

Supplemental material

The Effect of E4/DRSP on Menstrual Symptoms and Health-Related Quality of Life in Adolescents

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Table S1 Overview of shift analysis with % of participants remaining stable, improving and worsening and % of participants with severe or strong symptoms at baseline for menstrual and premenstrual symptoms as measured by MDQ.

Domains	Symptom	Stage	Stable	Improving	Worsening	Severe/strong at baseline	
Physical							
Pain	Muscle stiffness	Premenstrual	74.5%	11.8%	13.7%	0%	
		Menstrual	52.9%	23.5%	23.5%	3.9%	
	Headache	Premenstrual	58.8%	13.7%	27.5%	2.0%	
		Menstrual ✓	49.0%	25.5%	25.5%	13.7%	
	Cramps	Premenstrual	45.1%	31.4%	23.5%	7.8%	
		Menstrual ✓	29.4%	<u>52.9%</u>	<u>17.6%</u>	45.1%	
	Backache	Premenstrual	54.9%	23.5%	21.6%	9.8%	
		Menstrual ✓	43.1%	<u>39.2%</u>	<u>17.6%</u>	27.5%	
	Fatigue	Premenstrual	37.3%	25.5%	37.3%	9.8%	
		Menstrual ✓	37.3%	35.3%	27.5%	25.5%	
	General aches and pain	Premenstrual	35.3%	33.3%	31.4%	5.9%	
		Menstrual ✓	41.2%	<u>47.1%</u>	<u>11.8%</u>	27.5%	
	Water Retention	Weight gain	Premenstrual	62.7%	17.6%	19.6%	2.0%
			Menstrual	66.7%	17.6%	15.7%	2.0%
Skin blemish or disorder		Premenstrual	60.8%	25.5%	13.7%	5.9%	
		Menstrual	52.9%	25.5%	21.6%	7.8%	
Painful or tender breasts		Premenstrual ✓	31.4%	<u>45.1%</u>	<u>23.5%</u>	13.7%	
		Menstrual ✓	39.2%	<u>45.1%</u>	<u>15.7%</u>	21.6%	

	Swelling (breast, abdomen)	Premenstrual ✓	49.0%	31.4%	19.6%	11.8%
		Menstrual ✓	49.0%	31.4%	19.6%	11.8%
Emotional						
Negative Affect	Loneliness	Premenstrual ✓	49.0%	31.4%	19.6%	13.7%
		Menstrual ✓	41.2%	37.3%	21.6%	13.7%
	Anxiety	Premenstrual	56.9%	21.6%	21.6%	9.8%
		Menstrual ✓	47.1%	31.4%	21.6%	13.7%
	Mood swings	Premenstrual ✓	33.3%	37.3%	29.4%	23.5%
		Menstrual ✓	35.3%	<u>45.1%</u>	<u>19.6%</u>	51.0%
	Crying	Premenstrual ✓	49.0%	31.4%	19.6%	17.6%
		Menstrual ✓	43.1%	<u>43.1%</u>	<u>13.7%</u>	27.5%
	Irritability	Premenstrual ✓	33.3%	43.1%	23.5%	25.5%
		Menstrual ✓	45.1%	35.3%	19.6%	33.3%
	Tension	Premenstrual	51.0%	31.4%	17.6%	7.8%
		Menstrual ✓	45.1%	<u>39.2%</u>	<u>15.7%</u>	17.6%
	Feeling sad or blue	Premenstrual ✓	51.0%	33.3%	15.7%	13.7%
		Menstrual ✓	37.3%	<u>45.1%</u>	<u>17.6%</u>	15.7%
	Restlessness	Premenstrual	56.9%	25.5%	17.6%	5.9%
		Menstrual	54.9%	29.4%	15.7%	9.8%
Insomnia	Premenstrual	54.9%	27.5%	17.6%	5.9%	
	Menstrual	62.7%	23.5%	13.7%	3.9%	
Forgetfulness	Premenstrual	62.7%	15.7%	21.6%	5.9%	
	Menstrual	58.8%	19.6%	21.6%	5.9%	
Confusion	Premenstrual	70.6%	15.7%	13.7%	2.0%	
	Menstrual	66.7%	19.6%	13.7%	0%	
Poor Judgement	Premenstrual	80.4%	13.7%	5.9%	3.9%	
	Menstrual	74.5%	17.6%	7.8%	3.9%	
Difficulty concentrating	Premenstrual	56.9%	23.5%	19.6%	5.9%	
	Menstrual	58.8%	29.4%	11.8%	7.8%	
Distractibility	Premenstrual	60.8%	27.5%	11.8%	5.9%	
	Menstrual	52.9%	33.3%	13.7%	5.9%	

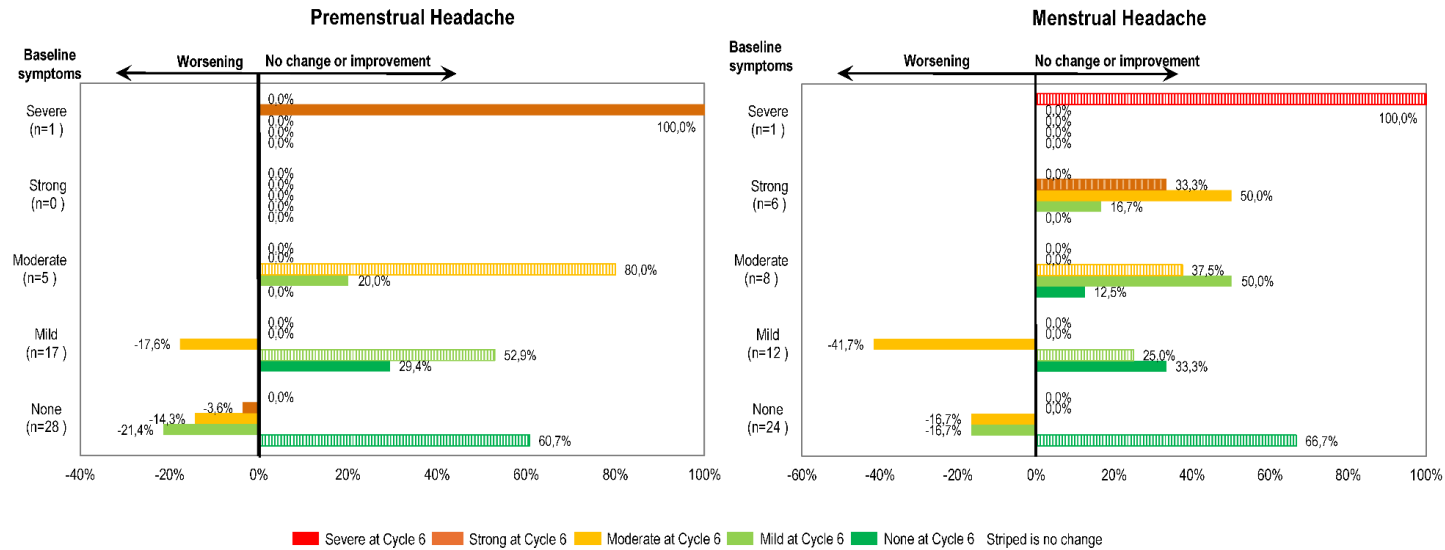
Minor accidents	Premenstrual	68.6%	21.6%	9.8%	2.0%
	Menstrual	68.6%	17.6%	13.7%	0%
Poor motor coordination	Premenstrual	76.5%	11.8%	11.8%	5.9%
	Menstrual	70.6%	11.8%	17.6%	3.9%

✓ Highlights cases where $\geq 40\%$ of participants experienced a change in symptom severity (either improvement or worsening), and where $\geq 10\%$ had severe or strong symptoms at baseline. Using these criteria, 21 symptoms qualified, including cramps, backache, fatigue, general aches and pains, breast tenderness, swelling, mood swings, crying, irritability, tension, and feeling sad or blue. Underlined numbers: Indicate a $\geq 20\%$ difference between the proportions of participants who improved versus those who worsened.

Additional shift analysis figures for premenstrual and menstrual symptom scores for symptoms that showed a change in intensity in at least 40% of participants among those who reported strong or severe symptoms at baseline (representing at least 10% of the analysis population). Percentage of participants shifting to another severity category (improving or worsening) or remaining in the same severity category (stable) at Cycle 6 for the following premenstrual and menstrual symptoms:

Figure S1. Headache; **Figure S2.** Backache; **Figure S3.** Fatigue; **Figure S4.** General Aches and Pain; **Figure S5.** Painful and Tender Breasts; **Figure S6.** Swelling (Breast, Abdomen); **Figure S7.** Loneliness; **Figure S8.** Anxiety; **Figure S9.** Crying; **Figure 10.** Irritability; **Figure S11.** Tension; **Figure S12.** Feeling Sad or Blue.

Figure S1. Percentage of participants shifting to another severity category (improving or worsening) or remaining in the same severity category (stable) at Cycle 6 for premenstrual and menstrual headache.



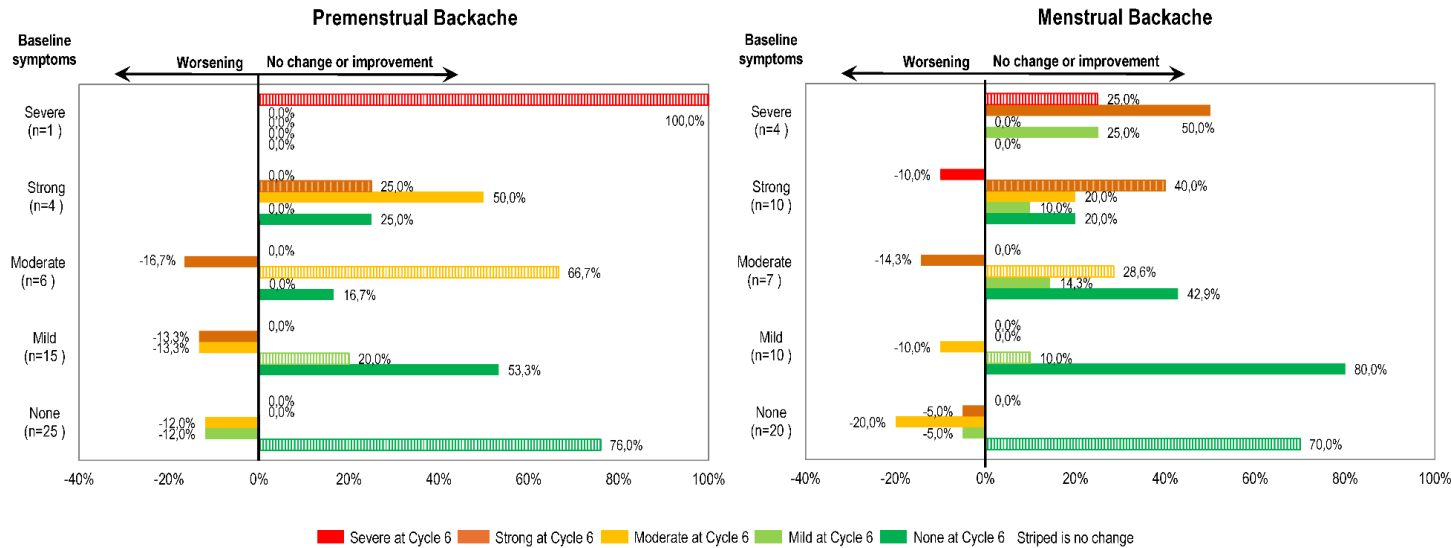
Premenstrual Headache:

Severe baseline symptoms (n=1): 0 (0%) worsened, 0 (0%) without change, 1 (100%) improved.
 Strong baseline symptoms (n=0): 0 (0%) worsened, 0 (0%) without change, 0 (0%) improved.
 Moderate symptoms (n=5): 0 (0%) worsened, 4 (80.0%) without change, 1 (20.0%) improved.
 Mild symptoms (n=17): 3 (17.6%) worsened, 9 (52.9%) without change, 5 (29.4%) improved.
 No baseline symptoms (n=28): 11 (39.3%) worsened, 17 (60.7%) without change, (0%) improved.

Menstrual Headache:

Severe baseline symptoms (n=1): 0 (0%) worsened, 1 (100%) without change, 0 (0%) improved.
 Strong baseline symptoms (n=6): 0 (0%) worsened, 2 (33.3%) without change, 4 (66.7%) improved.
 Moderate symptoms (n=8): 0 (0%) worsened, 3 (37.5%) without change, 5 (62.5%) improved.
 Mild symptoms (n=12): 5 (41.7%) worsened, 3 (25.0%) without change, 4 (33.3%) improved.
 No baseline symptoms (n=24): 8 (33.3%) worsened, 16 (66.7%) without change, (0%) improved.

Figure S2. Percentage of participants shifting to another severity category (improving or worsening) or remaining in the same severity category (stable) at Cycle 6 for premenstrual and menstrual backache.



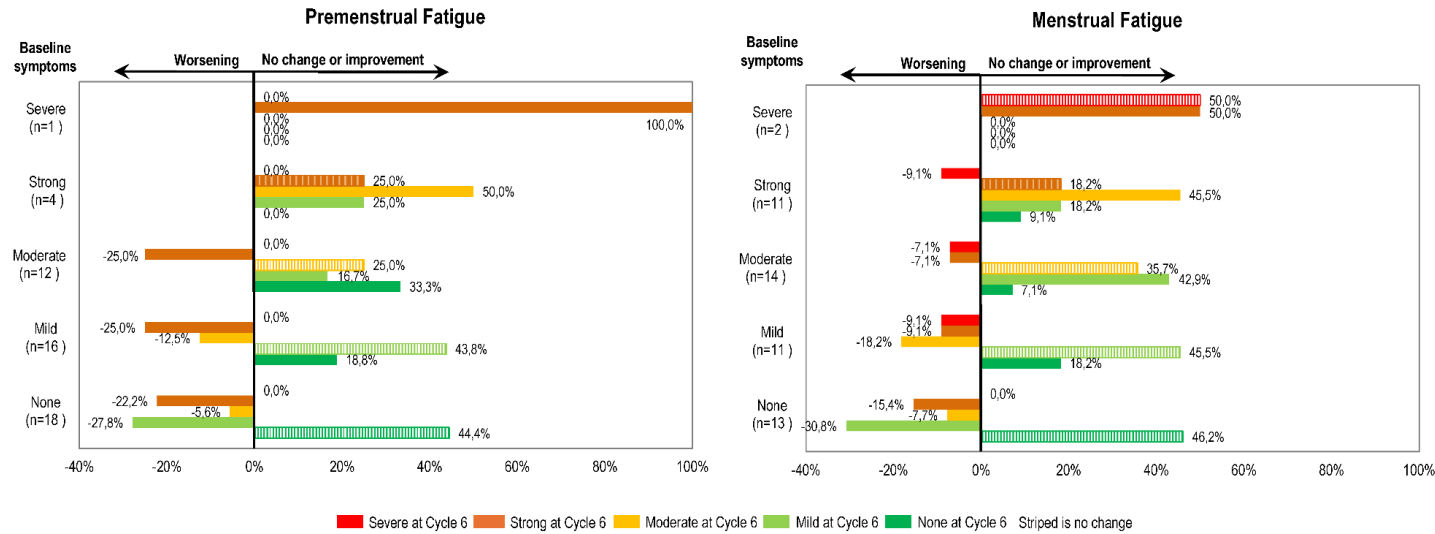
Premenstrual Backache:

Severe baseline symptoms (n=1): 0 (0%) worsened, 1 (100%) without change, 0 (0%) improved.
 Strong baseline symptoms (n=4): 0 (0%) worsened, 1 (25.0%) without change, 3 (75.0%) improved.
 Moderate symptoms (n=6): 1 (16.7%) worsened, 4 (66.7%) without change, 1 (16.7%) improved.
 Mild symptoms (n=15): 4 (26.6%) worsened, 3 (20.0%) without change, 8 (53.3%) improved.
 No baseline symptoms (n=25): 6 (24.0%) worsened, 19 (76.0%) without change, (0%) improved.

Menstrual Backache:

Severe baseline symptoms (n=4): 0 (0%) worsened, 1 (25.0%) without change, 3 (75.0%) improved.
 Strong baseline symptoms (n=10): 1 (10.0%) worsened, 4 (40.0%) without change, 5 (50.0%) improved.
 Moderate symptoms (n=7): 1 (14.3%) worsened, 2 (28.6%) without change, 4 (57.1%) improved.
 Mild symptoms (n=10): 1 (10.0%) worsened, 1 (10.0%) without change, 8 (80.0%) improved.
 No baseline symptoms (n=20): 6 (30.0%) worsened, 14 (70.0%) without change, (0%) improved.

Figure S3. Percentage of participants shifting to another severity category (improving or worsening) or remaining in the same severity category (stable) at Cycle 6 for premenstrual and menstrual fatigue.



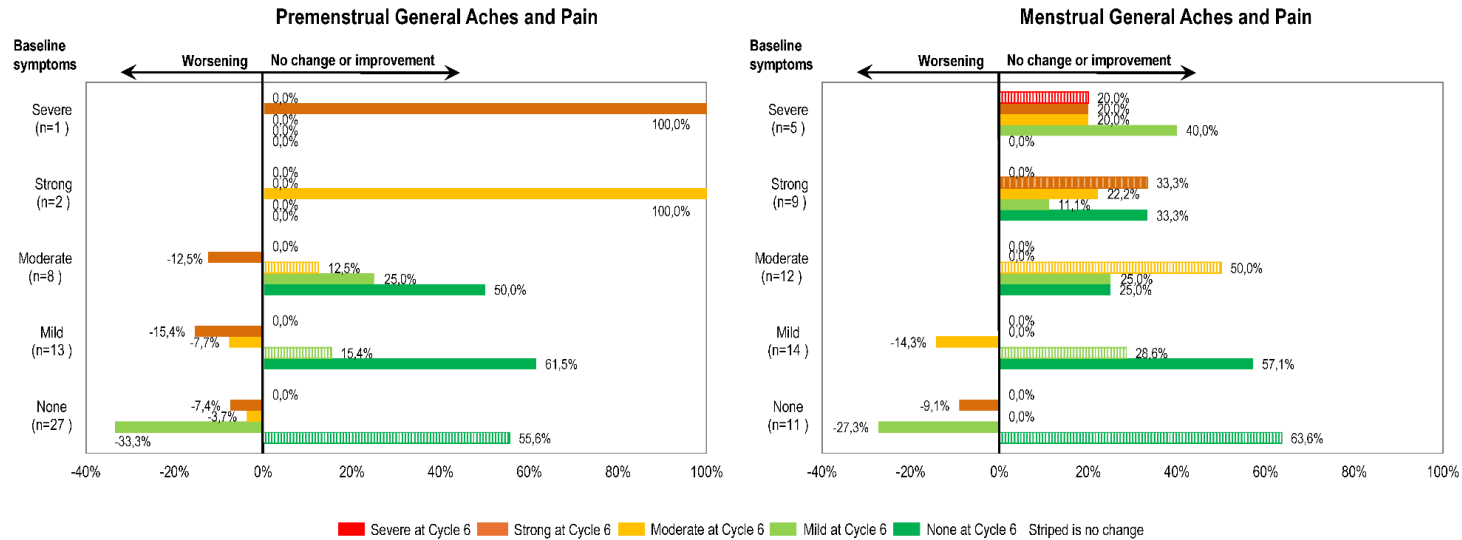
Premenstrual Fatigue:

Severe baseline symptoms (n=1): 0 (0%) worsened, 0 (0%) without change, 1 (100%) improved.
 Strong baseline symptoms (n=4): 0 (0%) worsened, 1 (25.0%) without change, 3 (75.0%) improved.
 Moderate symptoms (n=12): 3 (25.0%) worsened, 3 (25.0%) without change, 6 (50.0%) improved.
 Mild symptoms (n=16): 6 (37.5%) worsened, 7 (43.8%) without change, 3 (18.8%) improved.
 No baseline symptoms (n=18): 10 (55.6%) worsened, 8 (44.4%) without change, (0%) improved.

Menstrual Fatigue:

Severe baseline symptoms (n=2): 0 (0%) worsened, 1 (50.0%) without change, 1 (50.0%) improved.
 Strong baseline symptoms (n=11): 1 (9.1%) worsened, 2 (18.2%) without change, 8 (72.8%) improved.
 Moderate symptoms (n=14): 2 (14.2%) worsened, 5 (35.7%) without change, 7 (50.0%) improved.
 Mild symptoms (n=11): 4 (36.4%) worsened, 5 (45.4%) without change, 2 (18.2%) improved.
 No baseline symptoms (n=13): 7 (53.9%) worsened, 6 (46.2%) without change, (0%) improved.

Figure S4. Percentage of participants shifting to another severity category (improving or worsening) or remaining in the same severity category (stable) at Cycle 6 for premenstrual and menstrual general aches and pains.



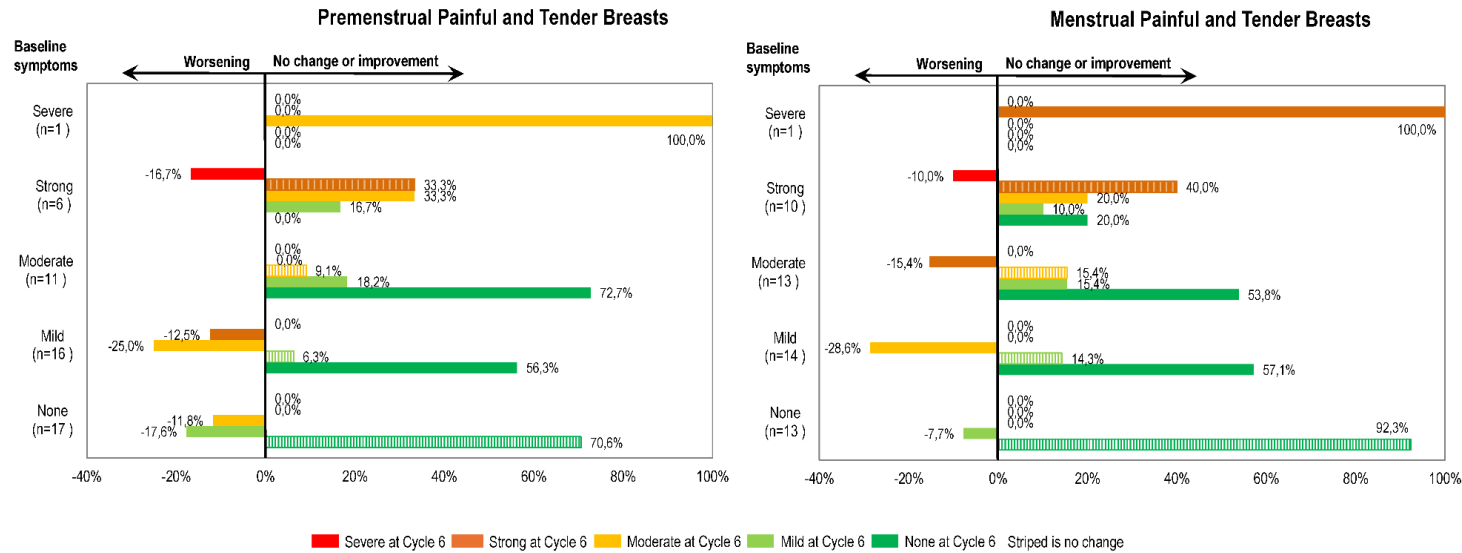
Premenstrual General Aches and Pain:

Severe baseline symptoms (n=1): 0 (0%) worsened, 1 (0%) without change, 1 (100%) improved.
 Strong baseline symptoms (n=2): 0 (0%) worsened, 0 (0%) without change, 2 (100%) improved.
 Moderate symptoms (n=8): 1 (12.5%) worsened, 1 (12.5%) without change, 6 (75.0%) improved.
 Mild symptoms (n=13): 3 (23.1%) worsened, 2 (15.4%) without change, 8 (61.5%) improved.
 No baseline symptoms (n=27): 12 (44.4%) worsened, 15 (55.6%) without change, (0%) improved.

Menstrual General Aches and Pain:

Severe baseline symptoms (n=5): 0 (0%) worsened, 0 (0%) without change, 4 (80.0%) improved.
 Strong baseline symptoms (n=9): 0 (0%) worsened, 3 (33.3%) without change, 6 (66.7%) improved.
 Moderate symptoms (n=12): 0 (0%) worsened, 6 (50.0%) without change, 6 (50.0%) improved.
 Mild symptoms (n=14): 2 (14.3%) worsened, 4 (28.6%) without change, 8 (57.1%) improved.
 No baseline symptoms (n=11): 4 (36.4%) worsened, 7 (63.6%) without change, (0%) improved.

Figure S5. Percentage of participants shifting to another severity category (improving or worsening) or remaining in the same severity category (stable) at Cycle 6 for premenstrual and menstrual painful and tender breasts.



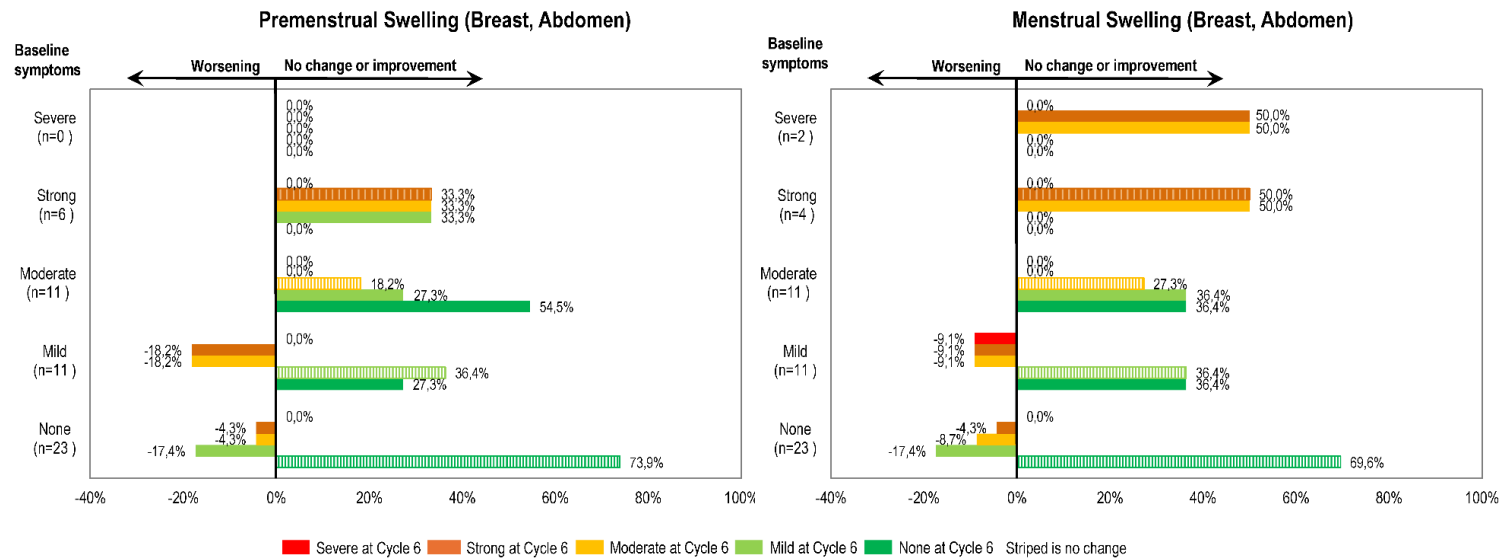
Premenstrual Painful and Tender Breasts:

Severe baseline symptoms (n=1): 0 (0%) worsened, 0 (0%) without change, 1 (100%) improved.
 Strong baseline symptoms (n=6): 1 (16.7%) worsened, 2 (33.3%) without change, 3 (50.0%) improved.
 Moderate symptoms (n=11): 0 (0%) worsened, 1 (9.1%) without change, 10 (90.9%) improved.
 Mild symptoms (n=16): 6 (37.5%) worsened, 1 (6.3%) without change, 9 (56.3%) improved.
 No baseline symptoms (n=17): 5 (29.4%) worsened, 12 (70.6%) without change, (0%) improved.

Menstrual Painful and Tender Breasts:

Severe baseline symptoms (n=1): 0 (0%) worsened, 0 (0%) without change, 1 (100%) improved.
 Strong baseline symptoms (n=10): 1 (10%) worsened, 4 (40.0%) without change, 5 (50.0%) improved.
 Moderate symptoms (n=13): 2 (15.4%) worsened, 2 (15.4%) without change, 9 (69.2%) improved.
 Mild symptoms (n=14): 4 (28.6%) worsened, 2 (14.3%) without change, 8 (57.1%) improved.
 No baseline symptoms (n=13): 1 (7.7%) worsened, 12 (92.3%) without change, (0%) improved.

Figure S6. Percentage of participants shifting to another severity category (improving or worsening) or remaining in the same severity category (stable) at Cycle 6 for premenstrual and menstrual swelling (Breast, abdomen).



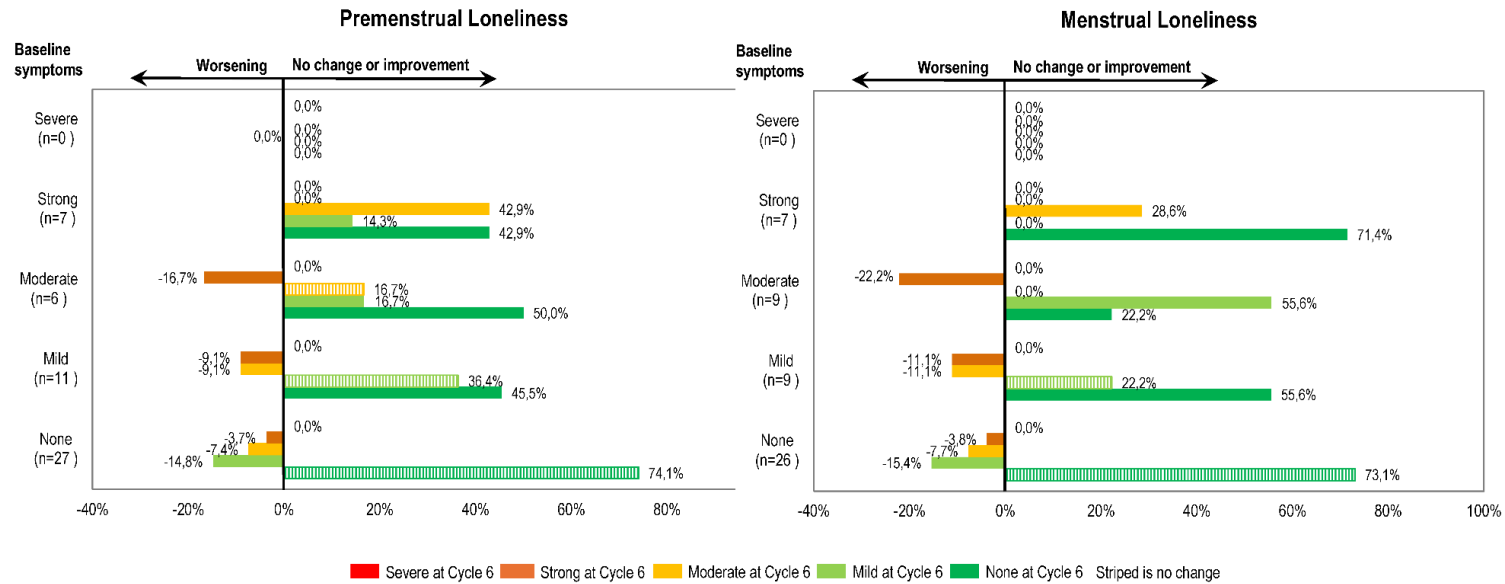
Premenstrual Swelling (Breast, Abdomen):

Severe baseline symptoms (n=0): 0 (0%) worsened, 0 (0%) without change, 0 (0%) improved.
 Strong baseline symptoms (n=6): 0 (0%) worsened, 2 (33.3%) without change, 4 (66.7%) improved.
 Moderate symptoms (n=11): 0 (0%) worsened, 2 (18.18%) without change, 9 (81.82%) improved.
 Mild symptoms (n=11): 4 (36.4%) worsened, 4 (36.4%) without change, 3 (27.3%) improved.
 No baseline symptoms (n=23): 6 (26.1%) worsened, 17 (73.9%) without change, (0%) improved.

Menstrual Swelling (Breast, Abdomen):

Severe baseline symptoms (n=2): 0 (0%) worsened, 0 (0%) without change, 2 (0%) improved.
 Strong baseline symptoms (n=4): 0 (0%) worsened, 2 (50.0%) without change, 2 (50.0%) improved.
 Moderate symptoms (n=11): 0 (0%) worsened, 3 (27.3%) without change, 8 (72.8%) improved.
 Mild symptoms (n=11): 3 (27.3%) worsened, 4 (36.4%) without change, 4 (36.4%) improved.
 No baseline symptoms (n=23): 7 (30.4%) worsened, 16 (69.6%) without change, (0%) improved.

Figure S7. Percentage of participants shifting to another severity category (improving or worsening) or remaining in the same severity category (stable) at Cycle 6 for premenstrual and menstrual loneliness.



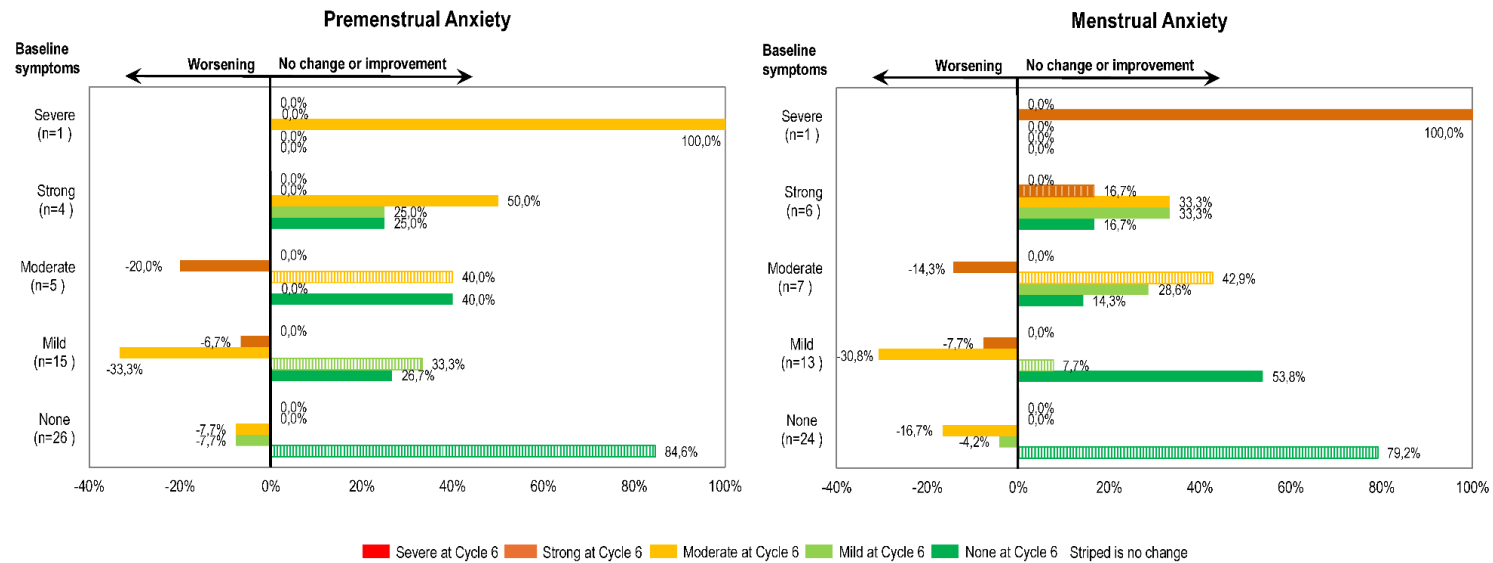
Premenstrual Loneliness:

Severe baseline symptoms (n=0): 0 (0%) worsened, 0 (0%) without change, 0 (0%) improved.
 Strong baseline symptoms (n=7): 0 (0%) worsened, 0 (0%) without change, 7 (100%) improved.
 Moderate symptoms (n=6): 1 (16.7%) worsened, 1 (16.7%) without change, 4 (66.7%) improved.
 Mild symptoms (n=11): 2 (18.2%) worsened, 4 (36.4%) without change, 5 (45.5%) improved.
 No baseline symptoms (n=27): 7 (25.9%) worsened, 20 (74.1%) without change, (0%) improved.

Menstrual Loneliness:

Severe baseline symptoms (n=0): 0 (0%) worsened, 0 (0%) without change, 0 (0%) improved.
 Strong baseline symptoms (n=7): 0 (0%) worsened, 0 (0%) without change, 7 (100%) improved.
 Moderate symptoms (n=9): 2 (22.2%) worsened, 0 (0%) without change, 7 (77.8%) improved.
 Mild symptoms (n=9): 2 (22.2%) worsened, 2 (22.2%) without change, 5 (55.6%) improved.
 No baseline symptoms (n=26): 7 (26.9%) worsened, 19 (73.1%) without change, (0%) improved.

Figure S8. Percentage of participants shifting to another severity category (improving or worsening) or remaining in the same severity category (stable) at Cycle 6 for premenstrual and menstrual anxiety.



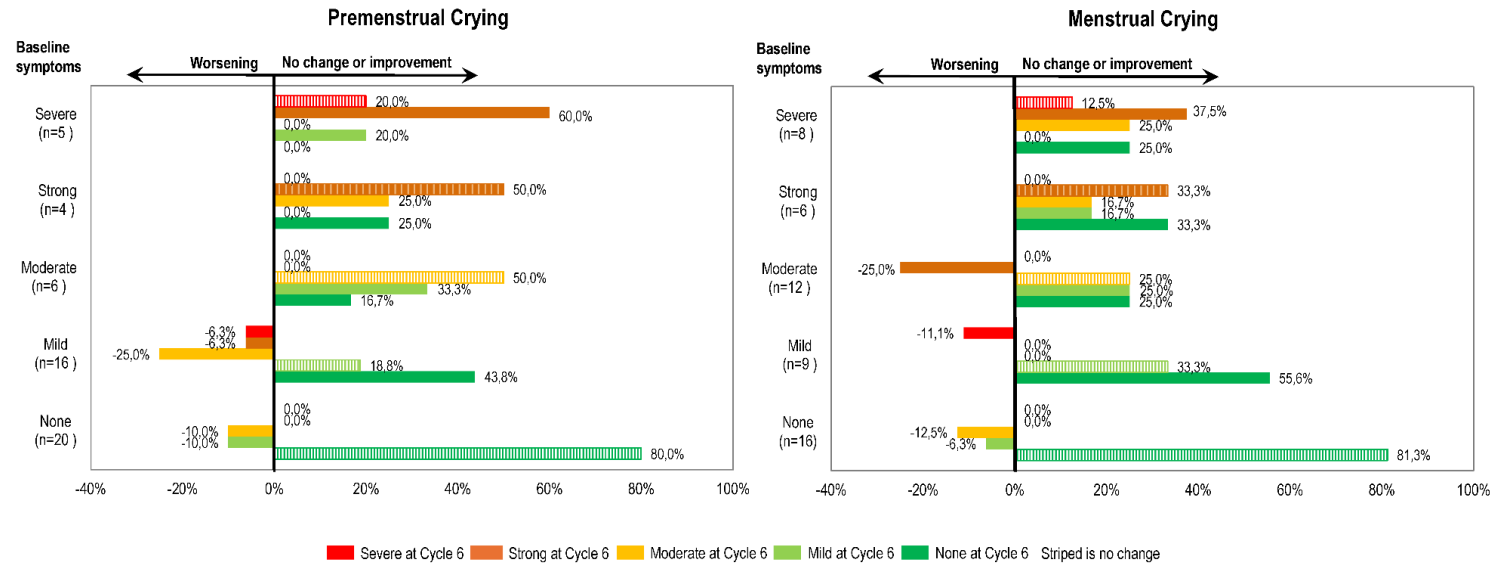
Premenstrual Anxiety:

Severe baseline symptoms (n=1): 0 (0%) worsened, 0 (0%) without change, 1 (100%) improved.
 Strong baseline symptoms (n=4): 0 (0%) worsened, 0 (0%) without change, 4 (100%) improved.
 Moderate symptoms (n=5): 1 (20.0%) worsened, 2 (40.0%) without change, 2 (40.0%) improved.
 Mild symptoms (n=15): 6 (40.0%) worsened, 5 (33.3%) without change, 4 (26.7%) improved.
 No baseline symptoms (n=26): 4 (15.4%) worsened, 22 (84.6%) without change, (0%) improved.

Menstrual Anxiety:

Severe baseline symptoms (n=1): 0 (0%) worsened, 0 (0%) without change, 1 (100%) improved.
 Strong baseline symptoms (n=6): 0 (0%) worsened, 1 (16.7%) without change, 5 (83.3%) improved.
 Moderate symptoms (n=7): 1 (14.3%) worsened, 3 (42.9%) without change, 3 (42.9%) improved.
 Mild symptoms (n=13): 5 (38.5%) worsened, 1 (7.7%) without change, 7 (53.8%) improved.
 No baseline symptoms (n=24): 5 (20.8%) worsened, 19 (79.2%) without change, (0%) improved.

Figure S9. Percentage of participants shifting to another severity category (improving or worsening) or remaining in the same severity category (stable) at Cycle 6 for premenstrual and menstrual crying.



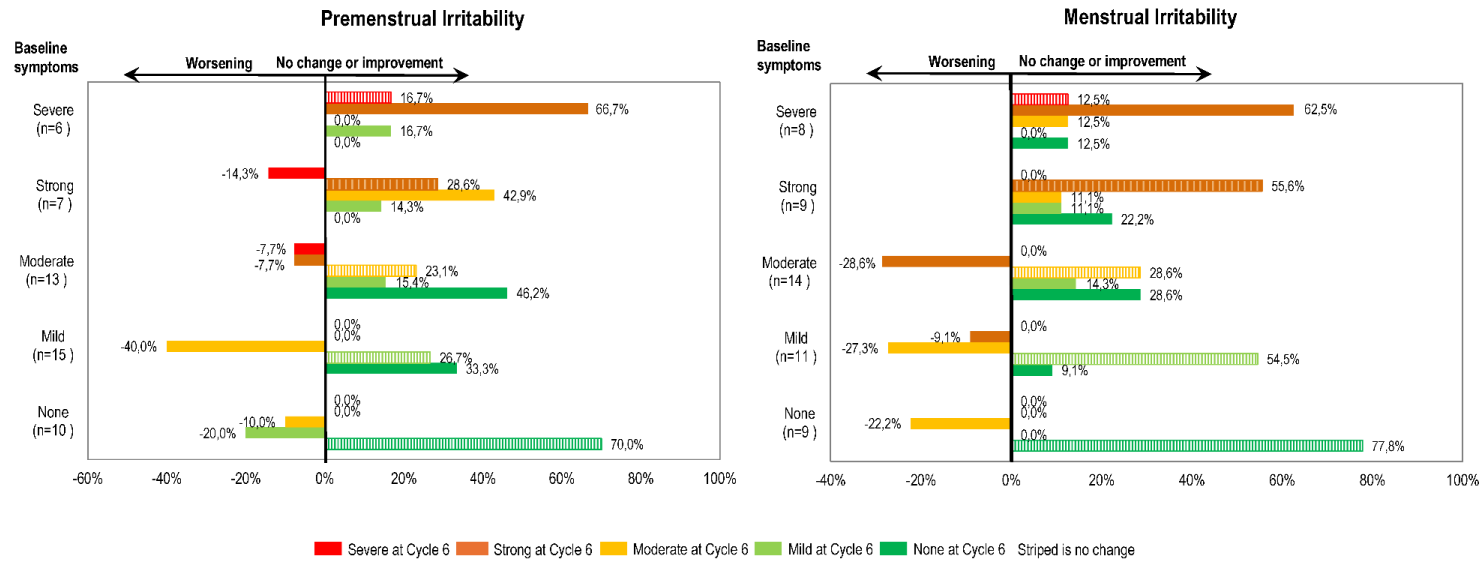
Premenstrual Crying:

Severe baseline symptoms (n=5): 0 (0%) worsened, 1 (20.0%) without change, 4 (80.0%) improved.
 Strong baseline symptoms (n=4): 0 (0%) worsened, 2 (50.0%) without change, 2 (50.0%) improved.
 Moderate symptoms (n=6): 0 (0%) worsened, 3 (50.0%) without change, 3 (50.0%) improved.
 Mild symptoms (n=16): 6 (37.5%) worsened, 3 (18.8%) without change, 7 (43.8%) improved.
 No baseline symptoms (n=20): 4 (20.0%) worsened, 16 (80.0%) without change, (0%) improved.

Menstrual Crying:

Severe baseline symptoms (n=8): 0 (0%) worsened, 1 (12.5%) without change, 7 (87.5%) improved.
 Strong baseline symptoms (n=6): 0 (0%) worsened, 2 (33.3%) without change, 4 (66.7%) improved.
 Moderate symptoms (n=12): 3 (25.0%) worsened, 3 (25.0%) without change, 6 (50.0%) improved.
 Mild symptoms (n=9): 1 (11.1%) worsened, 3 (33.3%) without change, 5 (55.6%) improved.
 No baseline symptoms (n=16): 3 (18.8%) worsened, 13 (81.3%) without change, (0%) improved.

Figure S10. Percentage of participants shifting to another severity category (improving or worsening) or remaining in the same severity category (stable) at Cycle 6 for premenstrual and menstrual irritability.



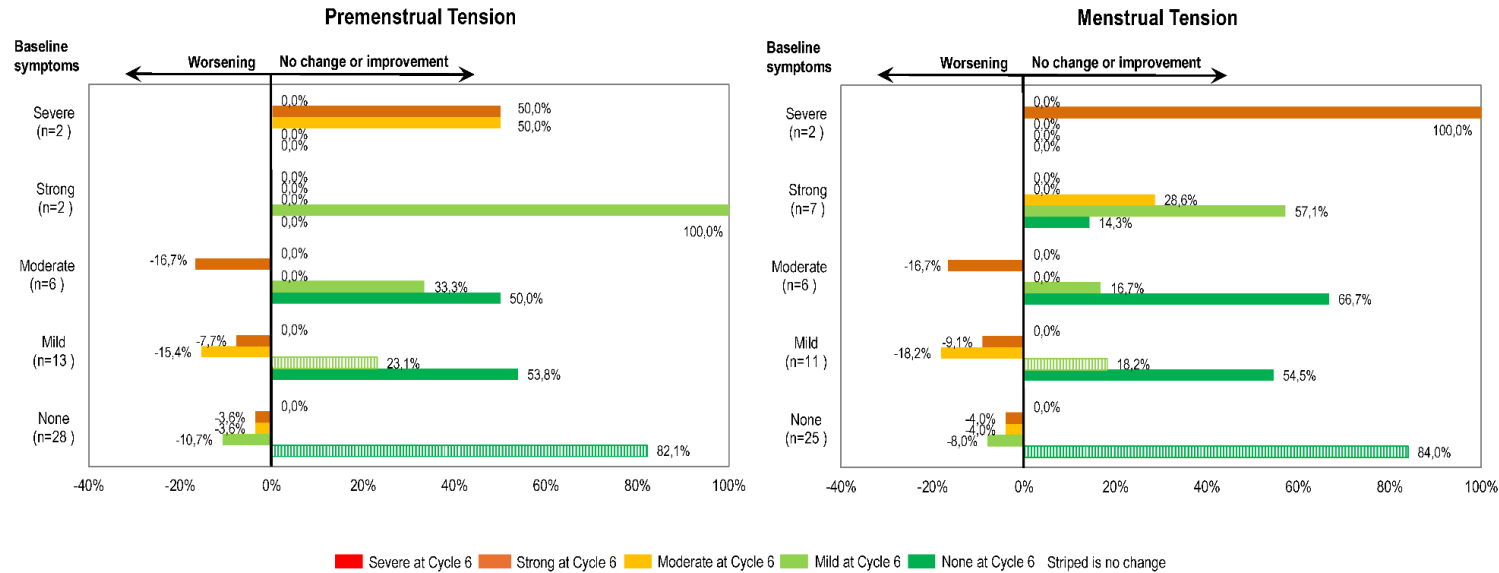
Premenstrual Irritability:

Severe baseline symptoms (n=6): 0 (0%) worsened, 1 (16.7%) without change, 5 (83.3%) improved.
 Strong baseline symptoms (n=7): 1 (14.3%) worsened, 2 (28.6%) without change, 4 (57.1%) improved.
 Moderate symptoms (n=13): 2 (15.4%) worsened, 3 (23.1%) without change, 8 (61.5%) improved.
 Mild symptoms (n=15): 6 (40.0%) worsened, 4 (26.7%) without change, 5 (33.3%) improved.
 No baseline symptoms (n=10): 3 (30.0%) worsened, 7 (70.0%) without change, (0%) improved.

Menstrual Irritability:

Severe baseline symptoms (n=8): 0 (0%) worsened, 1 (12.5%) without change, 7 (87.5%) improved.
 Strong baseline symptoms (n=9): 0 (0%) worsened, 5 (55.6%) without change, 4 (44.4%) improved.
 Moderate symptoms (n=14): 4 (28.6%) worsened, 4 (28.6%) without change, 6 (42.9%) improved.
 Mild symptoms (n=11): 4 (36.4%) worsened, 6 (54.5%) without change, 1 (9.1%) improved.
 No baseline symptoms (n=9): 2 (22.2%) worsened, 7 (77.8%) without change, (0%) improved.

Figure S11. Percentage of participants shifting to another severity category (improving or worsening) or remaining in the same severity category (stable) at Cycle 6 for premenstrual and menstrual tension.



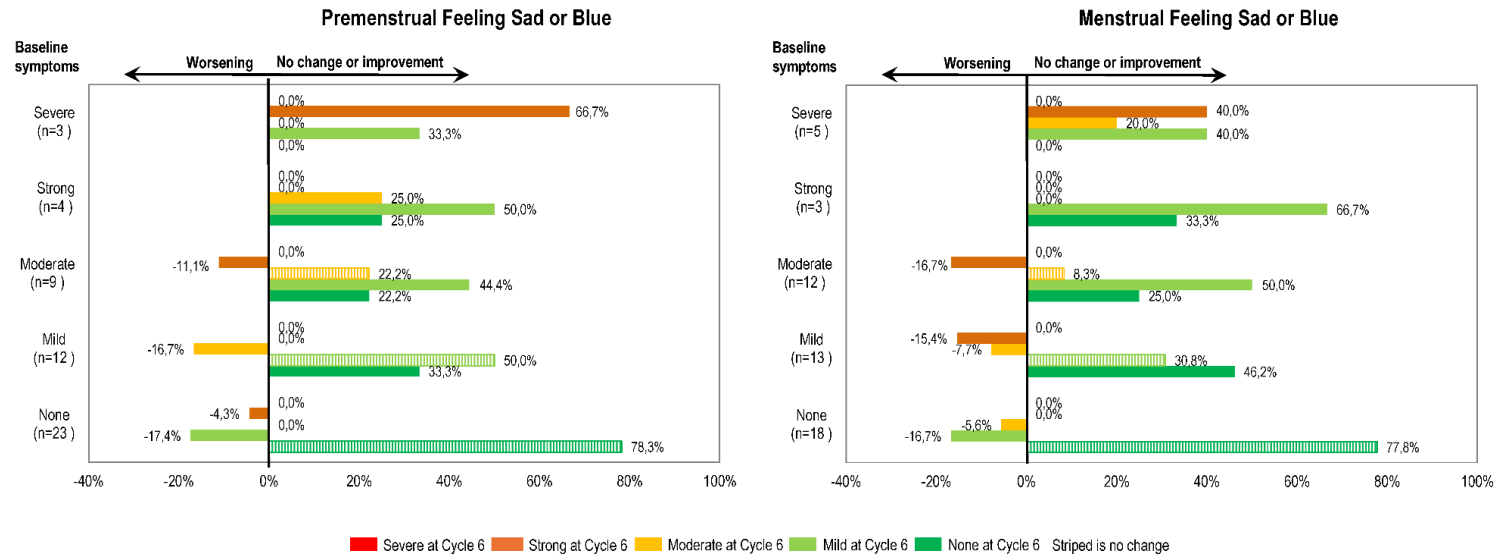
Premenstrual Tension:

Severe baseline symptoms (n=2): 0 (0%) worsened, 0 (0%) without change, 2 (100%) improved.
 Strong baseline symptoms (n=2): 0 (0%) worsened, 0 (0%) without change, 2 (100%) improved.
 Moderate symptoms (n=6): 1 (16.7%) worsened, 0 (0%) without change, 5 (83.3%) improved.
 Mild symptoms (n=13): 3 (23.1%) worsened, 3 (23.1%) without change, 7 (53.8%) improved.
 No baseline symptoms (n=28): 5 (17.9%) worsened, 23 (82.1%) without change, (0%) improved.

Menstrual Tension:

Severe baseline symptoms (n=2): 0 (0%) worsened, 0 (0%) without change, 2 (100%) improved.
 Strong baseline symptoms (n=7): 0 (0%) worsened, 0 (0%) without change, 7 (100%) improved.
 Moderate symptoms (n=6): 1 (16.7%) worsened, 0 (0%) without change, 5 (83.3%) improved.
 Mild symptoms (n=11): 3 (27.3%) worsened, 2 (18.2%) without change, 6 (54.5%) improved.
 No baseline symptoms (n=25): 4 (16.0%) worsened, 21 (84.0%) without change, (0%) improved.

Figure S12. Percentage of participants shifting to another severity category (improving or worsening) or remaining in the same severity category (stable) at Cycle 6 for premenstrual and menstrual feeling sad or blue.



Premenstrual Feeling Sad or Blue:

Severe baseline symptoms (n=3): 0 (0%) worsened, 0 (0%) without change, 3 (100%) improved.
 Strong baseline symptoms (n=4): 0 (0%) worsened, 0 (0%) without change, 4 (100%) improved.
 Moderate symptoms (n=9): 1 (11.1%) worsened, 2 (22.2%) without change, 6 (66.7%) improved.
 Mild symptoms (n=12): 2 (16.7%) worsened, 6 (50.0%) without change, 4 (33.3%) improved.
 No baseline symptoms (n=23): 5 (21.7%) worsened, 18 (78.3%) without change, (0%) improved.

Menstrual Feeling Sad or Blue:

Severe baseline symptoms (n=5): 0 (0%) worsened, 0 (0%) without change, 5 (100%) improved.
 Strong baseline symptoms (n=3): 0 (0%) worsened, 0 (0%) without change, 3 (100%) improved.
 Moderate symptoms (n=12): 2 (16.7%) worsened, 1 (8.3%) without change, 9 (75.0%) improved.
 Mild symptoms (n=13): 3 (23.1%) worsened, 4 (30.8%) without change, 6 (46.2%) improved.
 No baseline symptoms (n=18): 4 (22.2%) worsened, 14 (77.8%) without change, (0%) improved.