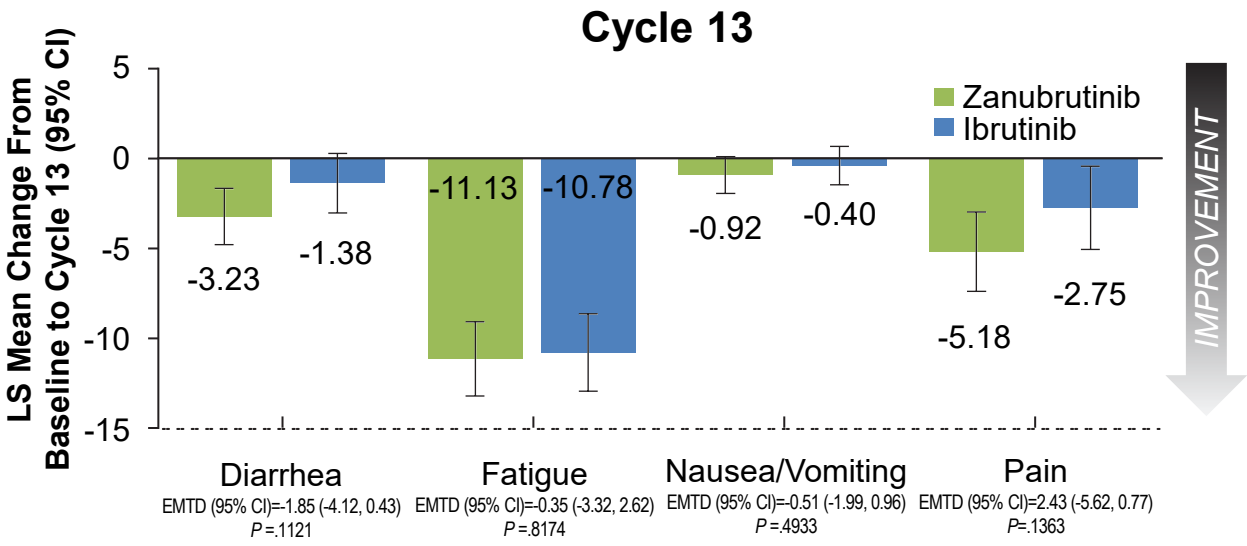
Both arms improved from baseline to both cycle 7 and cycle 13

All improvements were clinically meaningful for the zanubrutinib arm

CI, confidence interval; EMTD, estimated mean treatment difference; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; GHS, global health status; LS, least squares.

LS Mean Change From Baseline for EORTC QLQ-C30 in Symptom Scales





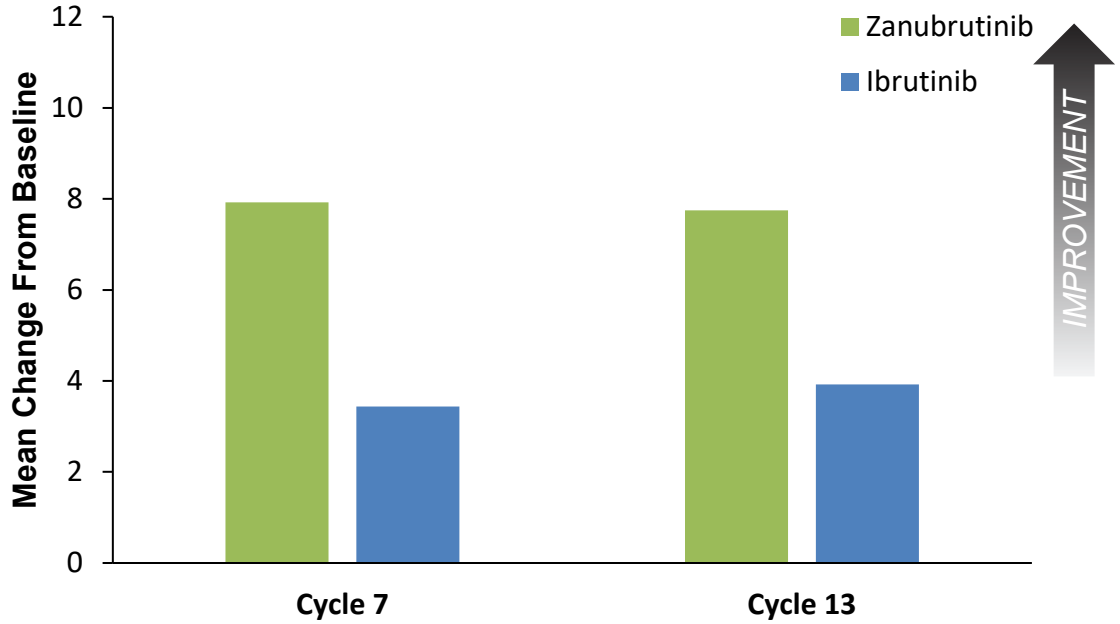
Both arms experienced a decrease in fatigue and pain, with the zanubrutinib arm experiencing clinically meaningful improvements in both symptoms at both cycles

More improvement was observed for diarrhea in the zanubrutinib arm

CI, confidence interval; EMTD, estimated mean treatment difference; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; LS, least squares.

EQ-VAS

- At baseline, the EQ-VAS scores were similar between treatment arms
  - Zanubrutinib: mean (SD): 70.79 (19.40)
  - Ibrutinib: mean (SD): 72.59 (17.38)
- The mean change from baseline in the EQ-VAS demonstrated more improvement with zanubrutinib to cycle 13
- At cycle 7
  - Zanubrutinib: mean change from baseline (SD): 7.92 (18.25)
  - Ibrutinib: mean change from baseline (SD): 3.44 (16.97)
- At cycle 13
  - Zanubrutinib: mean change from baseline (SD): 7.75 (18.81)
  - Ibrutinib: mean change from baseline (SD): 3.92 (16.78)



EQ-VAS, European Quality of Life visual analog scale; SD, standard deviation.

Conclusions

- Results at 6 and 12 months suggest treatment with zanubrutinib positively affected and improved HRQoL outcomes in patients with R/R CLL/SLL
  - Clinically meaningful improvements from baseline were observed for GHS, physical and role functioning, fatigue and pain in the zanubrutinib arm at 6 and 12 months
- Given the generally good HRQoL at baseline in both arms, the differences between the arms were not significant
- Long-term follow-up as well as additional analyses linking PRO endpoints to clinical outcomes will further determine the full extent to which zanubrutinib improves patient HRQoL

CLL, chronic lymphocytic leukemia; GHS, global health status; HRQoL, health-related quality of life; PRO, patient-reported outcome; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

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Backup Slides

Results of Descriptive Analysis

		Zanubrutinib (n=327)	Ibrutinib (n=325)
Global health status	Cycle 7		
	Mean (SD)	8.45 (18.904)	4.62 (20.278)
	Cycle 13		
	Mean (SD)	8.18 (20.732)	5.05 (18.900)
Appetite loss	Cycle 7		
	Mean (SD)	-6.18 (23.617)	-4.82 (23.399)
	Cycle 13		
	Mean (SD)	-7.02 (21.913)	-4.12 (22.427)
Cognitive functioning	Cycle 7		
	Mean (SD)	3.15 (15.862)	1.16 (16.064)
	Cycle 13		
	Mean (SD)	1.43 (15.456)	1.39 (16.372)
Constipation	Cycle 7		
	Mean (SD)	-1.94 (19.217)	-1.30 (18.625)
	Cycle 13		
	Mean (SD)	-2.26 (19.111)	-1.59 (15.409)
Diarrhea	Cycle 7		
	Mean (SD)	-3.15 (17.733)	0.78 (16.874)
	Median	0.00	0.00
	Cycle 13		
	Mean (SD)	-4.40 (18.083)	0.00 (17.127)
Dyspnea	Cycle 7		
	Mean (SD)	-9.94 (22.564)	-7.42 (22.512)
	Cycle 13		
	Mean (SD)	-7.89 (24.517)	-6.37 (23.741)

SD, standard deviation.

Results of Descriptive Analysis

		Zanubrutinib (n=327)	Ibrutinib (n=325)
Emotional functioning	Cycle 7		
	Mean (SD)	5.79 (17.471)	3.10 (17.507)
	Cycle 13		
	Mean (SD)	5.54 (17.472)	5.48 (15.728)
Fatigue	Cycle 7		
	Mean (SD)	-12.63 (21.292)	-10.24 (22.357)
	Cycle 13		
	Mean (SD)	-11.59 (23.344)	-9.65 (21.849)
Financial difficulties	Cycle 7		
	Mean (SD)	-4.24 (21.925)	-3.50 (20.000)
	Cycle 13		
	Mean (SD)	-5.36 (23.253)	-6.27 (19.608)
Insomnia	Cycle 7		
	Mean (SD)	-7.64 (26.145)	-5.47 (26.330)
	Cycle 13		
	Mean (SD)	-9.05 (27.171)	-6.91 (27.262)
Nausea and vomiting	Cycle 7		
	Mean (SD)	-0.91 (7.811)	-0.85 (9.920)
	Cycle 13		
	Mean (SD)	-0.83 (8.306)	-0.27 (10.216)
Pain	Cycle 7		
	Mean (SD)	-4.61 (22.220)	-4.13 (23.937)
	Cycle 13		
	Mean (SD)	-5.36 (21.794)	-3.19 (24.377)
Physical functioning	Cycle 7		
	Mean (SD)	6.65 (16.025)	4.56 (16.654)
	Cycle 13		
	Mean (SD)	6.19 (17.382)	3.75 (14.870)
Role functioning	Cycle 7		
	Mean (SD)	7.33 (25.901)	4.86 (22.124)
	Cycle 13		
	Mean (SD)	7.92 (26.321)	3.85 (21.822)
Social functioning	Cycle 7		
	Mean (SD)	5.39 (21.693)	5.32 (21.293)
	Cycle 13		
	Mean (SD)	7.20 (20.708)	6.87 (21.192)

SD, standard deviation.