

2.1. Efficacy Results and Tabulations of Individual Patient Data

2.1.1. ANALYSIS OF EFFICACY

The efficacy was by means of analysing the results obtained in both, primary and secondary variables.

2.1.2. STATISTICAL/ANALYTICAL ISSUES

a. EPISODES OF WHEEZING ATTACKS

This outcome was the primary variable to assess the efficacy of the treatment. The number of these attacks before the initiation of the treatment was recorded. After the initiation of the treatment (active or placebo), any new episode was recorded, including the duration (number of days). As descriptive statistics, the results were expressed as the mean (with the 95% confidence interval) and the median (with first and third quartile: IQ range) of the number of episodes.

BEFORE THE INITIATION OF TREATMENT

Descriptive statistics

- Active group: The mean was 9.3 (8.2-10.4) and the median 8.0 (7.0-10.0). (Figure 6 and Table 4)
- Placebo group: The mean was 10.3 (8.9-11.6) and the median 9.0 (7.0-11.3). (Figure 6 and Table 4)

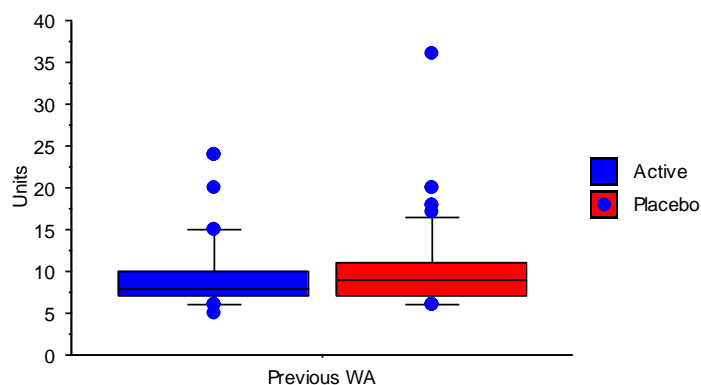


Figure 1: Box-plot of previous WA

Comparative statistics

The differences between both groups of treatment were not significant. Mann Whitney's test *P* value: 0.102, (Table 4).

Hodges-Lehman estimator was -1.0 (-2.0, 0.0)

PREVIOUS MONTHLY WA

Descriptive statistics

- Active group: The mean was 0.8 (0.7-0.9) and the median 0.7 (0.6-0.8). (Figure 7 and Table 4)
- Placebo group: The mean was 0.9 (0.8-1.1) and the median 0.8 (0.6-1.0). (Figure 7 and Table 4)

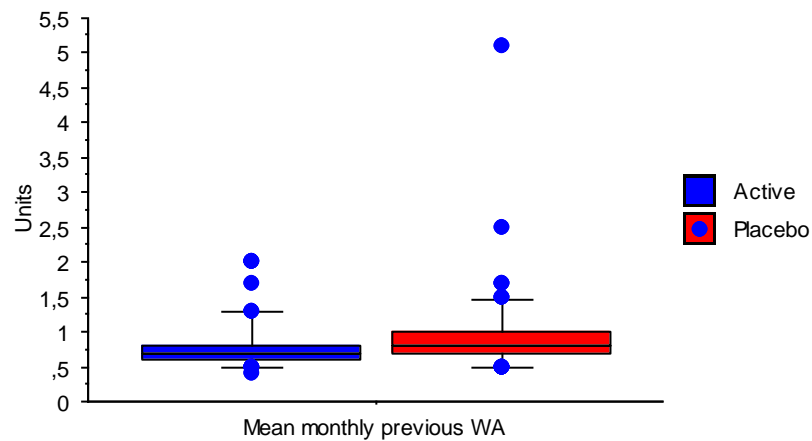


Figure 2: *Box-plot of the mean of monthly previous WA*

Comparative statistics

The differences between both groups of treatment were not significant. Mann Whitney's test P value: 0.053, (Table 4).

Hodges-Lehman estimator was -0.1 (-0.2, 0.0)

AFTER THE INITIATION OF THE TREATMENT TO THE END OF THE TRIAL

Descriptive statistics

- Active group: The mean was 2.8 (2.4-3.3) and the median 3.0 (2.0-4.0). (Figure 8 and Table 4)
- Placebo group: The mean was 5.3 (4.5-6.2) and the median 5.0 (3.0-7.0). (Figure 8 and Table 4)

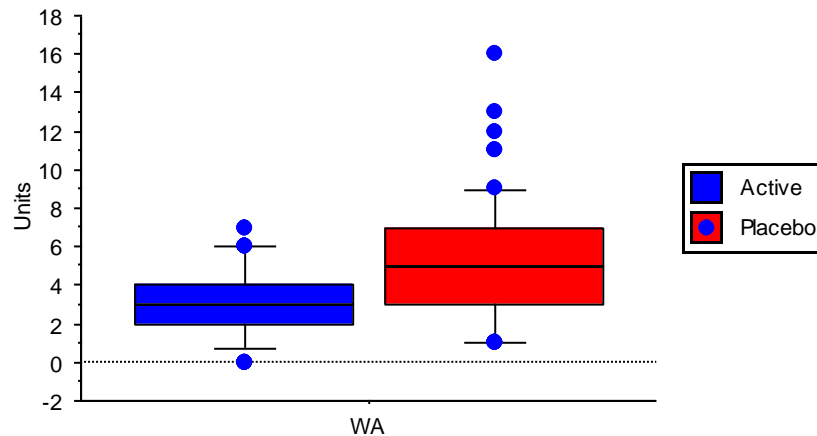


Figure 3: Box-plot of WA

Comparative statistics

The active group had an improvement of 40% over placebo. The differences between both groups of treatment were significant. Mann Whitney's test P value: <0.001 (Table 4).

Hodges-Lehmann estimator was -2.0 (-3.0, -1.0)

DURING THE FIRST MONTH OF THE TREATMENT

Descriptive statistics

- Active group: The mean was 0.5 (0.3-0.7) and the median 0.0 (0.0-1.0). (Figure 9 and Table 4)
- Placebo group: The mean was 0.8 (0.6-1.1) and the median 1.0 (0.0-1.0). (Figure 9 and Table 4)

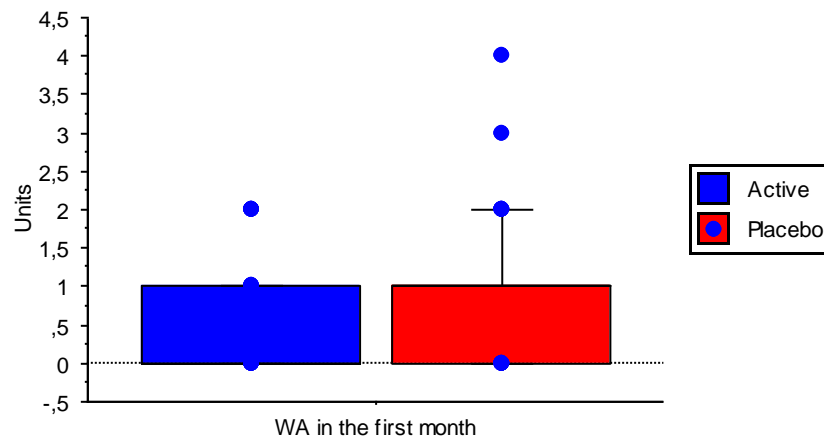


Figure 4: *Box-plot of WA in the first month*

Comparative statistics

The active group had an improvement of 100% over placebo.

The differences between both groups of treatment were not significant. Mann Whitney's test P value: 0.054 (Table 4).

Hodges-Lehmann estimator was 0.0 (0.0, 0.0)

DURING THE SECOND MONTH OF THE TREATMENT

Descriptive statistics

- Active group: The mean was 0.4 (0.2-0.5) and the median 0.0 (0.0-1.0). (Figure 10 and Table 4)
- Placebo group: The mean was 0.6 (0.4-0.7) and the median 0.5 (0.0-1.0). (Figure 10 and Table 4)

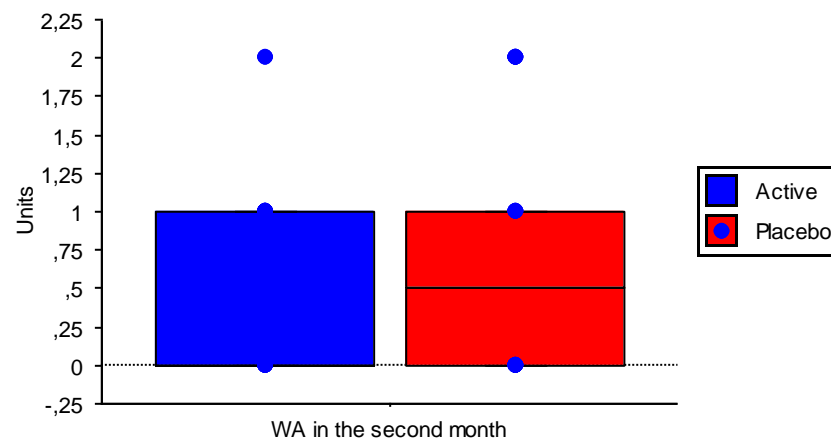


Figure 5: *Box-plot of WA in the second month*

Comparative statistics

The differences between both groups of treatment were not significant. Mann-Whitney's test P value: 0.063 (Table 4).

Hodges-Lehmann estimator was 0.0 (0.0, 0.0)

ACCUMMULATED WA DURING THE FIRST 2 MONTHS OF TREATMENT

Descriptive statistics

- Active group: The mean was 0.9 (0.6-1.1) and the median 1.0 (0.0-1.0). (Figure 11 and Table 4)
- Placebo group: The mean was 1.4 (1.1-1.7) and the median 1.0 (1.0-2.0). (Figure 11 and Table 4)

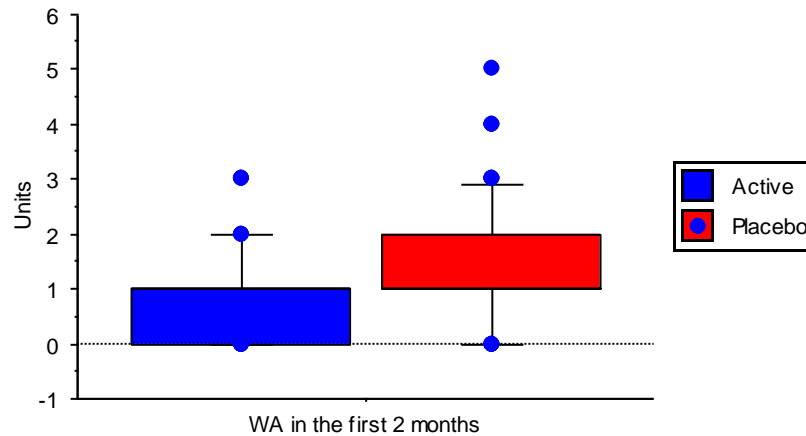


Figure 6: *Box-plot of WA in the second month*

Comparative statistics

The differences between both groups of treatment were significant. Mann Whitney's test P value: 0.007 (Table 4).

Hodges-Lehmann estimator was 0.0 (-1.0, 0.0)

IN THE THIRD MONTH OF THE TREATMENT

Descriptive statistics

- Active group: The mean was 0.3 (0.2-0.5) and the median 0.0 (0.0-1.0). (Figure 12 and Table 4)
- Placebo group: The mean was 0.6 (0.4-0.8) and the median 0.5 (0.0-1.0). (Figure 12 and Table 4)

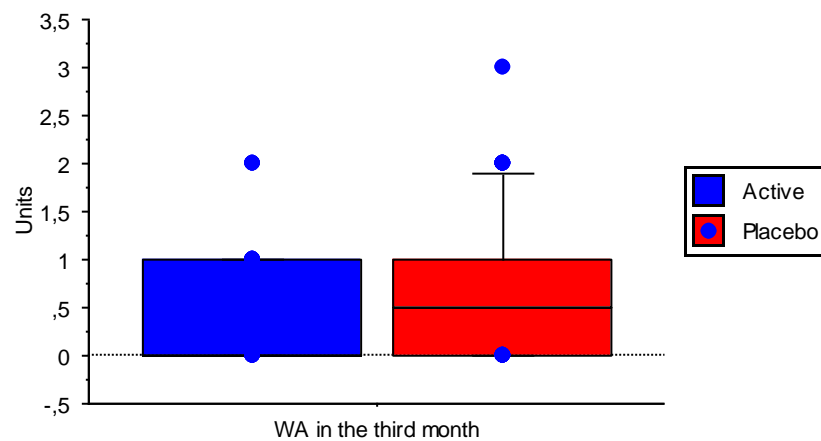


Figure 7: Box-plot of WA in the third month

Comparative statistics

The active group had an improvement of 100% over placebo. The differences between both groups of treatment were significant. Mann Whitney's test P value: 0.022 (Table 4).

Hodges-Lehmann estimator was 0.0 (0.0, 0.0)

ACCUMMULATED WA DURING THE FIRST 3 MONTHS OF TREATMENT

Descriptive statistics

- Active group: The mean was 1.2 (0.9-1.4) and the median 1.0 (0.0-2.0). (Figure 13 and Table 4)
- Placebo group: The mean was 2.0 (1.6-2.4) and the median 2.0 (1.0-3.0). (Figure 13 and Table 4)

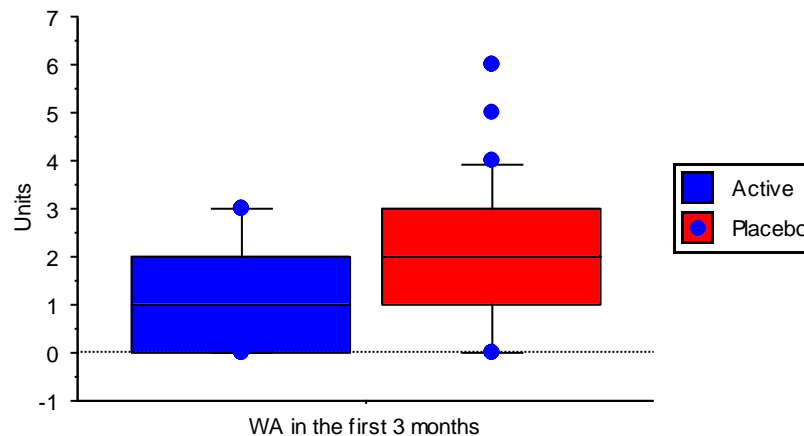


Figure 8: *Box-plot of WA in the first three months*

Comparative statistics

The active group had an improvement of 50% over placebo. The differences between both groups of treatment were significant. Mann Whitney's test P value: 0.002 (Table 4).

Hodges-Lehmann estimator was -1.0 (-1.0, 0.0)

IN THE 4-5-6-MONTHS OF TREATMENT

Descriptive statistics

- Active group: The mean was 0.6 (0.4-0.8) and the median 0.0 (0.0-1.0). (Figure 14 and Table 4)
- Placebo group: The mean was 1.1 (0.8-1.3) and the median 1.0 (0.0-2.0). (Figure 14 and Table 4)

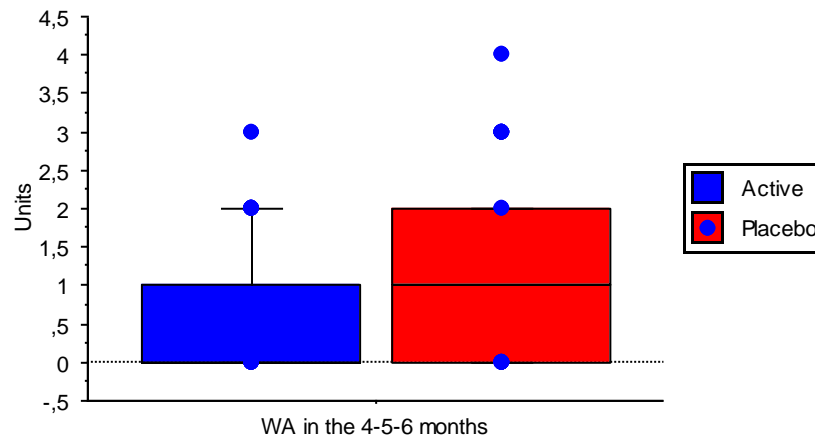


Figure 9: *Box-plot of WA in the 4-5-6 months of treatment*

Comparative statistics

The active group had an improvement of 100% over placebo. The differences between both groups of treatment were significant. Mann Whitney's test P value: 0.018 (Table 4).

Hodges-Lehmann estimator was 0.0 (-1.0, 0.0)

ACCUMMULATED WA IN THE FIRST 6 MONTHS (PERIOD OF TREATMENT)

Descriptive statistics

- Active group: The mean was 1.8 (1.5-2.1) and the median 2.0 (1.0-3.0). (Figure 15 and Table 4)
- Placebo group: The mean was 3.1 (2.6-3.5) and the median 3.0 (2.0-4.0). (Figure 15 and Table 4)

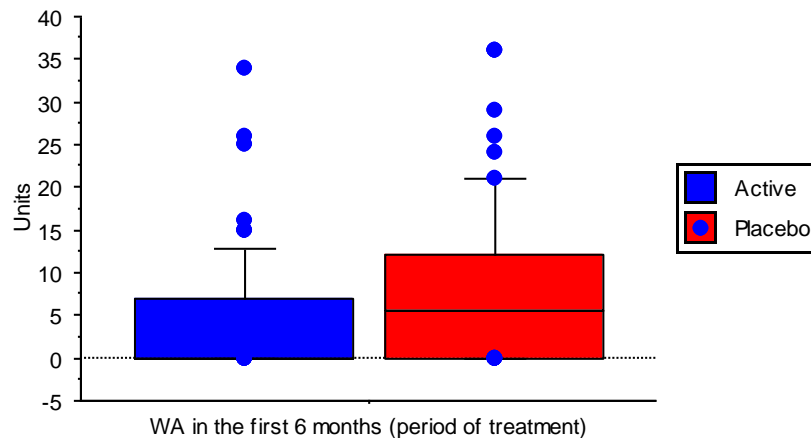


Figure 10: *Box-plot of WA in the first six months of treatment*

Comparative statistics

The active group had an improvement of 33% over placebo. The differences between both groups of treatment were significant. Mann Whitney's test P value: <0.001 (Table 4).

Hodges-Lehmann estimator was -1.0 (-2.0, -1.0)

FROM THE END OF SIXTH MONTH (END OF TREATMENT) TO THE END OF THE TRIAL

Descriptive statistics

- Active group: The mean was 1.0 (0.7-1.4) and the median 1.0 (0.0-2.0). (Figure 16 and Table 4)
- Placebo group: The mean was 2.3 (1.8-2.8) and the median 2.0 (1.0-3.0). (Figure 16 and Table 4)

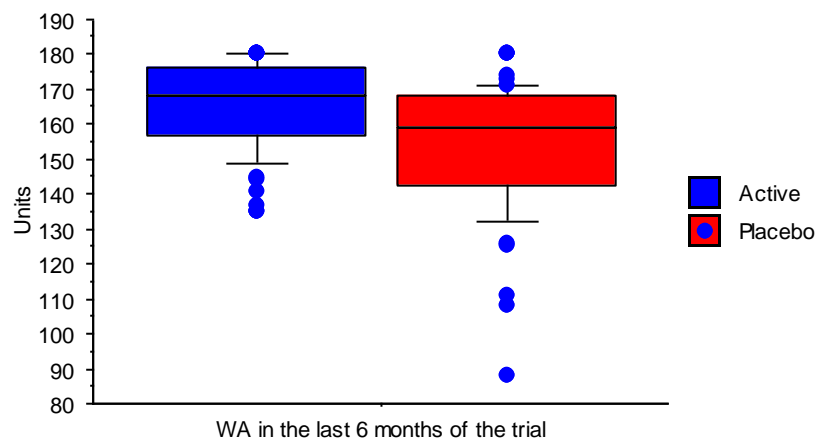
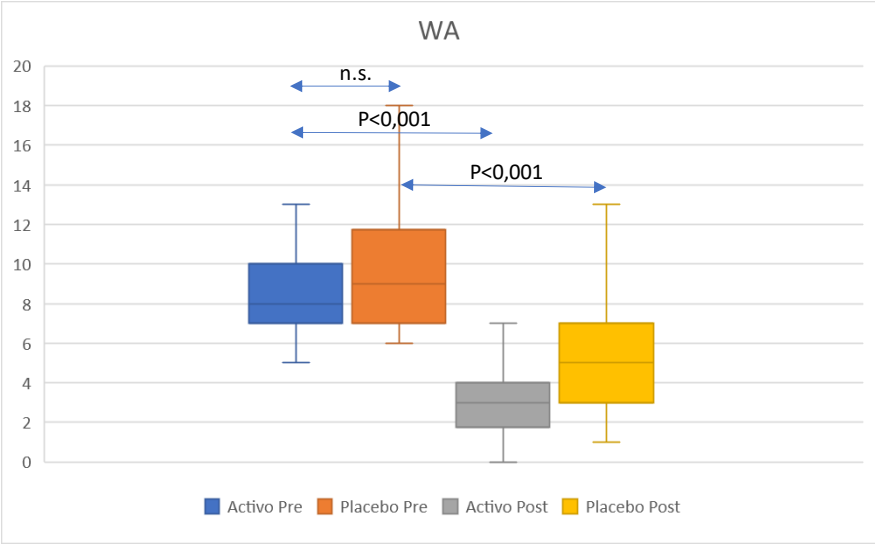


Figure 11: *Box-plot of WA in the last 6 months of the trial*

Comparative statistics

The active group had an improvement of 50% over placebo. The differences between both groups of treatment were significant. Mann Whitney's test P value: <0.001 (Table 4).

Hodges-Lehmann estimator was -1.0 (-2.0, -1.0)



Activo				Placebo			
Pre	Post	% mejoría	P (Wilcoxon)	Pre	Post	% mejoría	P (Wilcoxon)
8 (7-10)	3 (2-4)	63%	<0,0001	9 (7-11)	5 (7-3)	44%	<0,0001

Figure 12: Comparison between groups of the evolutions of WA

b. WHEEZING DAYS

DAYS WITH WA AFTER THE INITIATION OF THE TREATMENT TO THE END OF THE TRIAL

Descriptive statistics

- Active group: The mean was 22.9 (18.0-27.8) and the median 19.0 (8.5-35.5). (Figure 18 and Table 4)
- Placebo group: The mean was 46.1 (37.6-54.5) and the median 42.0 (21.5-59.8). (Figure 18 and Table 4)

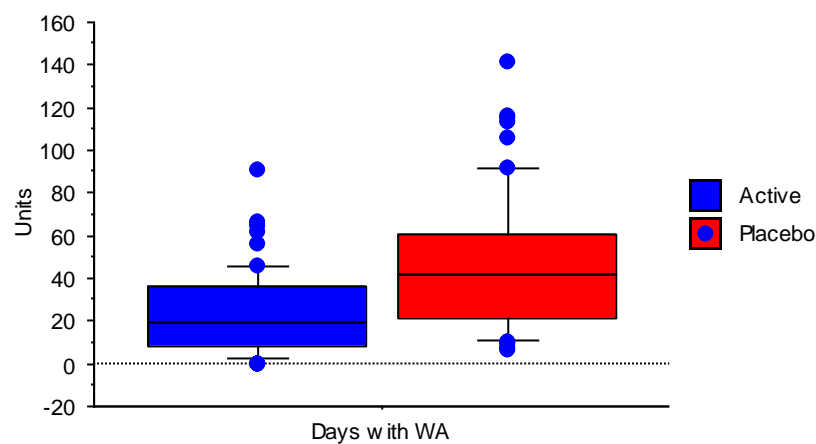


Figure 13: Box-plot of days with WA during the trial

Comparative statistics

The active group had an improvement of 55% over placebo. The differences between both groups of treatment were significant. Mann Whitney's test P value: <0.001 (Table 4).

Hodges-Lehmann estimator was -20.0 (-30.0, -11.0).

DAYS WITH WA IN THE FIRST MONTH OF TREATMENT

Descriptive statistics

- Active group: The mean was 4.4 (2.7-6.1) and the median 0.0 (0.0-7.8). (Figure 19 and Table 4)
- Placebo group: The mean was 6.9 (4.4-9.4) and the median 3.5 (0.0-11.0). (Figure 19 and Table 4)

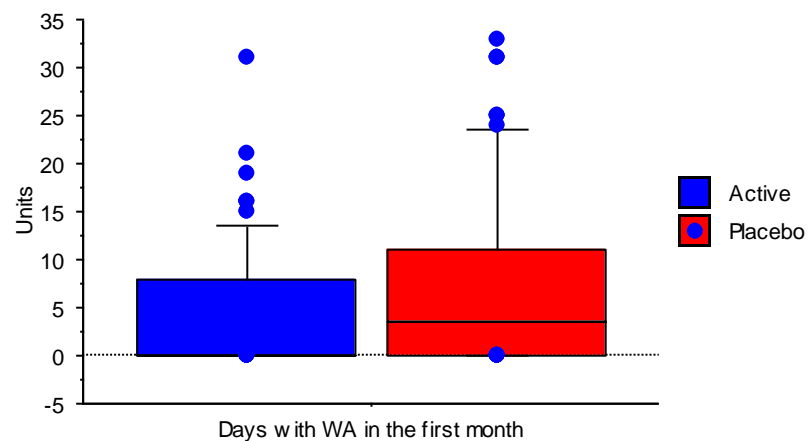


Figure 14: *Box-plot of days with WA in the first month*

Comparative statistics

The active group had an improvement of 100% over placebo. However, the differences between both groups of treatment were not significant. Mann Whitney's test P value: 0.122 (Table 4).

Hodges-Lehmann estimator was 0.0 (-2.0, 0.0)

DAYS WITH WA IN THE SECOND MONTH OF TREATMENT

Descriptive statistics

- Active group: The mean was 3.0 (1.7-4.4) and the median 0.0 (0.0-4.0). (Figure 20 and Table 4)
- Placebo group: The mean was 5.9 (3.8-7.9) and the median 2.0 (0.0-10.0). (Figure 20 and Table 4)

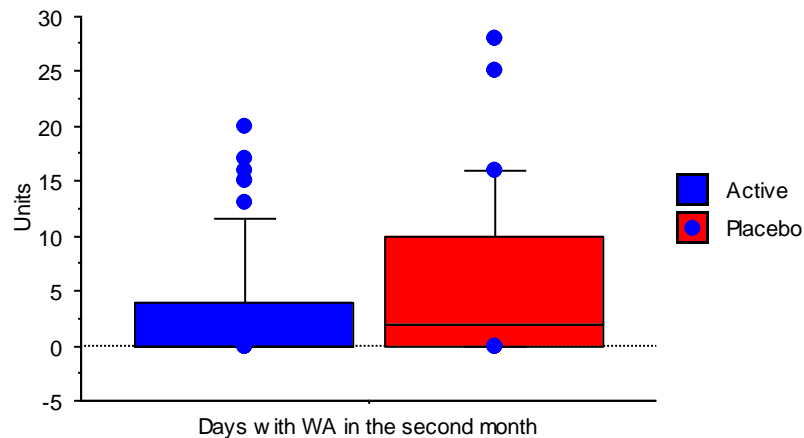


Figure 15: *Box-plot of days with WA in the second month*

Comparative statistics

The active group had an improvement of 100% over placebo. The differences between both groups of treatment were significant. Mann Whitney's test P value: 0.031 (Table 4).

Hodges-Lehmann estimator was 0.0 (-2.0, 0.0)

DAYS WITH WA IN THE THIRD MONTH OF TREATMENT

Descriptive statistics

- Active group: The mean was 2.3 (1.3-3.4) and the median 0.0 (0.0-3.0). (Figure 21 and Table 4)
- Placebo group: The mean was 4.9 (3.3-6.6) and the median 1.5 (0.0-7.3). (Figure 21 and Table 4)

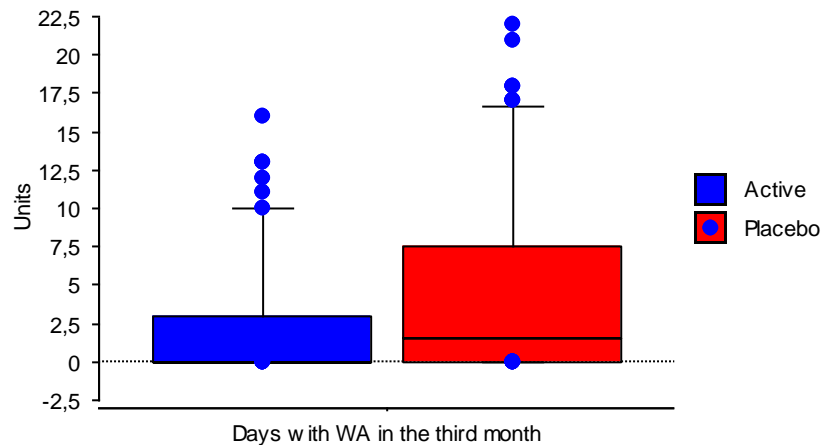


Figure 16: *Box-plot of days with WA in the third month*

Comparative statistics

The active group had an improvement of 100% over placebo. The differences between both groups of treatment were significant. Mann Whitney's test P value: 0.019 (Table 4).

Hodges-Lehmann estimator was 0.0 (-3.0, 0.0)

DAYS WITH WA IN THE 4-5-6 MONTHS OF TREATMENT

Descriptive statistics

- Active group: The mean was 4.5 (2.7-6.3) and the median 0.0 (0.0-6.8). (Figure 22 and Table 4)
- Placebo group: The mean was 7.9 (5.4-10.5) and the median 5.5 (0.0-12.0). (Figure 22 and Table 4)

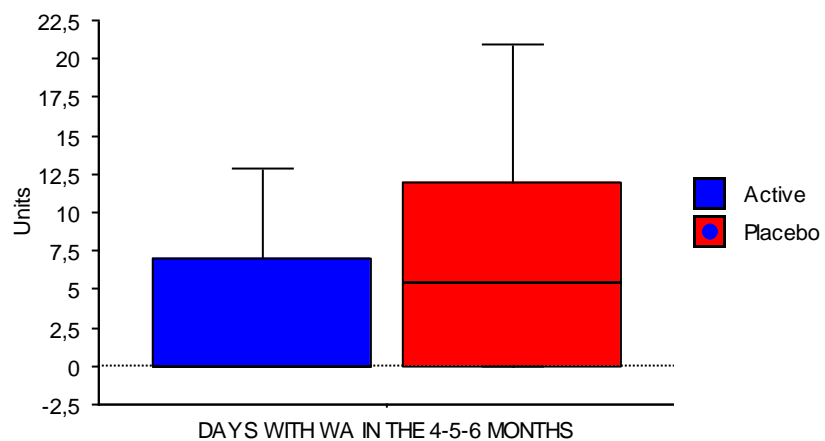


Figure 17: *Box-plot of days with WA in the 4-5-6 months*

Comparative statistics

The active group had an improvement of 100% over placebo. The differences between both groups of treatment were significant. Mann Whitney's test P value: 0.034 (Table 4).

Hodges-Lehmann estimator was 0.0 (-5.0, 0.0)

DAYS WITH WA FROM THE END OF TREATMENT TO THE END OF THE TRIAL

Descriptive statistics

- Active group: The mean was 8.6 (5.5-11.8) and the median 4.0 (0.0-11.8). (Figure 23 and Table 4)
- Placebo group: The mean was 20.4 (15.2-25.5) and the median 19.0 (5.8-30.3). (Figure 23 and Table 4)

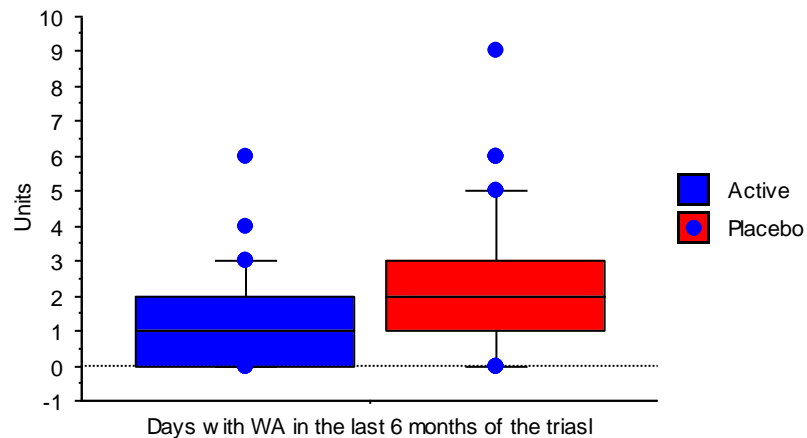


Figure 18: *Box-plot of days with WA in the last 6 months of the trial*

Comparative statistics

The active group had an improvement of 79% over placebo. The differences between both groups of treatment were significant. Mann Whitney's test P value: <0.001 (Table 4).

Hodges-Lehmann estimator was -10.0 (-15.0, -5.0)

**c. AVERAGE OF DAYS OF DURATION OF EACH WHEEZING ATTACK
AFTER THE INITIATION OF THE TREATMENT TO THE END OF THE TRIAL**

Descriptive statistics

- Active group: The mean was 7.1 (5.8-8.5) and the median 6.0 (4.0-9.5). (Figure 24 and Table 4)
- Placebo group: The mean was 8.9 (7.9-9.8) and the median 7.9 (6.2-11.0). (Figure 24 and Table 4)

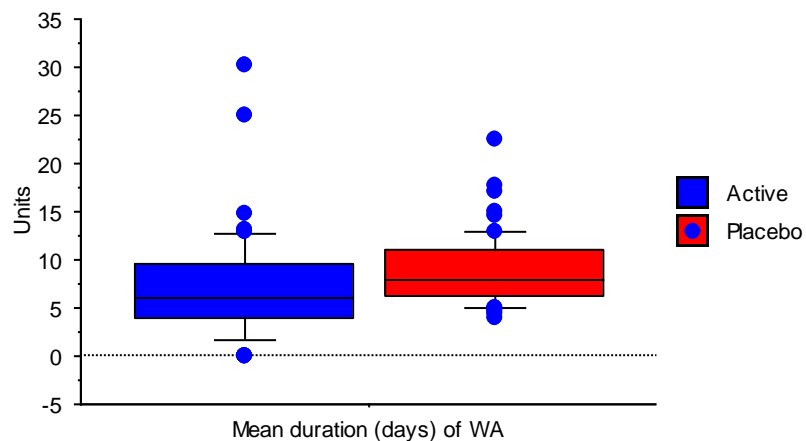


Figure 19: Box-plot of the mean duration (days) of the WA

Comparative statistics

The active group had an improvement of 24% over placebo. The differences between both groups of treatment were significant. Mann Whitney's test P value: 0.005 (Table 4).

Hodges-Lehmann estimator was -2.0 (-3.3, -0.6)

**d. DAYS FREE OF WA UNTIL THE FIRST EPISODE OF WA
AFTER THE INITIATION OF THE TREATMENT**

Descriptive statistics

It was considered 365 (one year) as the maximum possible value.

- Active group: The mean was 83.2 (56.1-110.2) and the median 41.0 (15.0-94.5). (Figure 25 and Table 4)
- Placebo group: The mean was 22.5 (11.7-33.3) and the median 5.0 (2.0-29.8). (Figure 25 and Table 4)

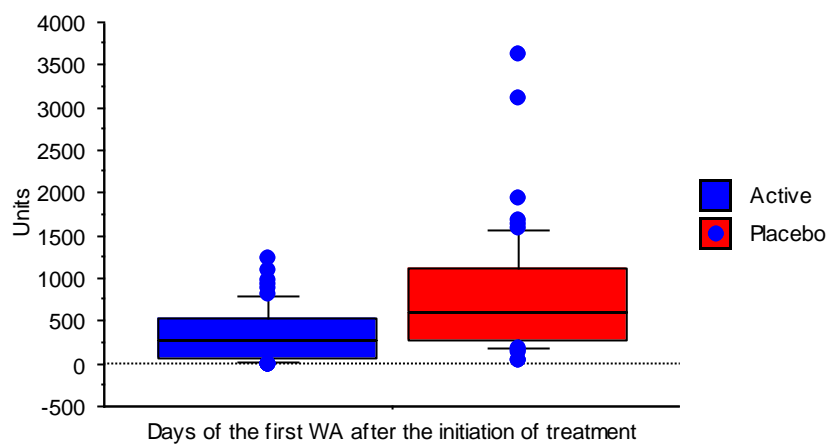


Figure 20: Box-plot of days free of WA until the first episode of WA

Comparative statistics

Active group had an improvement of 88% over placebo.

The differences between both groups of treatment were significant.
Mann Whitney's test P value: <0.001 (Table 4)

Hodges-Lehmann estimator was 27.0 (14.0, 43.0)

The Kaplan-Meier analysis showed that difference between both groups was significant (Wilcoxon P value <0.0001).

Test of equality of the survival distribution functions (DF = 1):

Statistic	Observed value	Critical value	p-value	alpha
Log-rank	13.019	3.841	0.000	0.050
Wilcoxon	26.830	3.841	< 0.0001	0.050
Tarone-Ware	21.140	3.841	< 0.0001	0.050

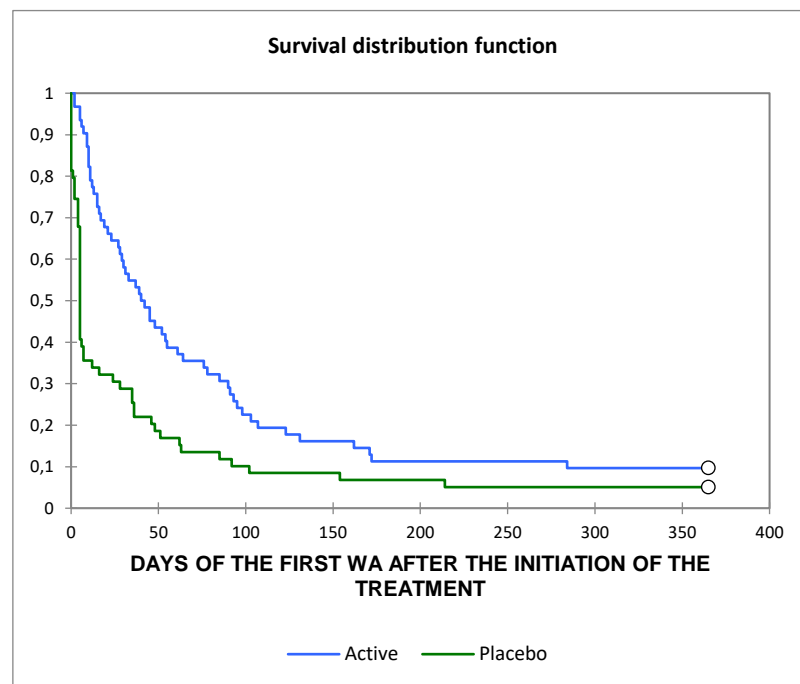


Figure 21: Days of the first WA after the initiation of the treatment

AFTER 1 MONTH OF THE TREATMENT

Descriptive statistics

It was considered 335 days as the maximum possible value.

- Active group: The mean was 95.9 (68.1-123.6) and the median 56.5 (21.3-106.3). (Figure 27 and Table 4)
- Placebo group: The mean was 48.3 (31.9-64.7) and the median 30.0 (11.8-54.3). (Figure 27 and Table 4)

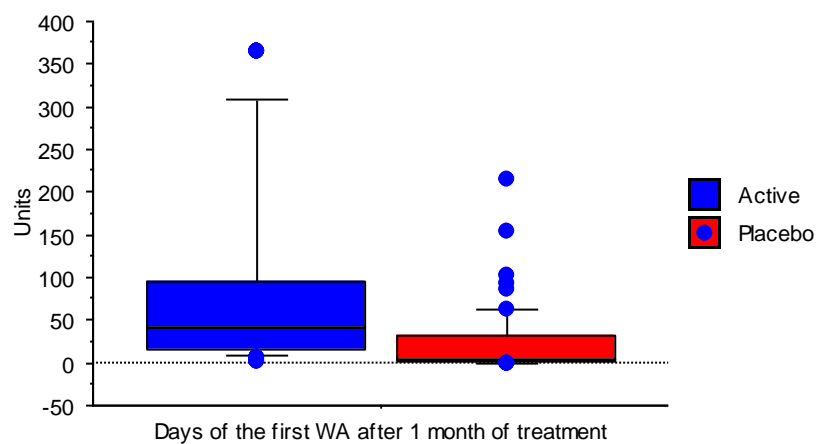


Figure 22: Box-plot of days of the first WA after 1 month of treatment

Comparative statistics

Active group had an improvement of 47% over placebo.

The differences between both groups of treatment were significant. Mann Whitney's test P value: 0.004 (Table 4).

Hodges-Lehmann estimator was 20.0 (6.0, 40.0)

The Kaplan-Meier analysis showed that difference between both groups was significant (Wilcoxon P value 0.017).

Test of equality of the survival distribution functions (DF = 1):

Statistic	Observed value	Critical value	p-value	alpha
Log-rank	5.021	3.841	0.025	0.050
Wilcoxon	5.716	3.841	0.017	0.050
Tarone-Ware	5.545	3.841	0.019	0.050

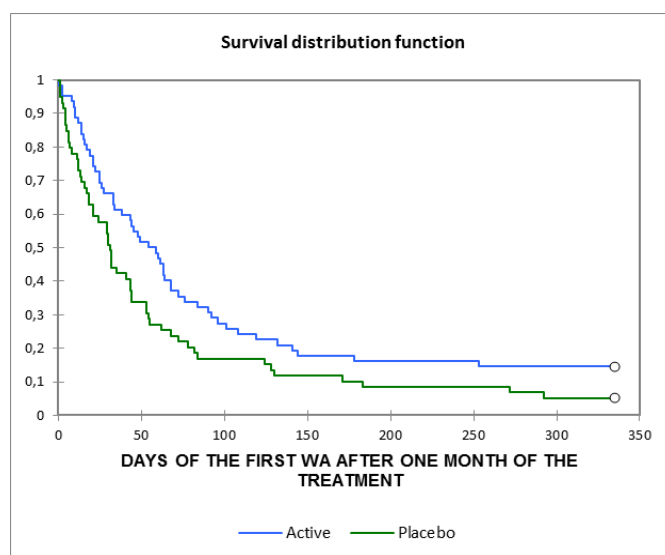


Figure 23: *Days of the first WA after one month of the treatment*

AFTER 2 MONTHS OF THE TREATMENT

Descriptive statistics

It was considered 305 days as the maximum possible value.

- Active group: The mean was 105.5 (77.2-133.7) and the median 60.5 (25.0-120.0). (Figure 29 and Table 4)
- Placebo group: The mean was 65.8 (42.3-89.3) and the median 27.0 (11.8-83.3). (Figure 29 and Table 4)

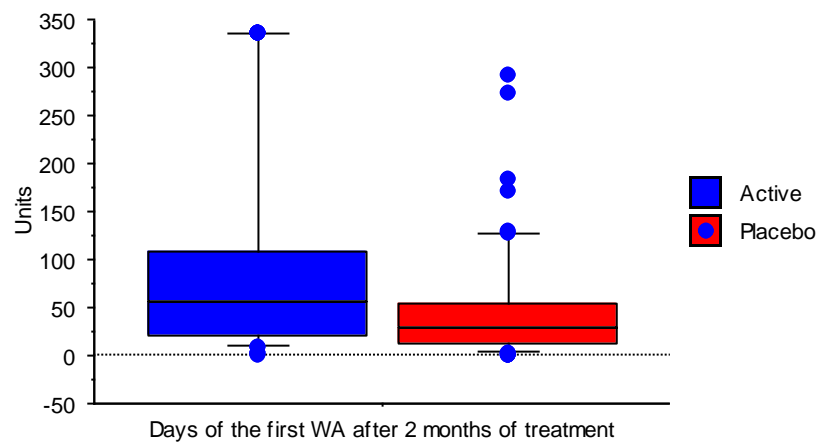


Figure 24: *Box-plot of days of the first WA after 2 months of treatment*

Comparative statistics

Active group had an improvement of 55% over placebo.

The differences between both groups of treatment were significant. Mann Whitney's test P value: 0.011 (Table 4).

Hodges-Lehmann estimator was 19.0 (3.0, 42.0)

The Kaplan-Meier analysis showed that difference between both groups was significant (Wilcoxon P value 0.038).

Test of equality of the survival distribution functions (DF = 1):

Statistic	Observed value	Critical value	p-value	alpha
Log-rank	3.075	3.841	0.079	0.050
Wilcoxon	4.318	3.841	0.038	0.050
Tarone-Ware	3.773	3.841	0.052	0.050

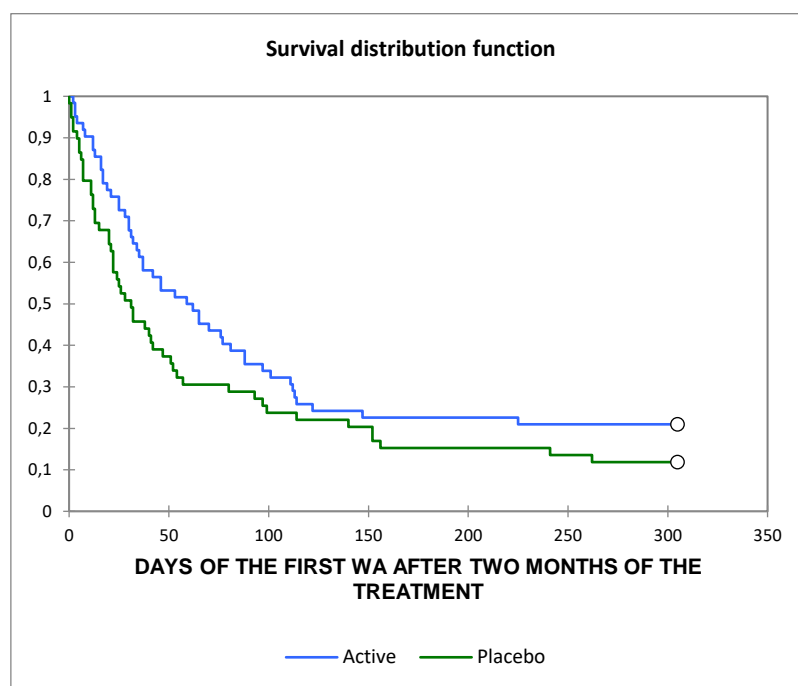


Figure 25: Days of the first WA after two months of the treatment

AFTER 3 MONTHS OF THE TREATMENT

Descriptive statistics

It was considered 275 days as the maximum possible value.

- Active group: The mean was 108.1 (80.2-136.1) and the median 57.0 (18.0-275.0). (Figure 31 and Table 4)
- Placebo group: The mean was 74.3 (50.8-97.8) and the median 30.5 (13.5-112.0). (Figure 31 and Table 4)

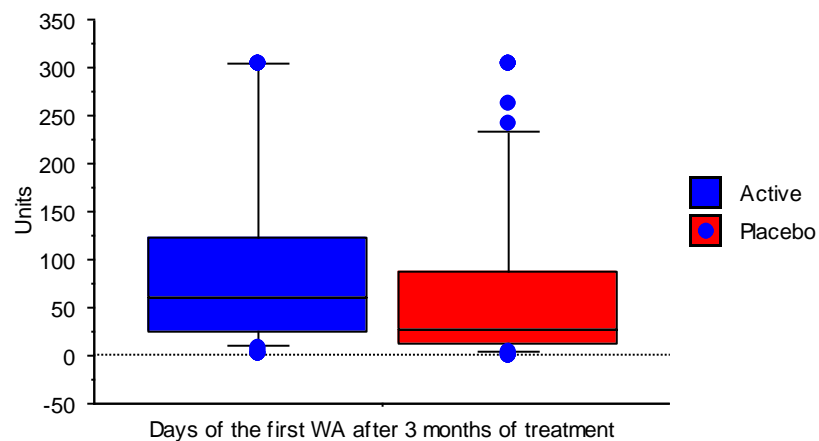


Figure 26: *Box-plot of days of the first WA after 3 months of treatment*

Comparative statistics

Active group had an improvement of 46% over placebo.

The differences between both groups of treatment were significant. Mann Whitney's test P value: 0.087 (Table 4).

Hodges-Lehmann estimator was 14.0 (0.0, 40.0)

The Kaplan-Meier analysis showed that difference between both groups was not significant (Wilcoxon P value 0.193).

Test of equality of the survival distribution functions (DF = 1):

Statistic	Observed value	Critical value	p-value	alpha
Log-rank	2.477	3.841	0.116	0.050
Wilcoxon	1.693	3.841	0.193	0.050
Tarone-Ware	2.027	3.841	0.154	0.050

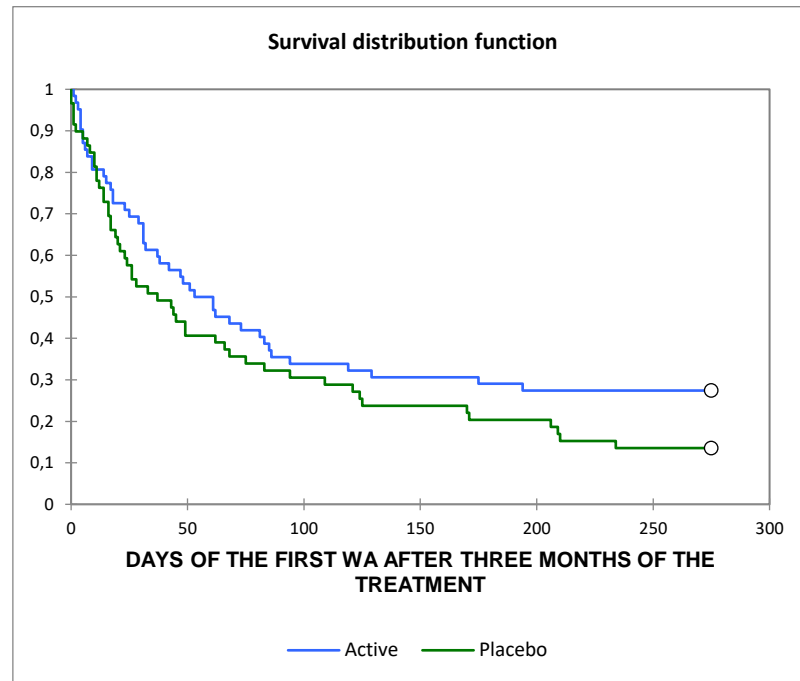


Figure 27: *Days of the first WA after three months of the treatment*

AFTER THE END (6 MONTHS) OF THE TREATMENT

Descriptive statistics

It was considered 180 (half year) as the maximum possible value.

- Active group: The mean was 120.8 (103.3-138.2) and the median 180.0 (48.5-180.0). (Figure 34 and Table 4)
- Placebo group: The mean was 76.9 (59.3-94.6) and the median 44.5 (20.0-121.5). (Figure 34 and Table 4)

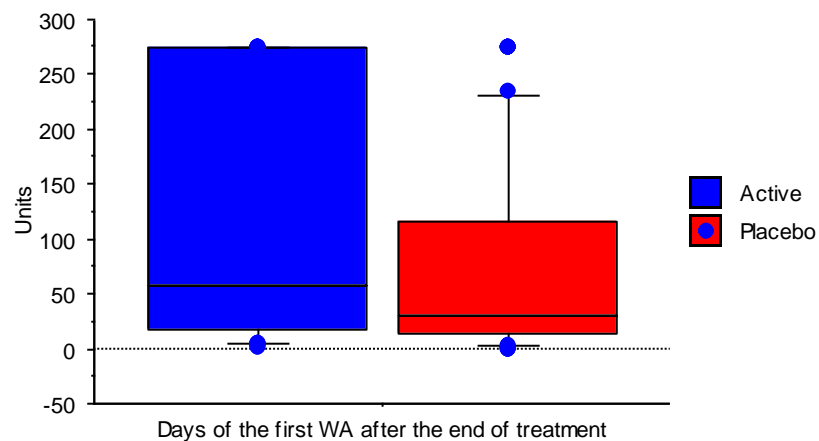


Figure 28: *Box-plot of days of the first WA after the end of the treatment*

Comparative statistics

Active group had an improvement of 75% over placebo. The differences between both groups of treatment were significant. Mann Whitney's test P value: <0.001 (Table 4).

Hodges-Lehmann estimator was 41.0 (6.0, 66.0)

The Kaplan-Meier analysis showed that difference between both groups was significant (Wilcoxon P value 0.001).

Test of equality of the survival distribution functions (DF = 1):

Statistic	Observed value	Critical value	p-value	alpha
Log-rank	11.203	3.841	0.001	0.050
Wilcoxon	10.665	3.841	0.001	0.050
Tarone-Ware	10.980	3.841	0.001	0.050

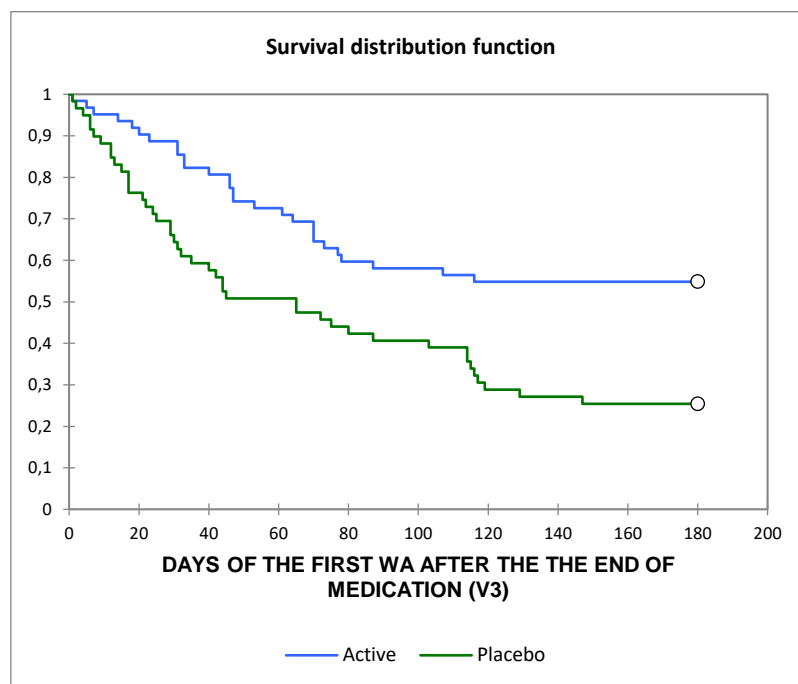


Figure 29: *Days of the first WA after the end of medication*

e. DAYS FREE OF WA

TOTAL DAYS FREE OF WA

Descriptive statistics

- Active group: The mean was 337.1 (332.2-342.0) and the median 341.0 (324.5-351.5). (Figure 35 and Table 4)
- Placebo group: The mean was 313.9 (305.5-322.4) and the median 318.0 (300.3-338.5). (Figure 35 and Table 4)

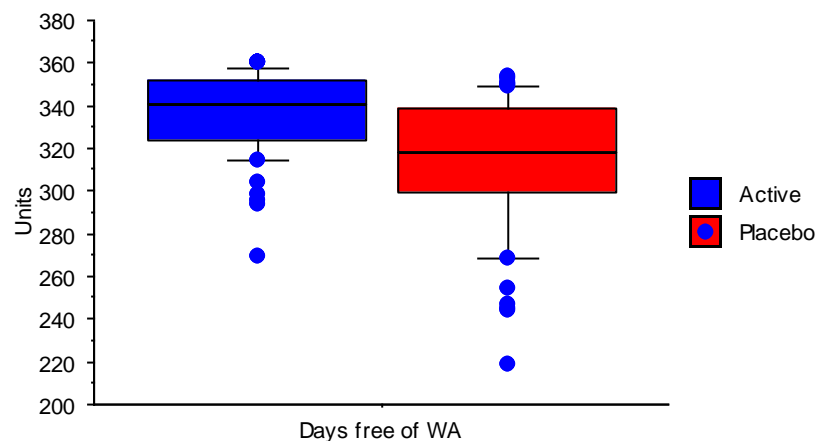


Figure 30: Box-plot of days free of WA

Comparative statistics

Active group had an improvement of 7% over placebo.

The differences between both groups of treatment were significant.
Mann Whitney's test P value: <0.001 (Table 4).

Hodges-Lehmann estimator was 20.0 (11.0, 30.0)

DAYS WITHOUT WA IN THE FIRST MONTH

Descriptive statistics

- Active group: The mean was 25.6 (24.0-27.3) and the median 30.0 (30.0-22.3). (Figure 36 and Table 4)
- Placebo group: The mean was 23.2 (20.7-25.6) and the median 26.5 (19.0-30.0). (Figure 36 and Table 4)

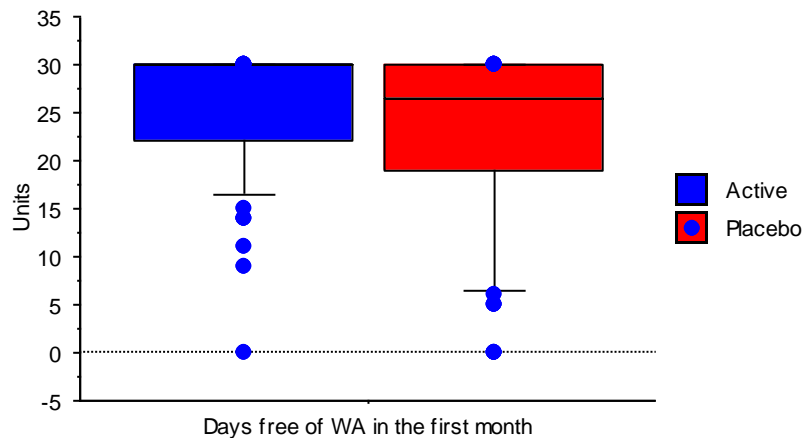


Figure 31: *Box-plot of days free of WA in the first month*

Comparative statistics

Active group had an improvement of 12% over placebo.

The differences between both groups of treatment were not significant.

Mann Whitney's test P value: 0.122 (Table 4).

Hodges-Lehmann estimator was 0.0 (0.0, 3.0)

DAYS WITHOUT WA IN THE FIRST TWO MONTHS

Descriptive statistics

- Active group: The mean was 52.6 (50.5-54.7) and the median 56.0 (47.3-60.0). (Figure 37 and Table 4)
- Placebo group: The mean was 47.2 (43.8-50.6) and the median 50.0 (40.0-58.0). (Figure 37 and Table 4)

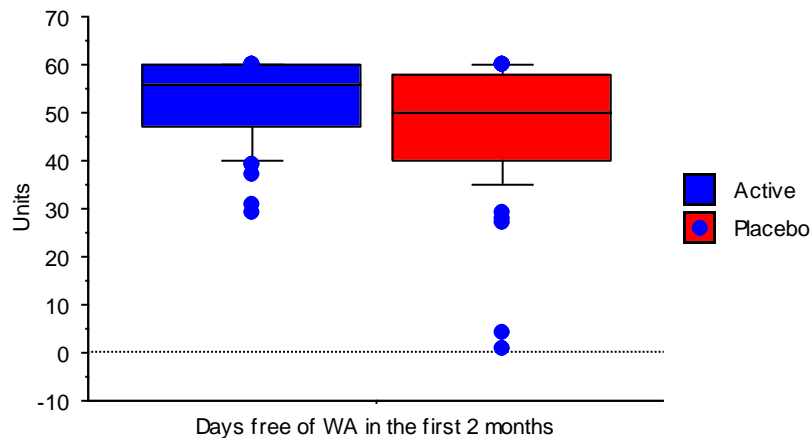


Figure 32: *Box-plot of days free of WA in the first 2 months*

Comparative statistics

Active group had an improvement of 11% over placebo.

The differences between both groups of treatment were significant.
Mann Whitney's test P value: 0.013 (Table 4).

Hodges-Lehmann estimator was 4.0 (0.0, 8.0)

DAYS WITHOUT WA IN THE FIRST THREE MONTH

Descriptive statistics

- Active group: The mean was 80.3 (77.8-82.8) and the median 82.5 (74.0-90.0). (Figure 38 and Table 4)
- Placebo group: The mean was 72.3 (68.2-76.3) and the median 74.5 (65.0-82.3). (Figure 38 and Table 4)

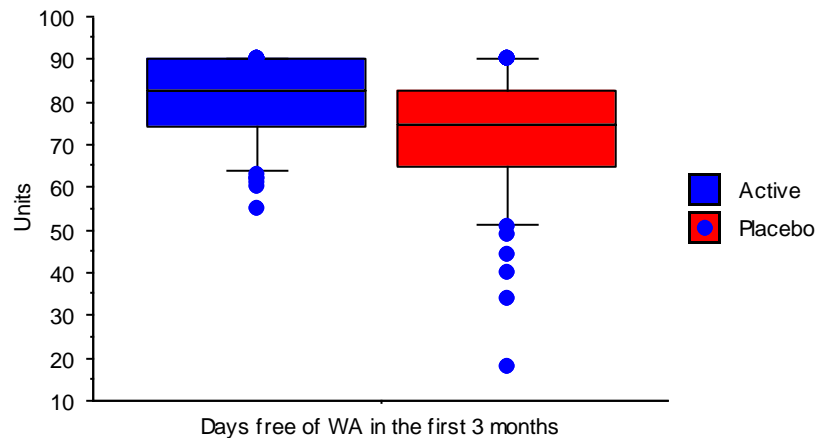


Figure 33: *Box-plot of days free of WA in the first 3 months*

Comparative statistics

Active group had an improvement of 10% over placebo.

The differences between both groups of treatment were significant. Mann Whitney's test P value 0.002 (Table 4).

Hodges-Lehmann estimator was 7.0 (2.0, 10.0)

DAYS WITHOUT WA IN THE FIRST SIX MONTH

Descriptive statistics

- Active group: The mean was 165.7 (162.6-168.9) and the median 168.5 (157.8-176.0). (Figure 39 and Table 4)
- Placebo group: The mean was 154.3 (149.2-159.4) and the median 159.0 (142.8-168.3). (Figure 39 and Table 4)

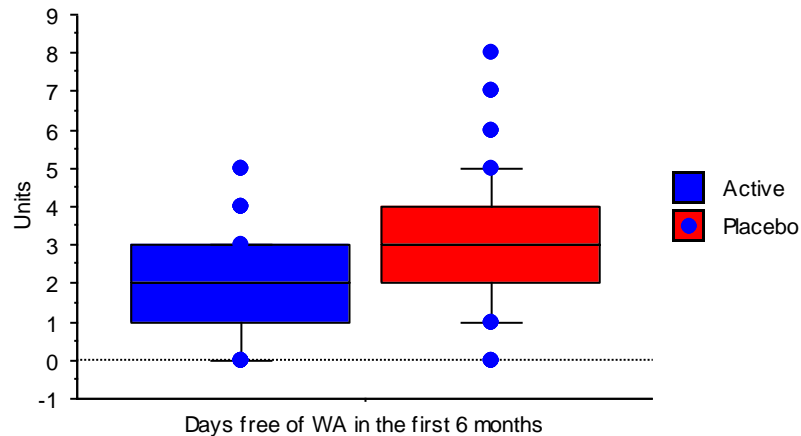


Figure 34: *Box-plot of days free of WA in the first 6 months*

Comparative statistics

Active group had an improvement of 6% over placebo.

The differences between both groups of treatment were significant. Mann Whitney's test P value <0.001 (Table 4).

Hodges-Lehmann estimator was 10.0 (5.0, 14.0)