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Efficacy results

Primary efficacy variable – Sum of pain intensity difference

Tab. 1: Pain intensity at different time points (sample 1, N=50)

Pain intensity (VRS 0-10)	Treatment											
	Placebo						Verum					
	N	Median	Min	Max	Mean	Std	N	Median	Min	Max	Mean	Std
Baseline	24	7.0	5.0	8.0	6.8	0.8	26	7.0	5.0	9.0	7.0	1.1
15 min	24	6.5	2.0	8.0	6.0	1.7	26	4.5	1.0	8.0	4.5	1.7
30 min	24	6.0	0.0	8.0	5.1	2.3	26	4.0	2.0	8.0	3.8	1.7
45 min	24	6.0	0.0	8.0	4.9	2.8	26	4.0	1.0	8.0	4.1	1.8
60 min	24	6.0	0.0	8.0	5.0	3.0	26	5.0	1.0	8.0	4.7	2.1
90 min	24	6.5	0.0	8.0	5.6	2.5	26	5.0	1.0	8.0	5.2	2.0
120 min	24	7.0	0.0	8.0	6.0	2.2	26	6.0	0.0	8.0	5.7	2.3

Tab. 2: Sum of pain intensity differences (sample 1, N=50)

SPID		Treatment	
		Placebo	Verum
	N	24	26
	Median	-3.5	-12.0
	Min	-39.0	-32.0
	Q1	-17.0	-21.0
	Q3	0.0	-9.0
	Max	5.0	0.0
	Mean	-8.3	-14.2
	Std	11.5	8.1

Tab. 3: Pain intensity at different time points (sample 2, N=115)

Pain intensity (VRS 0-10)	Treatment											
	Placebo						Verum					
	N	Median	Min	Max	Mean	Std	N	Median	Min	Max	Mean	Std
Baseline	58	7.0	4.0	10.0	7.0	1.5	57	7.0	5.0	10.0	6.9	1.3
15 min	58	6.0	0.0	10.0	5.9	2.1	57	5.0	1.0	10.0	5.2	2.1
30 min	58	6.0	0.0	9.0	5.2	2.2	57	4.0	0.0	9.0	4.4	2.2
45 min	58	5.0	0.0	9.0	5.0	2.3	57	4.0	0.0	10.0	4.2	2.2
60 min	58	6.0	0.0	9.0	5.3	2.3	57	5.0	0.0	10.0	4.4	2.5
90 min	58	6.0	0.0	9.0	5.4	2.6	57	5.0	0.0	10.0	4.8	2.5
120 min	58	6.0	0.0	9.0	5.4	2.6	57	6.0	0.0	10.0	5.4	2.6

Tab. 4: Sum of pain intensity differences (sample 2, N=115)

SPID		Treatment	
		Placebo	Verum
	N	58	57
	Median	-5.0	-11.0
	Min	-53.0	-45.0
	Q1	-15.0	-21.0
	Q3	-2.0	-3.0
	Max	4.0	0.0
	Mean	-9.7	-13.3
	Std	11.8	11.6

Tab. 5: Pain intensity at different time points (combined sample, N=165)

Pain intensity (VRS 0-10)	Treatment											
	Placebo						Verum					
	N	Median	Min	Max	Mean	Std	N	Median	Min	Max	Mean	Std
Baseline	82	7.0	4.0	10.0	6.9	1.3	83	7.0	5.0	10.0	7.0	1.2
15 min	82	6.0	0.0	10.0	5.9	2.0	83	5.0	1.0	10.0	5.0	2.0
30 min	82	6.0	0.0	9.0	5.2	2.2	83	4.0	0.0	9.0	4.2	2.0
45 min	82	6.0	0.0	9.0	4.9	2.4	83	4.0	0.0	10.0	4.2	2.1
60 min	82	6.0	0.0	9.0	5.2	2.5	83	5.0	0.0	10.0	4.5	2.3
90 min	82	6.0	0.0	9.0	5.4	2.6	83	5.0	0.0	10.0	5.0	2.3
120 min	82	6.0	0.0	9.0	5.6	2.5	83	6.0	0.0	10.0	5.5	2.5

The median in sum of pain intensity differences (SPID) was –12.0 for patients treated with verum and –5.0 for patients treated with placebo. The Hodges-Lehmann estimate for the 95% confidence interval for difference in medians is 1.0 – 7.0. The advantage for patients treated with verum was statistically significant (Wilxocon-Test p=0.0010).

Tab. 6: Sum of pain intensity differences (combined sample, N=165)

SPID		Treatment	
		Placebo	Verum
	N	82	83
	Median	-5.0	-12.0
	Min	-53.0	-45.0
	Q1	-15.0	-21.0
	Q3	-1.0	-5.0
	Max	5.0	0.0
	Mean	-9.3	-13.6
	Std	11.7	10.6

Secondary efficacy variables (Full Analysis Set)

Tab. 7: Pain intensity difference (PID)

PID (baseline-2 hrs)		All	
		Treatment	
		Placebo	Verum
	N	82	83
	Median	0.0	0.0
	Min	-9.0	-8.0
	Max	1.0	1.0
	Mean	-1.4	-1.5
	Std	2.3	2.3

The median change from baseline after 2 hours was 0 for both treatment groups. A detailed description of the difference in pain shows that there is only a slight advantage for patients treated with verum compared to patients treated with placebo (**Fehler! Verweisquelle konnte nicht gefunden werden.**Wilcoxon-Test, p=0.5709, 2 sided).

Tab. 8: Details on difference in pain at baseline and after 2 hours

PID (baseline-2 hrs)		All			
		Treatment			
		Placebo		Verum	
		N	%	N	%
	-9	2	2.4	.	.
	-8	1	1.2	3	3.6
	-7	1	1.2	1	1.2
	-6	2	2.4	6	7.2
	-5	6	7.3	1	1.2
	-4	2	2.4	2	2.4
	-3	5	6.1	5	6.0
	-2	2	2.4	12	14.5
	-1	12	14.6	11	13.3
	0	47	57.3	35	42.2
	1	2	2.4	7	8.4
	All	82	100	83	100

Tab. 9: Number of patients with worthwhile pain relief in the 1st hour

Worthwhile pain relief during 1st hour		All			
		Treatment			
		Placebo		Verum	
		N	%	N	%
	No	47	57.3	15	18.1
	Yes	35	42.7	68	81.9
	All	82	100	83	100

The advantage for patients treated with verum is statistically significant (Chi-Square-test: p< 0.001)

Tab. 10: Number of patients with worthwhile pain relief in the 2nd hour

Worthwhile pain relief within 2 hours		All			
		Treatment			
		Placebo		Verum	
		N	%	N	%
	No	46	56.1	13	15.7
	Yes	36	43.9	70	84.3
	All	82	100	83	100

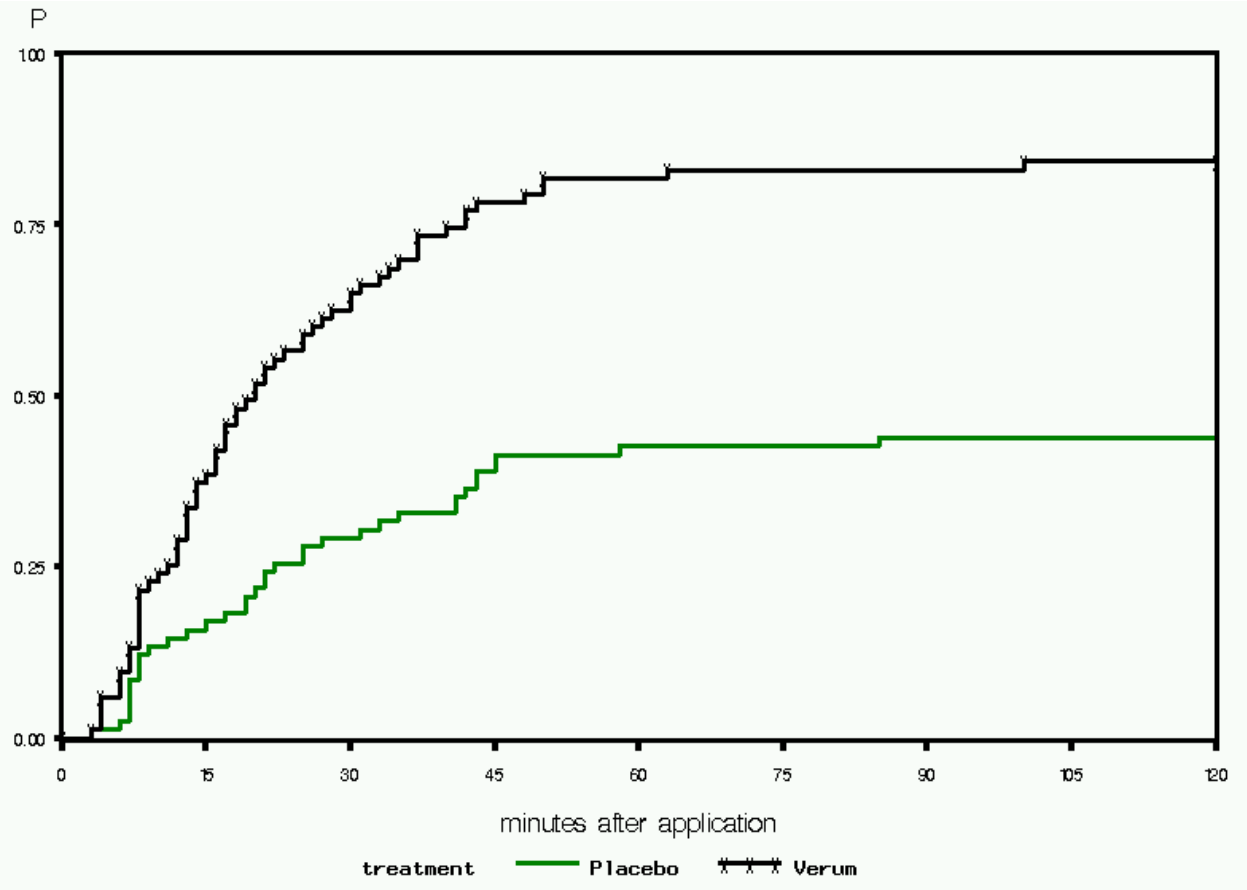
The advantage for patients treated with verum is statistically significant (Chi-Square-test: p< 0.001)

Tab. 11: Time to worthwhile pain relief

Median Estimates			
Treatment	50% Point Estimate	95% Confidence Interval	
		Lower	Upper
Placebo	.	45.000	.
Verum	20.000	16.000	27.000

The log-rank test shows a statistically significant difference between verum and placebo treatment ($p<0.001$).

Figure 1: Cumulative proportion of patients with worthwhile pain relief



Tab. 12: Complete pain relief within the 1st hour (pain zero (VRS 0-10))

Complete pain relief during 1st hour		All			
		Treatment			
		Placebo		Verum	
		N	%	N	%
	No	72	87.8	76	91.6
	Yes	10	12.2	7	8.4
	All	82	100	83	100

There was no statistical relevant difference between treatment groups (Chi-square-test: p=0.5902)

Tab. 13: Complete pain relief within the 2nd hour (pain zero (VRS 0-10))

Complete pain relief within 2 hours		All			
		Treatment			
		Placebo		Verum	
		N	%	N	%
	No	70	85.4	74	89.2
	Yes	12	14.6	9	10.8
	All	82	100	83	100

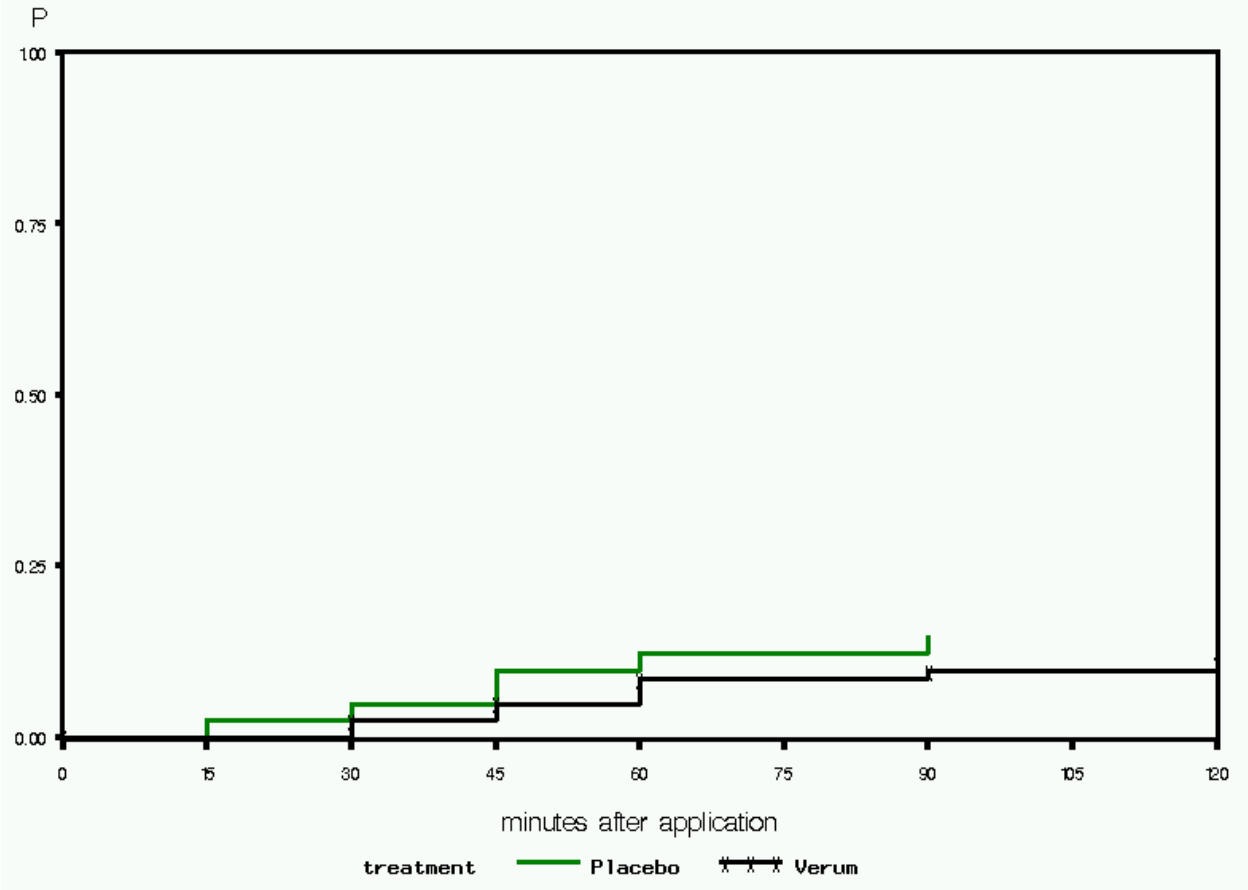
There was no statistical significant difference between treatment groups (Chi-square-test: p=0.6192).

Time to complete pain relief

As less than 50% of the patients in either treatment group had a complete pain relief within 2 hours, the median of this time could not be calculated by Kaplan-Meier-method.

The log-rank test shows no statistically significant difference between verum and placebo treatment (p<0.4428).

Figure 2: Cumulative proportion of patients with complete pain relief



Time to recurrence of pain (recurrence of pain to baseline intensity)

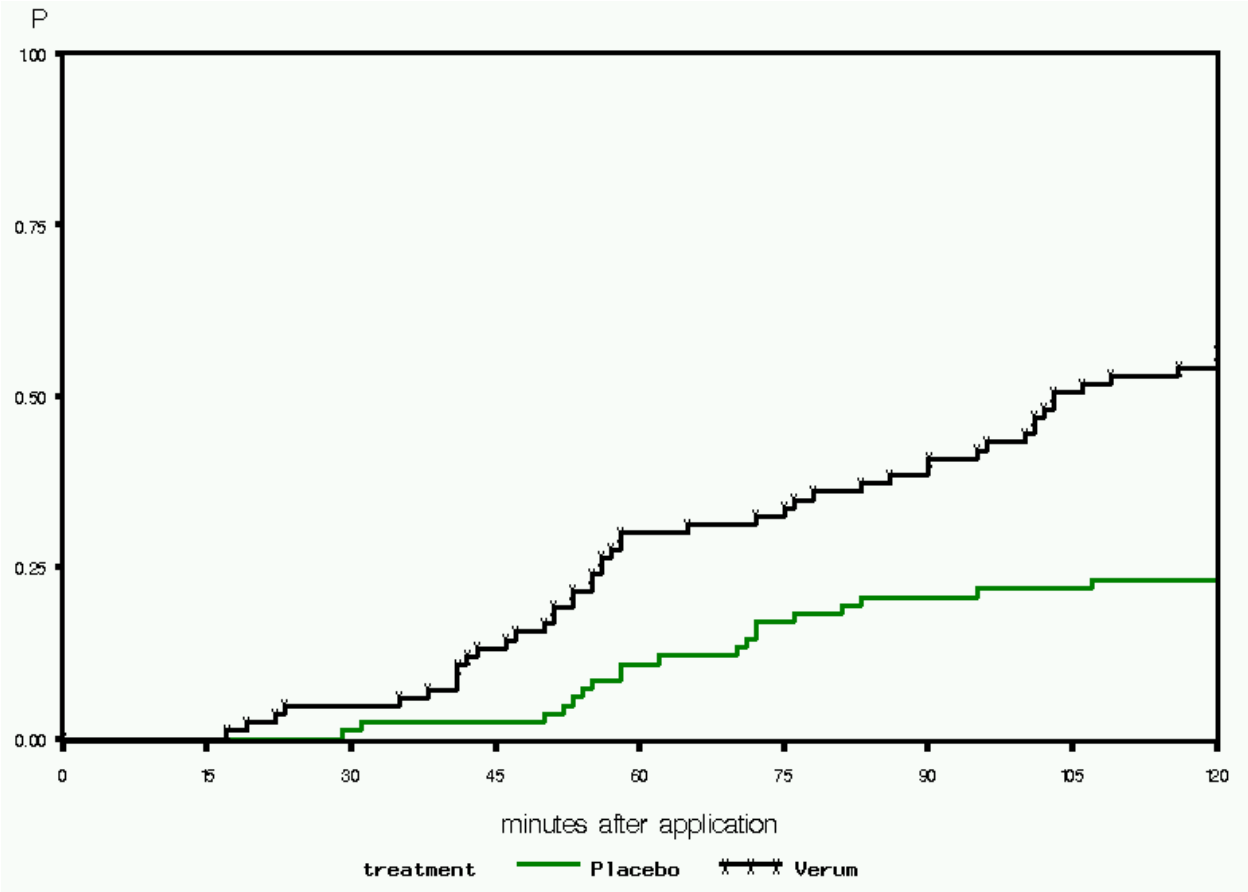
The median of the time to recurrence of pain could not be calculated for patients treated with placebo because of the low numbers and was calculated as 103 minutes for patients treated with verum.

The cumulative proportion of patients was statistically significantly higher (log-rank-test: p <0.001). This only reflects the fact that patients treated with verum had a greater chance because their pain was better released by verum.

Tab. 14: Time to recurrence of pain (recurrence of pain to baseline intensity)

Median Estimates			
Treatment	50% Point Estimate	95% Confidence Interval	
		Lower	Upper
Placebo	.	.	.
Verum	103.000	90.000	.

Figure 3: Cumulative proportion of patients with recurrence of pain to baseline intensity



Response to treatment (pain decrease of at least 50% within the 2 h period compared to baseline)

Tab. 15: Number of patients with Response to treatment

Response		All			
		Treatment			
		Placebo		Verum	
		N	%	N	%
	No	58	70.7	40	48.2
	Yes	24	29.3	43	51.8
	All	82	100	83	100

The advantage for patients treated with verum is statistically significant (Chi-Square-test: $p < 0.0053$).

Vital signs, physical findings and other observations related to safety

Tab. 16: Changes in physical examination

Any change in physical examniation ?		Cohort				All	
		1st sample		2nd sample		All	
		Treatment		Treatment		Treatment	
		Placebo	Verum	Placebo	Verum	Placebo	Verum
No	N	24	26	58	57	82	83
	%	100.0	100.0	100.0	100.0	100.0	100.0

Tab. 17: Vital signs – systolic -, diastolic blood pressure and pulse and changes from baseline

Change from baseline		Cohort				All	
		1st sample		2nd sample		All	
		Treatment		Treatment		Treatment	
		Placebo	Verum	Placebo	Verum	Placebo	Verum
Systol. BP [mmHg]	N	24	26	58	57	82	83
	Mean	2.33	3.23	-0.48	2.12	0.34	2.47
	Std	8.98	7.33	5.96	4.96	7.04	5.78
	Min	-20.00	-10.00	-16.00	-9.00	-20.00	-10.00
	Median	0.00	3.00	0.00	1.00	0.00	2.00
	Max	20.00	25.00	10.00	16.00	20.00	25.00
diastol. BP [mmHg]	N	24	26	58	57	82	83
	Mean	0.25	0.92	1.45	1.35	1.10	1.22
	Std	7.21	4.19	5.79	4.55	6.22	4.42
	Min	-15.00	-11.00	-15.00	-10.00	-15.00	-11.00
	Median	0.00	0.00	0.00	0.00	0.00	0.00
	Max	10.00	10.00	16.00	13.00	16.00	13.00
Pulse [beats/min.]	N	24	26	58	57	82	83
	Mean	4.50	2.23	1.62	3.54	2.46	3.13
	Std	6.22	7.15	5.58	5.60	5.89	6.11
	Min	-4.00	-26.00	-8.00	-8.00	-8.00	-26.00
	Median	4.00	2.50	2.00	4.00	2.00	4.00
	Max	24.00	12.00	20.00	27.00	24.00	27.00

Overall study population

In the overall study population no differences in physical examination between baseline and final examination were reported. None of the differences in vital signs

observed between different treatment groups (verum and placebo), different analysis samples, and between screening and final examination were of clinical relevance.

Local tolerability

Tab. 18: Number of patients with Any local tolerability problem

Any local tolerability problems?		Cohort				All	
		1st analysis sample		2nd analysis sample			
		Treatment		Treatment		Treatment	
		Placebo	Verum	Placebo	Verum	Placebo	Verum
No	N	24	26	58	57	82	83
	%	100.0	100.0	100.0	100.0	100.0	100.0

Only one AE occurred during the whole study. This AE was reported by a patient treated with placebo and the investigator classified this event as being unlikely related to treatment. Additionally no patient reported burning, redness or itching after the end of study as well as no symptoms were observed by the investigators.

Multicentre studies

Patients were recruited into the trial in 17 centers.

According to the statistical analysis plan centers with less than 4 patients were pooled with the next smallest center until a number of at least 4 patients was reached.

Therefore the following centers were combined:

- center no. 3 (n=1), no. 12 (n=1) and no. 19 (n=2) were combined into one new center (no. 21)
- center no. 11 (n=2) and no. 7 (n=4) were combined into one new center (no. 22)

Tab. 19: SPID of patients treated with placebo and verum within each center

SPID by center - aggr.	Treatment											
	Placebo						Verum					
Center No.	N	Median	Min	Max	Mean	Std	N	Median	Min	Max	Mean	Std
2	10	-3.0	-7.0	-1.0	-3.4	1.7	10	-14.5	-26.0	-9.0	-15.3	5.2
8	10	0.0	-14.0	0.0	-2.6	4.7	10	-8.0	-21.0	0.0	-7.9	6.0
9	9	-5.0	-28.0	0.0	-9.1	10.4	8	-8.5	-26.0	-1.0	-11.1	8.8
1	8	-18.0	-53.0	0.0	-23.0	22.6	8	-11.5	-45.0	0.0	-18.4	20.2
4	7	-5.0	-24.0	-3.0	-8.0	7.2	7	-15.0	-25.0	-9.0	-16.6	6.3
14	7	-20.0	-25.0	0.0	-15.0	10.1	7	-14.0	-30.0	0.0	-16.7	10.2
16	7	0.0	-11.0	5.0	-1.1	5.4	7	-5.0	-13.0	-1.0	-6.4	4.3
5	6	-5.5	-22.0	-1.0	-9.3	9.3	4	-19.5	-25.0	-14.0	-19.5	5.3
10	4	-2.5	-10.0	0.0	-3.8	4.3	4	-1.0	-2.0	0.0	-1.0	1.2
15	4	-2.5	-11.0	0.0	-4.0	5.2	4	-25.0	-34.0	-8.0	-23.0	11.0
6	3	-27.0	-28.0	-25.0	-26.7	1.5	4	-12.0	-26.0	-3.0	-13.3	9.5
17	3	-12.0	-15.0	-4.0	-10.3	5.7	4	-13.0	-15.0	-4.0	-11.3	5.0
22	3	-25.0	-25.0	-16.0	-22.0	5.2	3	-32.0	-36.0	-15.0	-27.7	11.2
21	1	-5.0	-5.0	-5.0	-5.0	.	3	-3.0	-22.0	0.0	-8.3	11.9

There were 5 centers (No. 1, no. 6, no. 10, no. 14 and no.21) with a better SPID (smaller median) in patients treated with placebo compared to 11 centers with a better SPID in patients treated with verum.

The difference in the primary efficacy variable – SPID – adjusted for the effect of centers was calculated according to the method of « van Elteren ». The van-Elteren test was calculated by SAS program « Proc Freq ».

The Cochran-Mantel-Haenszel test statistic for this model is 15.9521 with 1-degree of freedom.

The p-value for a difference in SPID between treatment with placebo and verum is <0.001 for a 2-sided test.

The result is in accordance with the unstratified test.