

## Supplementary Online Content

Himmelstein AL, Foster JC, Khatcheressian JL, et al. Effect of longer interval vs standard dosing of zoledronic acid on skeletal events in patients with bone metastasis: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2016.19425

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This supplementary material has been provided by the authors to give readers additional information about their work.

**eAppendix.** List of participating institutions

Altru Cancer Center, Grand Forks, ND, Grant Seeger

Avera Cancer Institute, Sioux Falls, SD, Amy Krie

Bay Area Tumor Institute NCORP, Oakland, CA, Jon Greif, supported by 5UG1CA189817

Carle Cancer Center NCI Community Oncology Research Program, Urbana, IL, Kendrith Rowland, supported by 5UG1CA189861

Coborn Cancer Center at Saint Cloud Hospital, Saint Cloud, MN, Donald Jurgens

Colorado Cancer Research Program NCORP, Denver, CO, Keren Sturtz, supported by 5UG1CA189805

Dana-Farber / Partners CancerCare LAPS, Boston, MA, Harold Burstein, supported by 5U10CA180867 and U10CA032291

Delaware/Christiana Care NCI Community Oncology Research Program, Newark, DE, Gregory Masters, supported by U10CA045418 and 5UG1CA189819

Duke University-Duke Cancer Institute LAPS, Durham, NC, Jeffrey Crawford, supported by U10CA047577 and 5U10CA180857

Eastern Maine Medical Center Cancer Care, Brewer, ME, Thomas Openshaw

Essentia Health NCI Community Oncology Research Program, Duluth, MN, Bret Friday, supported by 5UG1CA189812

Florida Hospital Orlando, Orlando, FL, Lee Zehngebot

Geisinger Cancer Institute NCI Community Oncology Research Program, Danville, PA, Srilatha Hosur, supported by 5UG1CA189847

Heartland Cancer Research NCORP, Decatur, IL, James Wade, supported by U10CA114558 and 5UG1CA189830

Hematology Oncology Associates of Central New York-East Syracuse, East Syracuse, NY, Jeffrey Kirshner, supported by U10CA045389

Iowa-Wide Oncology Research Coalition NCORP, Des Moines, IA, Robert Behrens, supported by 5UG1CA189816

JHU Sidney Kimmel Comprehensive Cancer Center LAPS, Baltimore, MD, Lisa Jacobs, supported by 5U10CA180867

Kansas City NCI Community Oncology Research Program, Prairie Village, KS, Rakesh Gaur, supported by UG1CA189853

Lehigh Valley Hospital-Cedar Crest, Allentown, PA, Suresh Nair

Mayo Clinic LAPS, Rochester, NY, Steven Alberts, supported by 5U10CA180790

MedStar Georgetown University Hospital, Washington, DC, Bruce Cheson, supported by U10CA077597

Medical Oncology and Hematology Associates-Laurel, Des Moines, IA, Robert Behrens

Michigan Cancer Research Consortium NCORP, Ann Arbor, MI, Philip Stella, supported by 5UG1CA189971

Missouri Valley Cancer Consortium, Omaha, NE, Gamini Soori

Mount Sinai Medical Center, Miami Beach, FL, Michael Schwartz, supported by U10CA045564

Mount Sinai Medical Center, New York, NY, Lewis Silverman, supported by U10CA004457

Nevada Cancer Research Foundation NCORP, Las Vegas, NV, John Ellerton, supported by U10CA035421 and 5UG1CA189829

New Hampshire Oncology Hematology PA-Hooksett, Hooksett, NH, Douglas Weckstein

North Shore-LIJ Health System NCORP, Manhasset, NY, Vincent P. Vinciguerra, supported by U10CA035279 and 5UG1CA189850

NorthShore University HealthSystem-Evanston Hospital, Evanston, IL, David Grinblatt

Northern Indiana Cancer Research Consortium, South Bend, IN, Rafat Ansari, supported by U10CA086726

Ochsner NCORP, New Orleans, LA, Jyotsna Fuloria, supported by U10CA035272 and UG1CA189870

Ohio State University Comprehensive Cancer Center LAPS, Columbus, OH, Richard Goldberg, supported by U10CA077658 and 5U10CA180850

Pacific Cancer Research Consortium NCORP, Seattle, WA, Keith Lanier, supported by 5UG1CA189953

Providence Milwaukie Hospital, Milwaukie, OR, Alison Conlin

Queens Hospital Center, Jamaica, NY, Mary Kemeny

Rhode Island Hospital, Providence, RI, Howard Safran, supported by U10CA008025

Roswell Park Cancer Institute LAPS, Buffalo, NY, Ellis Levine, supported by U10CA059518 and 5U10CA180866

Saint John Medical Center, Tulsa, OK, Coty Ho

Saint Joseph Regional Cancer Center, Bryan, TX

Sanford NCI Community Oncology Research Program of the North Central Plains, Sioux Falls, SD, Preston Steen, supported by 5UG1CA189825

Southeast Clinical Oncology Research (SCOR) Consortium NCORP, Winston-Salem, NC, James N. Atkins, supported by U10CA0458085 and UG1CA189858

State University of New York Upstate Medical University, Syracuse, NY, Stephen Graziano, supported by U10CA021060

Toledo Clinic Cancer Centers-Toledo, Toledo, OH, Rex Mowat

UC San Diego Moores Cancer Center, La Jolla, CA, Barbara Parker, supported by U10CA011789

UNC Lineberger Comprehensive Cancer Center LAPS, Chapel Hill, NC, Thomas Shea, supported by U10CA047559 and 5U10CA180838

University of Chicago Comprehensive Cancer Center LAPS, Chicago, IL, Hedy Kindler, supported by U10CA041287 and 5U10CA180836

University of Illinois, Chicago, IL, Arkadiusz Dudek, supported by U10CA074811

University of Iowa/Holden Comprehensive Cancer Center, Iowa City, IA, Daniel Vaena, supported by U10CA047642

University of Missouri-Ellis Fischel, Columbia, MO, Clint Kingsley, supported by U10CA012046

University of Nebraska Medical Center, Omaha, NE, Apar Ganti, supported by U10CA077298

University of Vermont College of Medicine, Burlington, VT, Claire Verschraegen,  
supported by U10CA077406

VCU Massey Cancer Center Minority Underserved NCORP, Richmond, VA, Charles E.  
Geyer, Jr., supported by U10CA052784 and 5UG1CA189869

Wake Forest University Health Sciences, Winston-Salem, NC, Heidi Klepin, supported  
by U10CA003927

Washington University-Siteman Cancer Center LAPS, Saint Louis, MO, Nancy Bartlett,  
supported by U10CA077440 and 5U10CA180833

Weill Medical College of Cornell University, New York, NY, Scott Tagawa, supported  
by U10CA007968

**eTable 1.** Patient baseline characteristics for C-telopeptide companion study

<b>Characteristic</b>	<b>ZA q 4 weeks (N=284)</b>	<b>ZA q 12 weeks (N=269)</b>
Age, median (range), years	65 (31-88)	66 (35-93)
Gender		
Male	123 (43.3%)	122 (45.4%)
Female	161 (56.7%)	147 (54.6%)
Race		
White	256 (90.1%)	224 (83.3%)
Black	27 (9.5%)	34 (12.6%)
Unknown/Other	1 (0.4%)	11 (4.1%)
BSA, mean (SD)	1.9 (0.3)	1.9 (0.2)
ECOG PS		
0	155 (54.6%)	125 (46.5%)
1	101 (35.6%)	114 (42.4%)
2	25 (8.8%)	28(10.4%)
Unspecified	3 (1.0%)	2 (0.7%)
Diagnosis		
Breast cancer	140 (49.3%)	130 (48.3%)
Prostate cancer	106 (37.3%)	104 (38.7%)
Multiple myeloma	38 (13.4%)	35 (13.0%)
Serum creatinine, median (Q1-Q3), mg/dL	0.9 (0.7-1.0)	0.9 (0.7-1.0)
Prior SRE	79 (27.8%)	66 (24.5%)
Prior oral bisphosphonate	21 (7.4%)	25 (9.3%)

SI conversion factors: To convert serum creatinine to  $\mu\text{mol/L}$ , multiply values by 88.4. Abbreviations: ZA, Zoledronic acid; BSA, Body surface area; SD, Standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; SRE, Skeletal-related events

**eTable 2.** Types of skeletal-related events by treatment group

<b>Incidence of SRE by arm</b>				
<b>All patients</b>				
	Arm A: Zoledronic Acid Q 4 Wks (N=911)	Arm B: Zoledronic Acid Q 12 Wks (N=911)	Total (N=1822)	p value
<b>Did patient have a SRE within 2 years of registration?</b>				.71 <sup>1</sup>
Missing	29	27	56	
No	622 (70.5%)	631 (71.4%)	1253 (71.0%)	
Yes	260 (29.5%)	253 (28.6%)	513 (29.0%)	
<b>Did patient have radiation to bone within 2 years of registration?</b>				.19 <sup>1</sup>
Missing	29	27	56	
No	697 (79.0%)	721 (81.6%)	1418 (80.3%)	
Yes	185 (21.0%)	163 (18.4%)	348 (19.7%)	
<b>Did patient have a clinical fracture within 2 years of registration?</b>				.16 <sup>1</sup>
Missing	29	27	56	
No	820 (93.0%)	805 (91.1%)	1625 (92.0%)	
Yes	62 (7.0%)	79 (8.9%)	141 (8.0%)	
<b>Did patient have a spinal cord compression within 2 years of registration?</b>				.40 <sup>1</sup>
Missing	29	27	56	
No	859 (97.4%)	854 (96.6%)	1713 (97.0%)	
Yes	23 (2.6%)	30 (3.4%)	53 (3.0%)	
<b>Did patient have surgery to bone within 2 years of registration?</b>				.01 <sup>1</sup>
Missing	29	27	56	
No	860 (97.5%)	842 (95.2%)	1702 (96.4%)	
Yes	22 (2.5%)	42 (4.8%)	64 (3.6%)	

<sup>1</sup>Fisher Exact

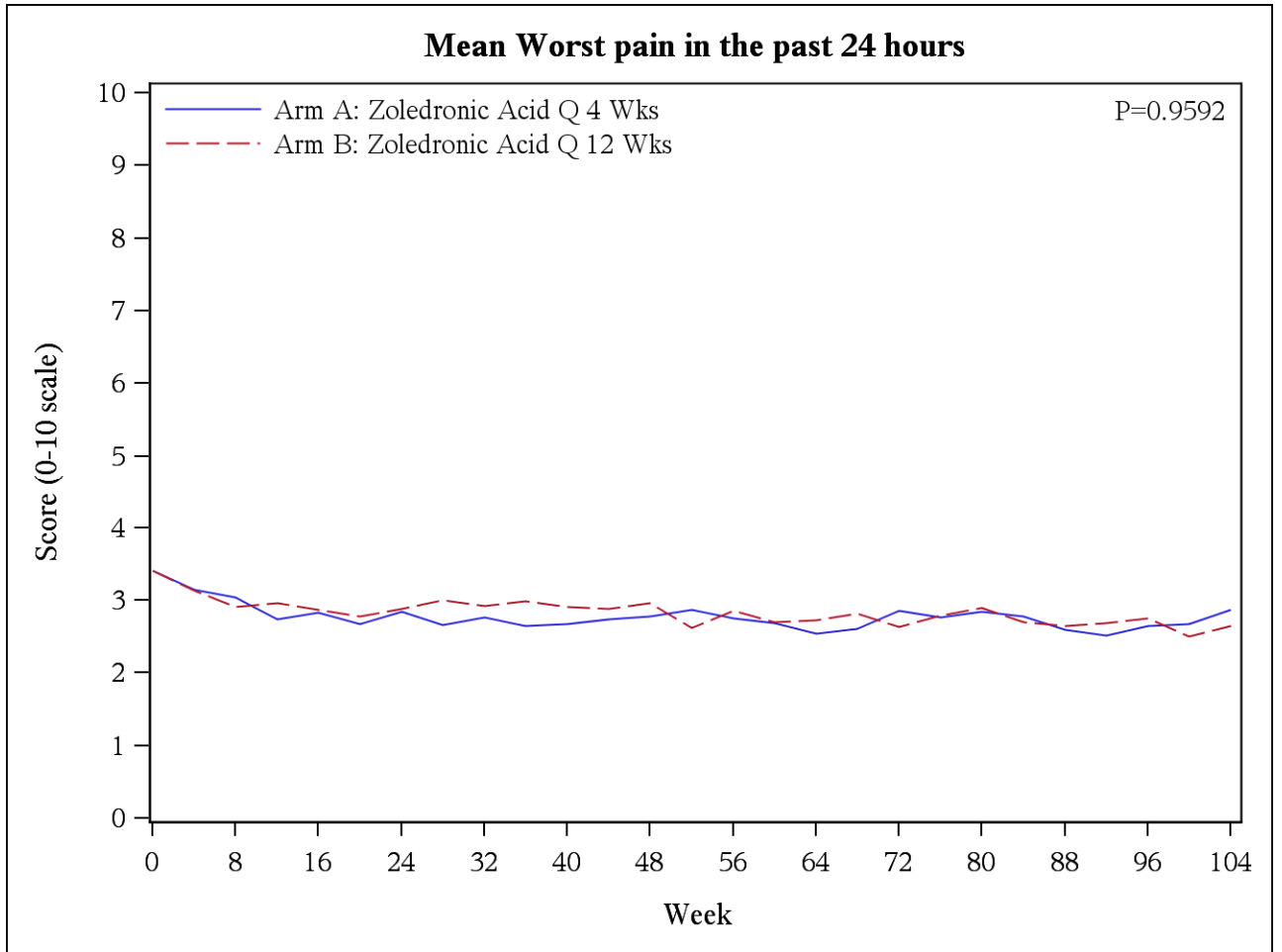
Abbreviation: SRE, Skeletal-related events

**eTable 3.** Adherence to treatment by group

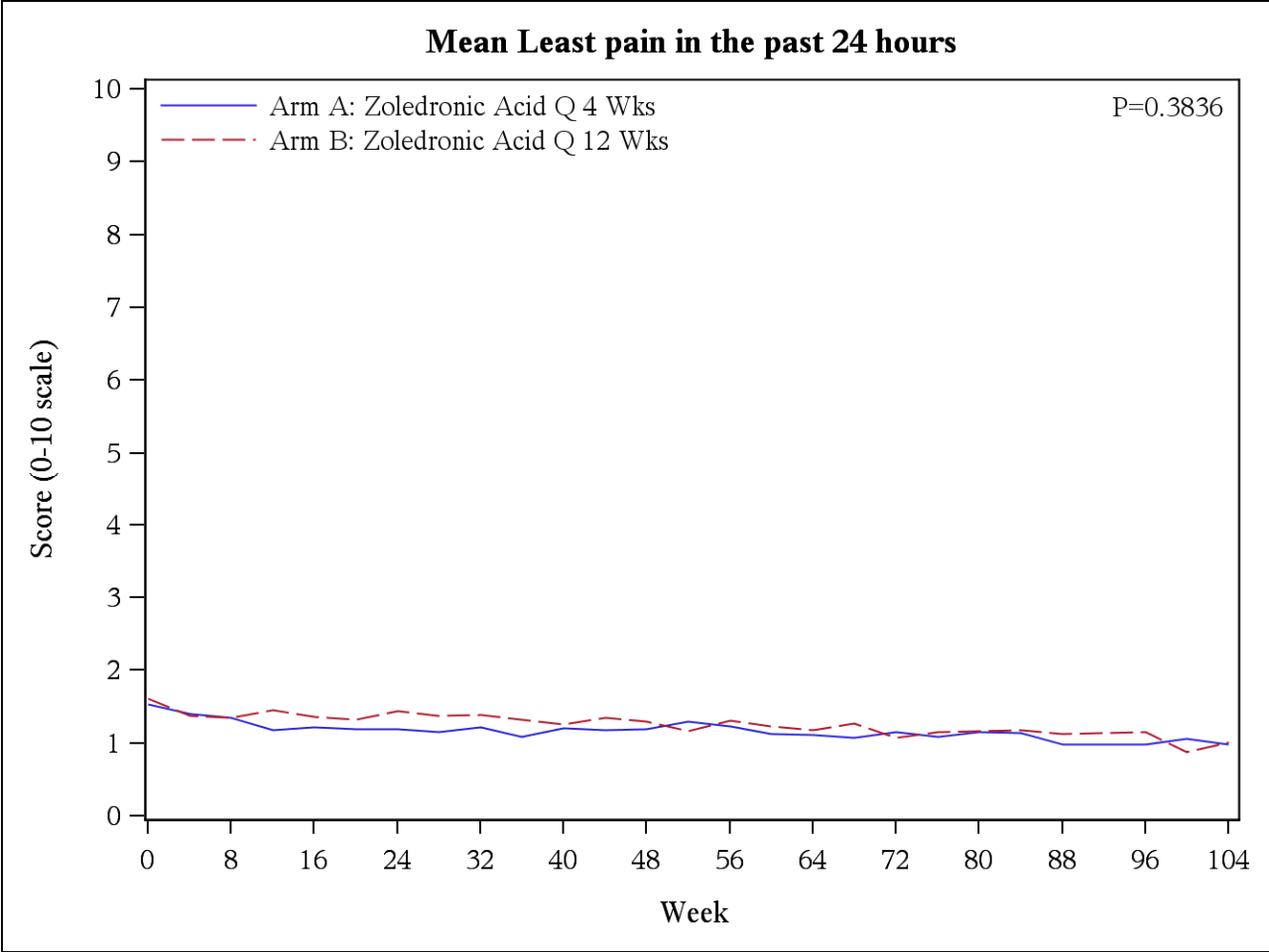
<b>Total Number of Doses, Dose Delays, and Delays per Number of Doses</b>				
	<b>Arm A: Zoledronic Acid Q 4 Wks (N=911)</b>	<b>Arm B: Zoledronic Acid Q 1 2 Wks (N=911)</b>	<b>Total (N=1822)</b>	<b>p value</b>
<b>Total number of doses given</b>				<.001 <sup>1</sup>
N	911	911	1822	
Mean (SD)	13.5 (8.8)	5.2 (3.3)	9.3 (7.8)	
Median	13.0	6.0	7.0	
Q1, Q3	5.0, 22.0	2.0, 8.0	3.0, 14.0	
Range	(0.0-26.0)	(0.0-24.0)	(0.0-26.0)	
<b>Total number of dose delays</b>				<.001 <sup>1</sup>
N	873	863	1736	
Mean (SD)	1.5 (1.9)	0.7 (1.3)	1.1 (1.7)	
Median	1.0	0.0	0.0	
Q1, Q3	0.0, 2.0	0.0, 1.0	0.0, 2.0	
Range	(0.0-13.0)	(0.0-12.0)	(0.0-13.0)	
<b>Number of delays per dose</b>				<.001 <sup>1</sup>
N	870	846	1716	
Mean (SD)	0.1 (0.3)	0.2 (0.3)	0.1 (0.3)	
Median	0.1	0.0	0.0	
Q1, Q3	0.0, 0.2	0.0, 0.2	0.0, 0.2	
Range	(0.0-4.5)	(0.0-4.0)	(0.0-4.5)	
<sup>1</sup> Kruskal Wallis				



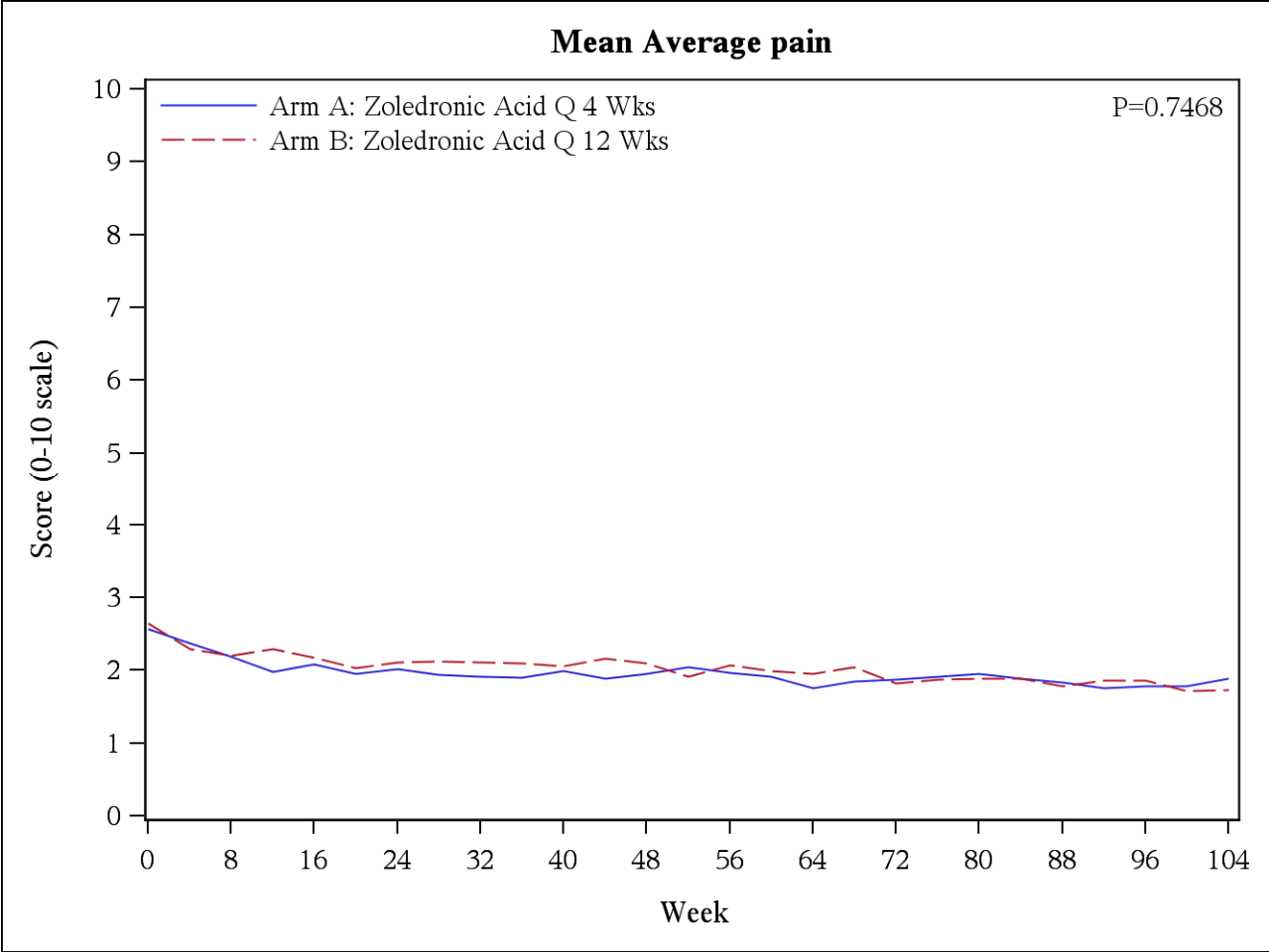
**eFigure 1.** Brief Pain Inventory mean worst pain



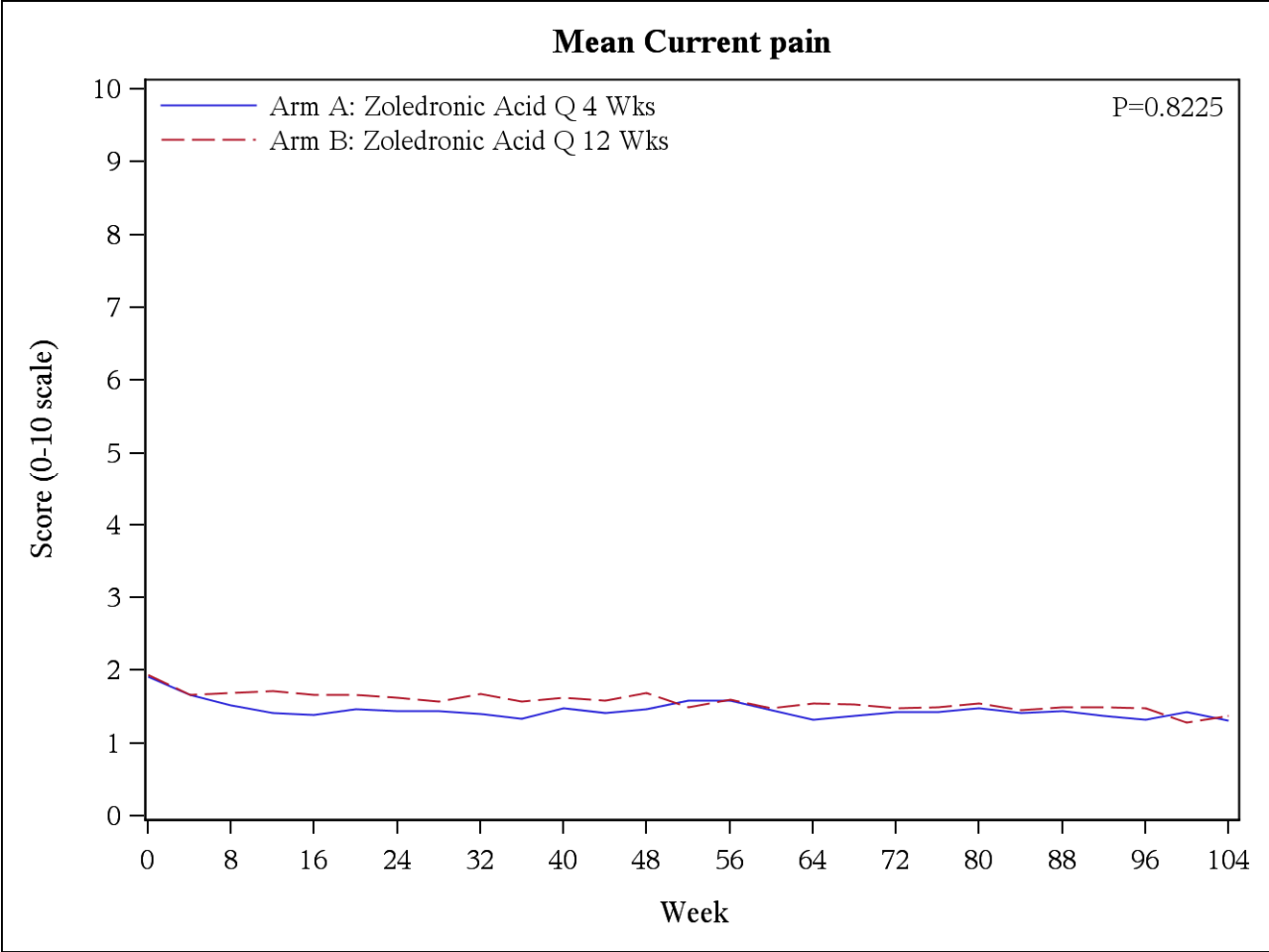
**eFigure 2.** Brief Pain Inventory mean least pain



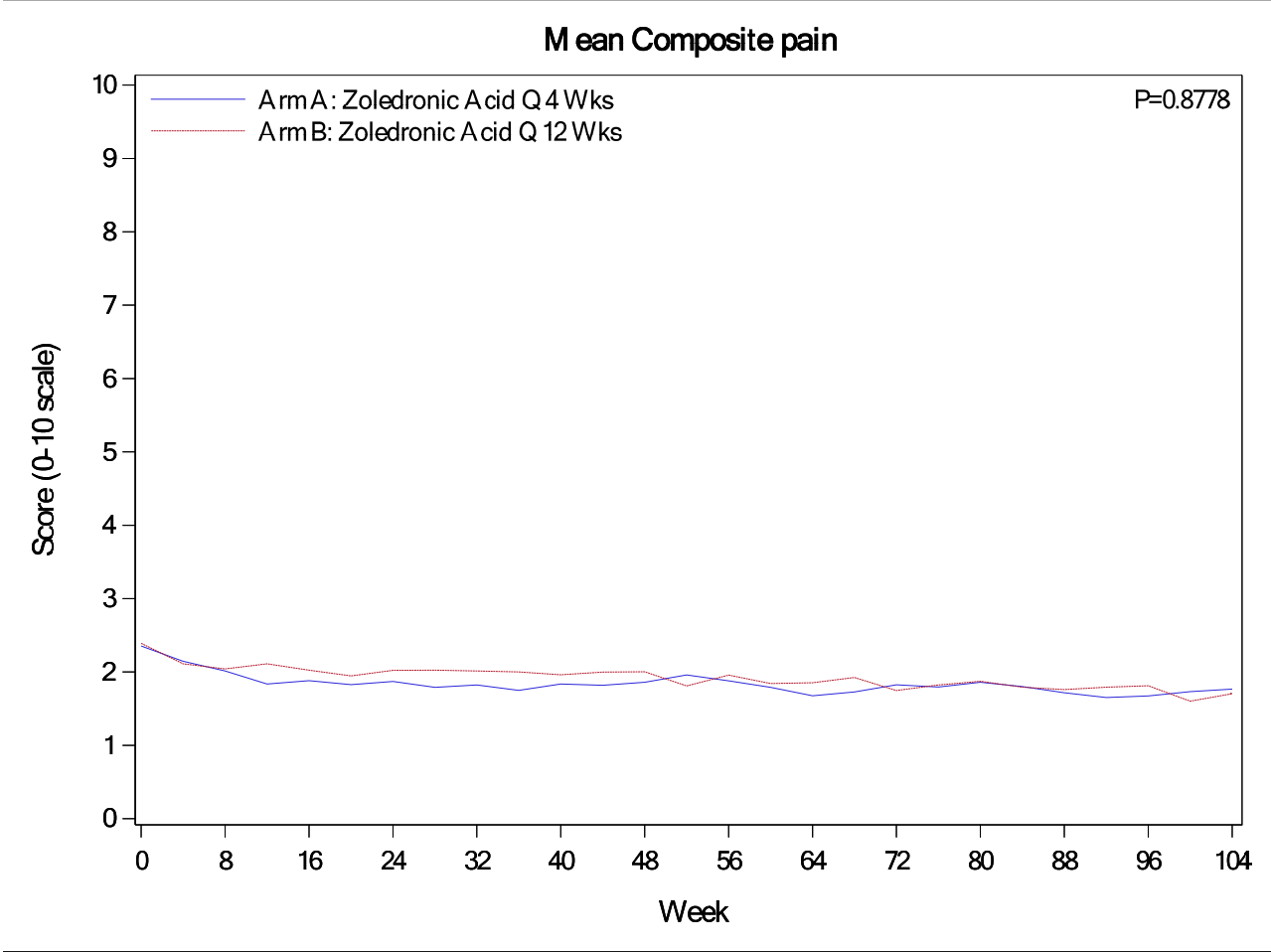
**eFigure 3.** Brief Pain Inventory mean average pain



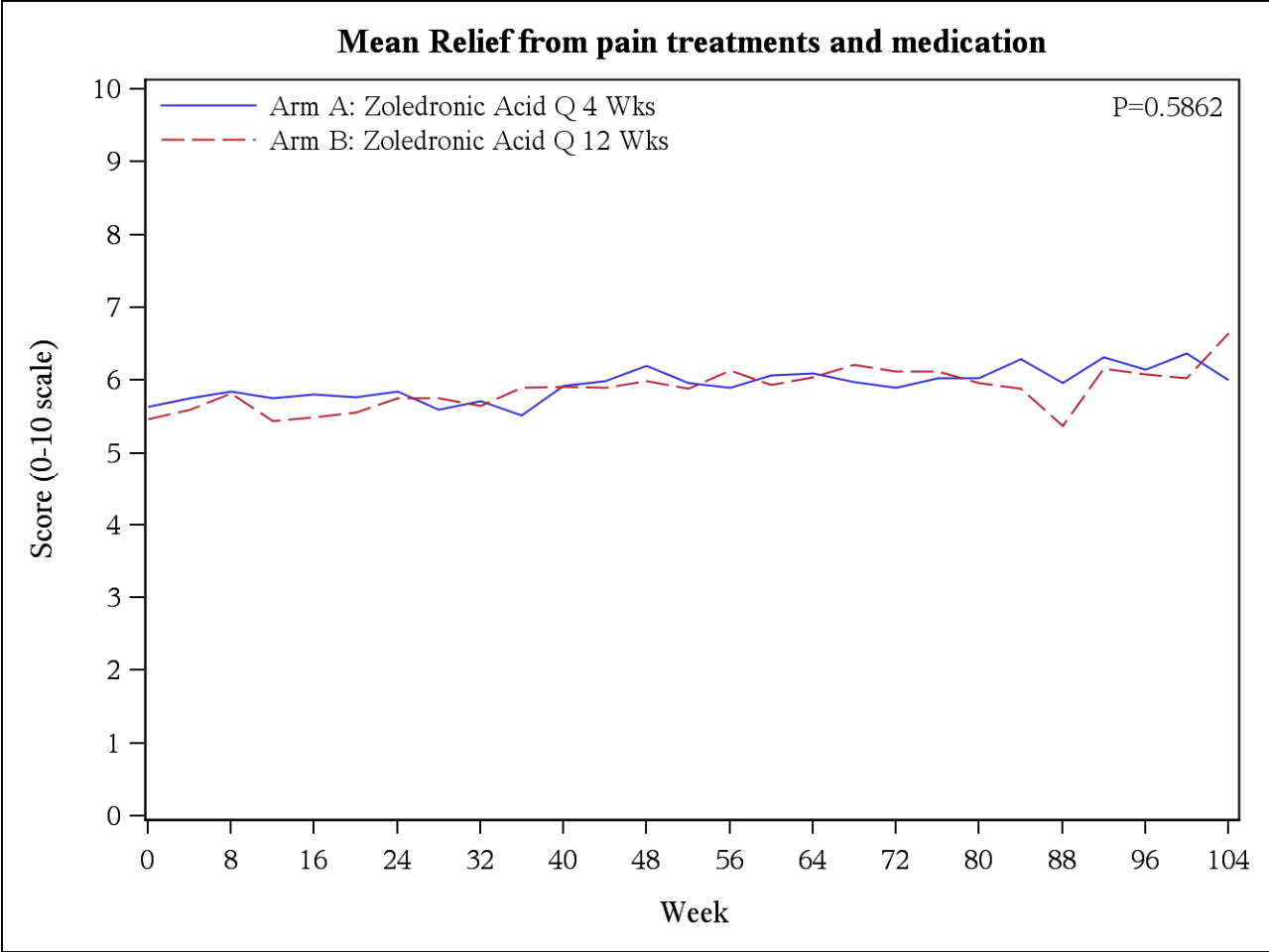
**eFigure 4.** Brief Pain Inventory mean current pain



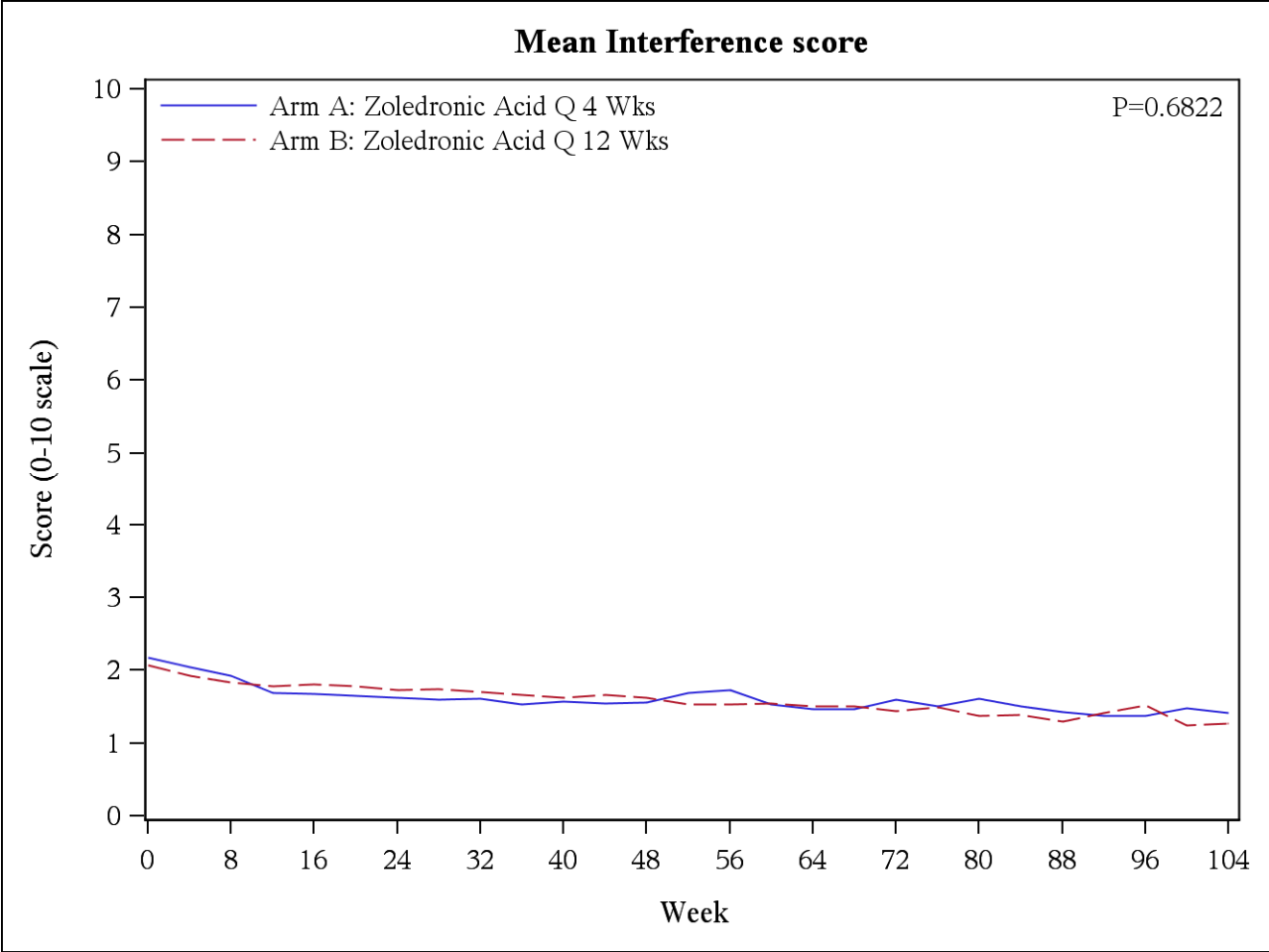
**eFigure 5.** Brief Pain Inventory mean composite pain



**eFigure 6.** Brief Pain Inventory mean relief from pain with treatments or medications



**eFigure 7.** Brief Pain Inventory mean interference score



**eFigure 8.** ECOG performance status

