

## Supplemental Online Content

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**eTable 1.** Further Sensitivity Analyses of Primary End Point

**eTable 2.** Perioperative Change of Health-Related Visual Analog Scale Score

**eFigure 1.** Visual Analog Scale for Well-Being

**eFigure 2.** Visual Analog Scale for Pain

**eFigure 3.** Visual Analog Scale for Sleeping Quality

**eFigure 4.** Visual Analog Scale for EuroQol Health

**eFigure 5.** Proportion of Responses by Level Of Severity for the EQ-5D-5L Mobility Dimension at Baseline and at 30-Day Follow-Up

**eFigure 6.** Proportion of Responses by Level of Severity for the EQ-5D-5L Self-Care Dimension at Baseline and at 30-Day Follow-Up

**eFigure 7.** Proportion of Responses by Level of Severity for the EQ-5D-5L Usual Activity Dimension at Baseline and at 30-Day Follow-Up

**eFigure 8.** Proportion of Responses by Level of Severity for the EQ-5D-5L Pain/Discomfort Dimension at Baseline and at 30-Day Follow-Up

**eFigure 9.** Proportion of Responses by Level of Severity for the EQ-5D-5L Anxiety/Depression Dimension at Baseline and at 30-Day Follow-Up

**eTable 3.** EQ-5D-5L Domains With Level of Problems per Point of Time

**eTable 4.** Breakdown of Other Adverse Events

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

**eTable 1.** Further Sensitivity Analyses of Primary End Point

	Midazolam	Placebo	Treatment effect (95%CI)	P-value
<b>EVAN-G global index score<sup>a</sup>, Mean (SD), Number of patients</b>				
effect among anxious patients, anxiety cut-off level $\geq 12$ <sup>c</sup>	68.2 (7.9), n=64	67.7 (11.5),n=81	0.7 (-2.9 to 4.3)	.70
effect among patients with frailty (with the timed Up & Go test being the marker of the functional status and assumption of albumin levels $\leq 3.3$ g/dL for patients with missing data ) <sup>d</sup>	66.9 (10.1), n=28	68.6 (9.7), n=14	-2.2 (-9.1 to 4.7)	.53
effect among patients with frailty (with the EQ-5D-5L result for “Self-Care” being the marker of the functional status) <sup>e</sup>	67.6 (9.9), n=31	67.2 (9.5), n=17	-0.2 (-6.6 to 6.1)	.94

**Abbreviation:** EQ, EuroQuol; EVAN-G, Evaluation du Vécu de l'Anesthésie Generale

<sup>a</sup> Five patients of the total cohort had missing scores in the global satisfaction score (midazolam = 3, placebo = 2).

<sup>b</sup> Evaluation du Vécu de l'Anesthésie Generale (EVAN-G), global patient satisfaction questionnaire comprising 26 items within six dimensions. The scores of negatively worded items were reversed (Items: 8, 11, 12, 13, 16, 17, 18, 19, 25, and 26).<sup>11</sup> For each individual, the mean score for each of the six dimensions (attention, privacy, information, pain, discomfort, and waiting) was calculated. If fewer than half of the items were missing, the mean of the non-missing items was substituted. The scores were linearly transformed to a scale from 0 to 100. The global index score was calculated as the mean of the dimension score.

<sup>c</sup> Anxiety was measured by the Amsterdam Preoperative Anxiety and Information Scale (APAIS).<sup>20</sup> In this sensitivity analysis the most anxious patients were defined as patients having an APAIS score of  $\geq 12$ .

<sup>d</sup> Patients were defined as frail for this sensitivity analysis, if at least four of the following six markers were present: Mini-Cog total score  $\leq 3$  points; albumin level of  $\leq 3.3$  g/dL;  $> 1$  fall in the last 6 months; hematocrit level of  $< 35\%$ ; pre-operative functional status is according to the Timed Up & Go test  $> 15$ sec. (patient is timed while the patient rises from an arm chair, walks 3 meters, turns, walks back, and sits down again);<sup>13</sup>  $\geq 3$  comorbidities present and the assumption that the albumin level for patients with missing data was  $\leq 3.3$  g/dL.

<sup>e</sup> Patients were defined as frail for this sensitivity analysis, if at least four of the following six markers were present: Mini-Cog<sup>12</sup> total score  $\leq 3$  points; albumin level of  $\leq 3.3$  g/dL;  $> 1$  fall in the last 6 months; hematocrit level of  $< 35\%$ ; pre-operative functional status is partially dependent or totally dependent (according to the EQ-5D-5L result for “Self-Care”  $> 1$ );<sup>19</sup> and  $\geq 3$  comorbidities present.

**eTable 2.** Perioperative Change of Health-Related Visual Analog Scale Score

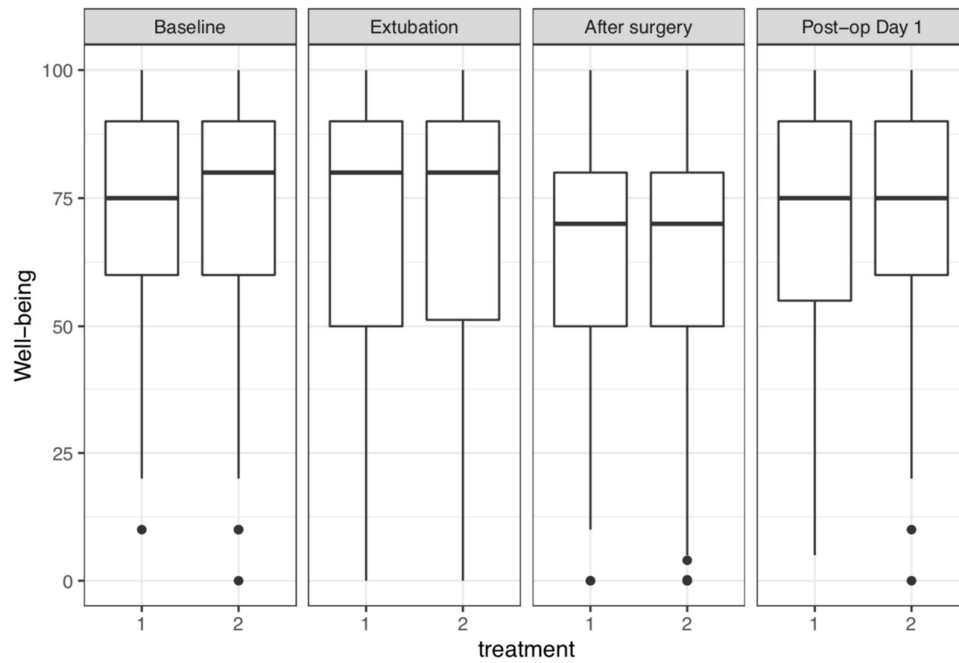
	Midazolam (n=304)	Placebo (n=303)	Difference in means of treatments (SE)
<b>Change VAS, mean (95% CI)</b>			
<b>Baseline to Extubation</b>			
Well-being	-0.8 (30.7), n=269	-1.7 (31.1), n=262	0.9 (2.7)
Pain	-9.1 (32.7), n=280	-11.0 (30.6), n=277	1.9 (2.7)
<b>Baseline to PACU/ICU after surgery</b>			
Well-being	-5.7 (28.6), n=289	-9.2 (28.9), n=285	3.5 (2.4)
Pain	0.1 (34.1), n=299	0.3 (36.2), n=296	-0.2 (2.9)
<b>Baseline to 1<sup>st</sup> POD</b>			
Well-being	-0.6 (24.5), n=301	-2.8 (22.8), n=299	2.2 (1.9)
Pain	-4.0 (31.7), n=301	-1.2 (32.6), n=301	-2.8 (2.6)
Sleep quality	-17.6 (35.1), n=301	-15.4 (36.1), n=300	-2.2 (2.9)
<b>Baseline to 30<sup>th</sup> POD</b>			
EQ health <sup>a</sup>	4.6 (21.0), n=283	1.7 (21.4), n=276	2.9 (1.8)

Abbreviations: EQ, EuroQuol; PACU, Postanesthesia care unit; POD, Postoperative day; SE, Standard error.

Visual analog scale is a psychometric response scale of 100 mm on a paper ranging from 0 to 100.

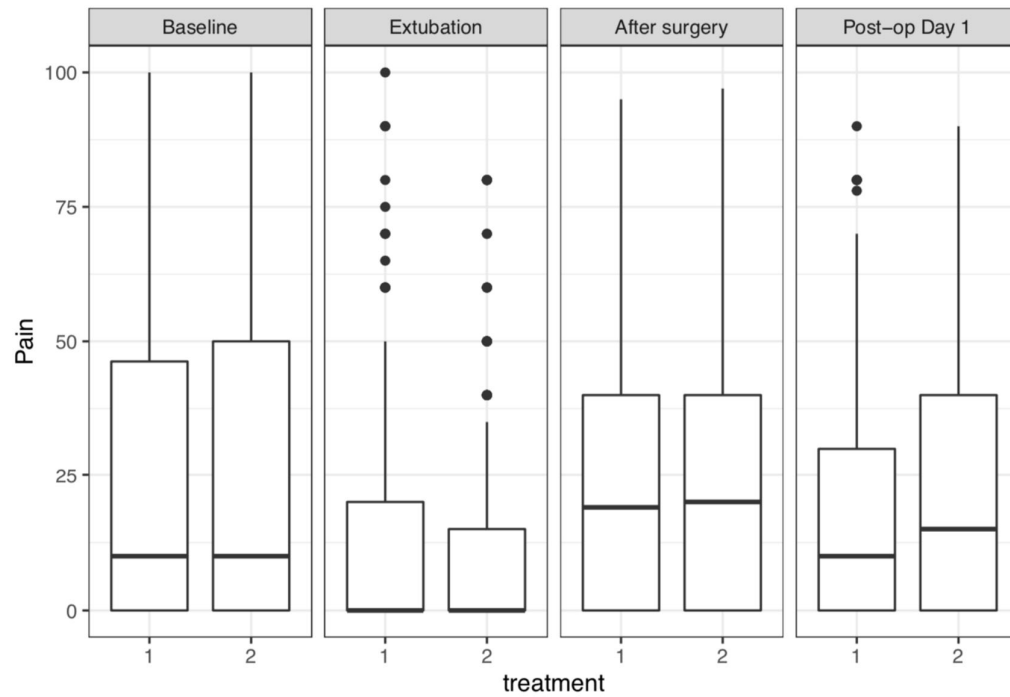
<sup>a</sup> The vertical visual analog scale was labeled as follows: 100 mm corresponding to ‘The best health you can imagine’ and 0 corresponding to ‘The worst health you can imagine’.

**eFigure 1.** Visual Analog Scale for Well-Being



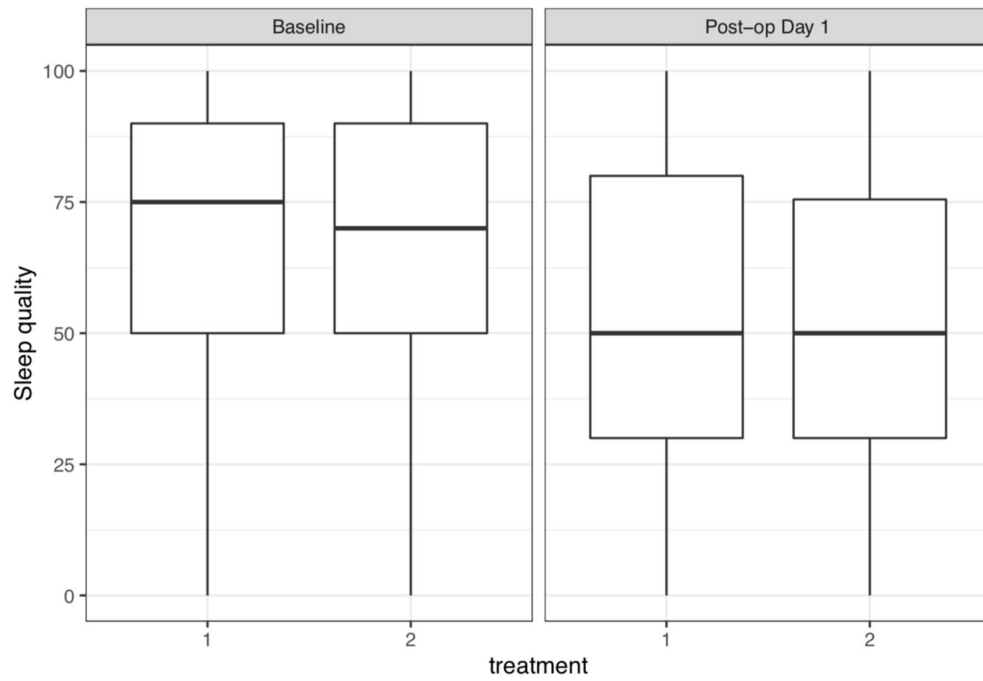
Box-plots for Visual Analog Scale (0-100) values of well-being at different time-points. Treatment 1: midazolam, treatment 2: placebo. The line in the box represents the median, the lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles) and the upper (lower) whiskers extend from the hinge to the largest (smallest) value no further than 1.5 times the interquartile range.

**eFigure 2.** Visual Analog Scale for Pain



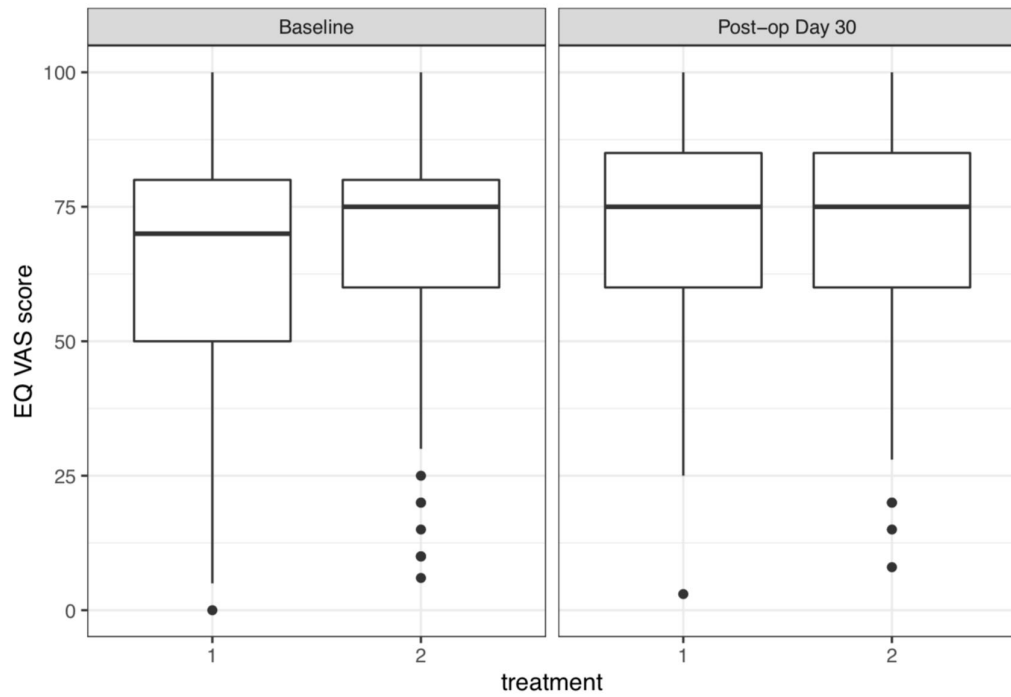
Box-plots for Visual Analog Scale (0-100) values of pain at different time-points. Treatment 1: midazolam, treatment 2: placebo. The line in the box represents the median, the lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles) and the upper (lower) whiskers extend from the hinge to the largest (smallest) value no further than 1.5 times the interquartile range.

**eFigure 3.** Visual Analog Scale for Sleeping Quality



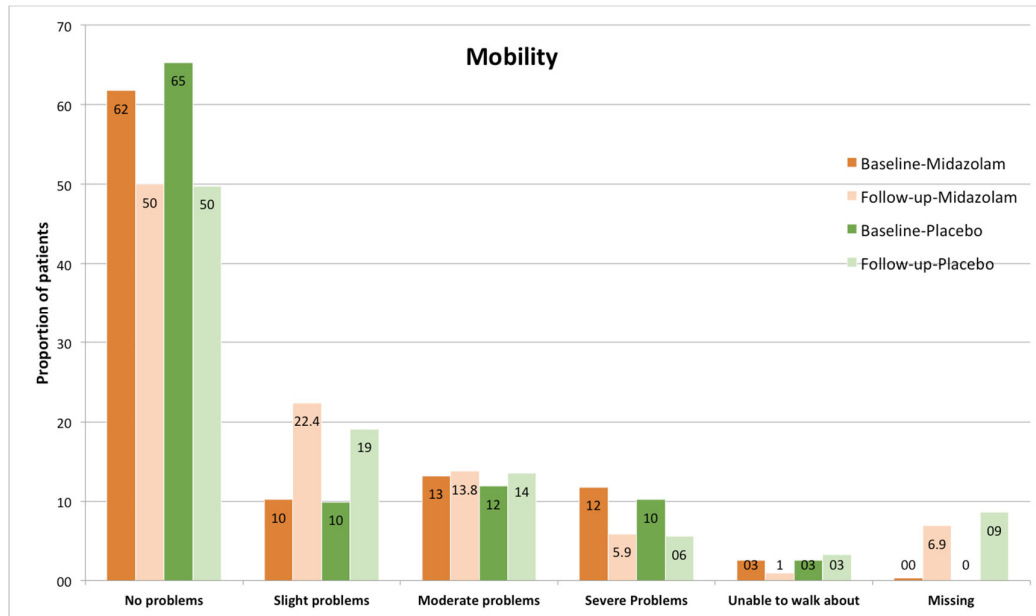
Box-plots for Visual Analog Scale (0-100) values of sleeping-quality at different time-points. Treatment 1: midazolam, treatment 2: placebo. The line in the box represents the median, the lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles) and the upper (lower) whiskers extend from the hinge to the largest (smallest) value no further than 1.5 times the interquartile range.

**eFigure 4.** Visual Analog Scale for EuroQol Health



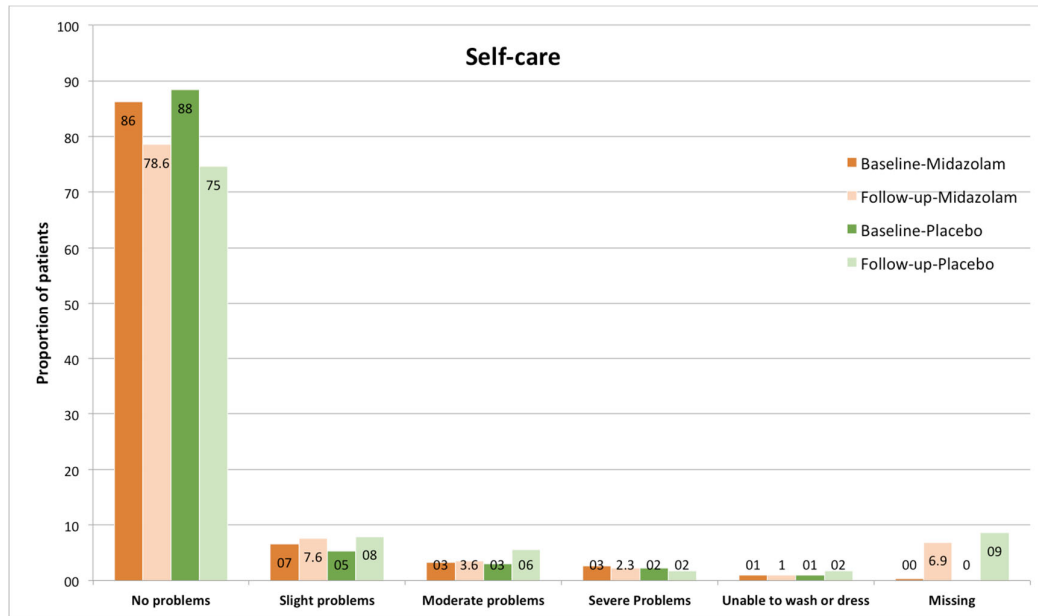
Box-plots for Visual Analog Scale (0-100) values of EuroQol (EQ) Health as part of the EQ-5d-5L<sup>19</sup> quality of life test at two different time-points. Treatment 1: midazolam, treatment 2: placebo. The line in the box represents the median, the lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles) and the upper (lower) whiskers extend from the hinge to the largest (smallest) value no further than 1.5 times the interquartile range.

**eFigure 5.** Proportion of Responses by Level Of Severity for the EQ-5D-5L Mobility Dimension at Baseline and at 30-Day Follow-Up

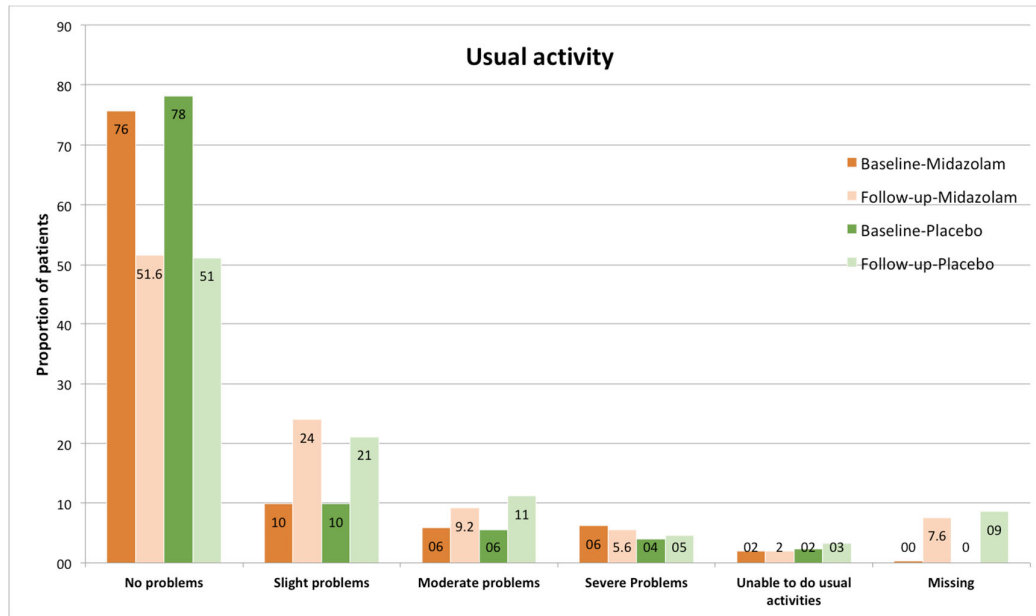




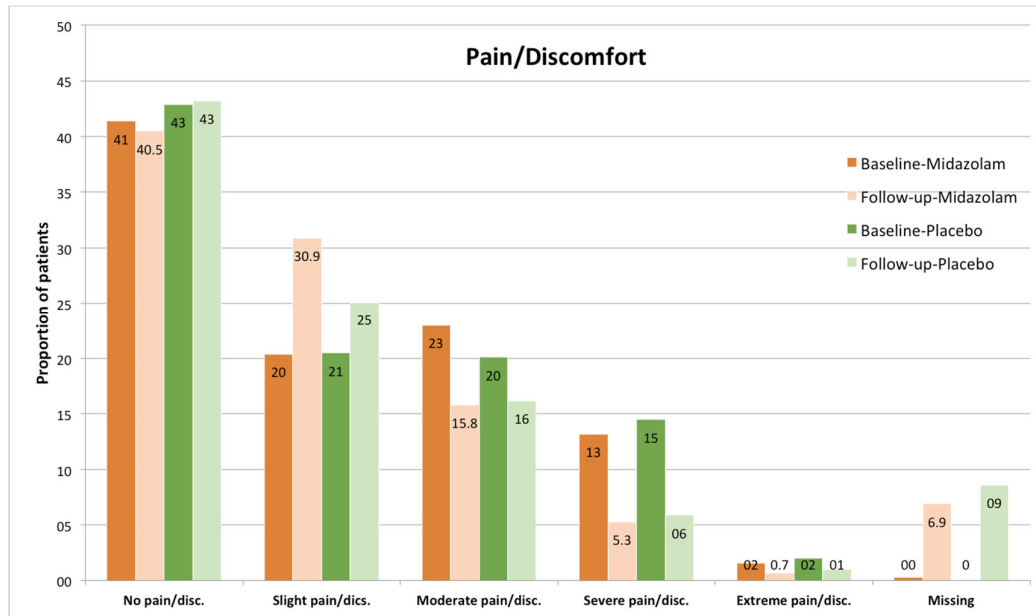
**eFigure 6.** Proportion of Responses by Level of Severity for the EQ-5D-5L Self-Care Dimension at Baseline and at 30-Day Follow-Up



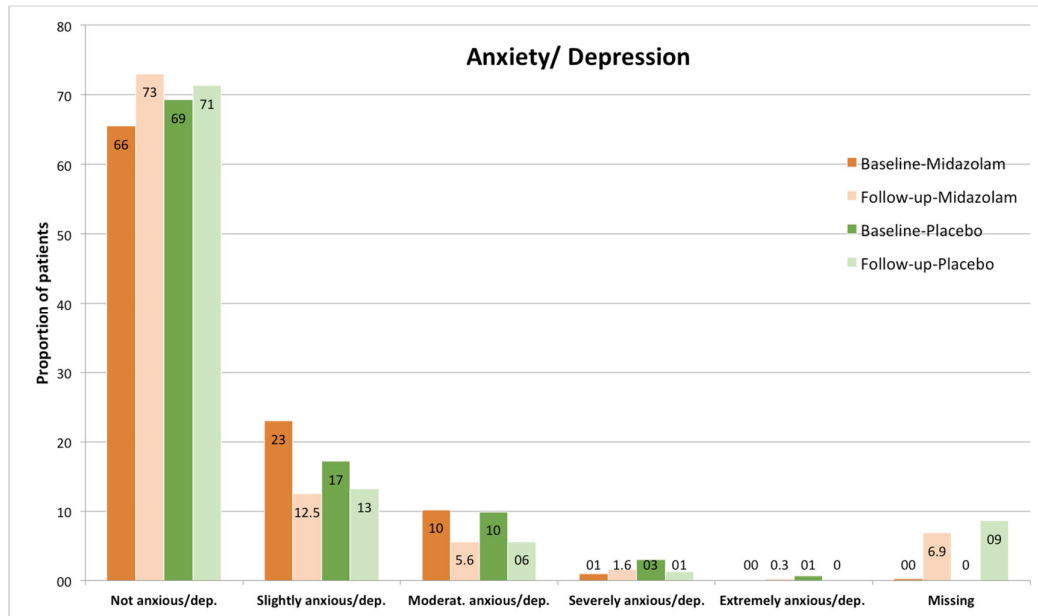
**eFigure 7.** Proportion of Responses by Level of Severity for the EQ-5D-5L Usual Activity Dimension at Baseline and at 30-Day Follow-Up



**eFigure 8.** Proportion of Responses by Level of Severity for the EQ-5D-5L Pain/Discomfort Dimension at Baseline and at 30-Day Follow-Up



**Figure 9.** Proportion of Responses by Level of Severity for the EQ-5D-5L Anxiety/Depression Dimension at Baseline and at 30-Day Follow-Up



**eTable 3.** EQ-5D-5L Domains With Level of Problems per Point of Time

	Midazolam			Placebo		
	Baseline	30-day Follow-up	<i>P</i> -value	Baseline	30-day Follow-up	<i>P</i> -value
<b>Mobility, n (%)</b>						
No problems	188 (61.8)	152 (50)	.29	198 (65.3)	151 (49.8)	.20
Slight problems	31 (10.2)	68 (22.4)		30 (9.9)	58 (19.1)	
Moderate problems	40 (13.2)	42 (13.8)		36 (11.9)	41 (13.5)	
Severe problems	36 (11.8)	18 (5.9)		31 (10.2)	17 (5.6)	
Unable to walk about	8 (2.6)	3 (1)		8 (2.6)	10 (3.3)	
Missing	1 (0.3)	21 (6.9)		0 (0)	26 (8.6)	
<b>Self-care, n (%)</b>						
No problems	262 (86.2)	239 (78.6)	.57	268 (88.4)	226 (74.6)	<.01
Slight problems	20 (6.6)	23 (7.6)		16 (5.3)	24 (7.9)	
Moderate problems	10 (3.3)	11 (3.6)		9 (3.0)	17 (5.6)	
Severe problems	8 (2.6)	7 (2.3)		7 (2.3)	5 (1.7)	
Unable to wash or dress	3 (1)	3 (1)		3 (1.0)	5 (1.7)	
Missing	1 (0.3)	21 (6.9)		0 (0)	26 (8.6)	
<b>Usual activity, n (%)</b>						
No problems	230 (75.7)	157 (51.6)	<.001	237 (78.2)	155 (51.2)	
Slight problems	30 (9.9)	73 (24)		30 (9.9)	64 (21.1)	
Moderate problems	18 (5.9)	28 (9.2)		17 (5.6)	34 (11.2)	
Severe problems	19 (6.2)	17 (5.6)		12 (4.0)	14 (4.6)	
Unable to do usual activities	6 (2)	6 (2)		7 (2.3)	10 (3.3)	
Missing	1 (0.3)	23 (7.6)		0 (0)	26 (8.6)	
<b>Pain/discomfort, n (%)</b>						
No pain/discomfort	126 (41.4)	123 (40.5)	<.001	130 (42.9)	131 (43.2)	<.01
Slight pain/ discomfort	62 (20.4)	94 (30.9)		62 (20.5)	76 (25.1)	
Moderate pain/ discomfort	70 (23)	48 (15.8)		61 (20.1)	49 (16.2)	
Severe pain/ discomfort	40 (13.2)	16 (5.3)		44 (14.5)	18 (5.9)	
Extreme pain/ discomfort	5 (1.6)	2 (0.7)		6 (2)	3 (1)	

Missing	1 (0.3)	21 (6.9)		0 (0)	26 (8.6)	
<b>Anxiety/depression, n (%)</b>						
Not anxious/depressive	199 (65.5)	222 (73)	<.01	210 (69.3)	216 (71.3)	<.001
Slightly anxious/ depressive	70 (23)	38 (12.5)		52 (17.2)	40 (13.2)	
Moderately anxious/ depressive	31 (10.2)	17 (5.6)		30 (9.9)	17 (5.6)	
Severely anxious/ depressive	3 (1)	5 (1.6)		9 (3)	4 (1.3)	
Extremely anxious/ depressive	0 (0)	1 (0.3)		2 (0.7)	0 (0)	
Missing	1 (0.3)	21 (6.9)		0 (0)	26 (8.6)	

**eTable 4.** Breakdown of Other Adverse Events

	<b>Midazolam (n=304)</b>	<b>Placebo (n=303)</b>
<b>Single adverse events, n (%)</b>		
Acute kidney injury	1 (<1)	0
Agitation	0	1 (<1)
Anemia	3 (1)	0
Cardiac arrest	0	1 (<1)
Cardiac failure (acute)	1 (<1)	2 (<1)
Central anticholinergic syndrome	0	1 (<1)
Death	0	1 (<1)
Depression	1 (<1)	0
Dizziness	3 (1)	0
Drowsiness	2 (<1)	0
Extravasation	0	1 (<1)
Eyebrow laceration after falling down in rehabilitation unit	1 (<1)	0
Hypovolemia	0	1 (<1)
Neurologic problem	1 (<1)	0
Pneumonia	2 (<1)	1 (<1)
POCD	0	2 (<1)
PONV	20 (7)	19 (6)
Postoperative bleeding	1 (<1)	2 (<1)
Postoperative delirium	4 (1)	3 (1)
Pulmonary embolism	1 (<1)	0
Re-surgery	0	1 (<1)
Shivering	1 (<1)	0
Stroke	0	2 (<1)
Surgical adverse event	1 (<1)	3 (1)
Syncope	1 (<1)	1 (<1)
Thorax-rigidity	0	1 (<1)

Abbreviation: POCD, postoperative cognitive dysfunction; PONV, postoperative nausea or vomiting