

Supplemental Digital Content (SDC)

Symptomatic treatment of mosquito bites with a thermo-therapeutic medical device: a prospective, intra-individually compared, placebo-controlled, randomised clinical trial

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SDC, Table S1

Descriptive statistics for raw data of the visual analogue scale [mm] of itching (per-protocol population).

		PP N=19							
		Descriptive statistics						95% CI	
		n	Mean	Standard deviation	Minimum	Median	Maximum	Lower limit	Upper limit
PD									
	Baseline	19	60.4	17.8	31	69.0	84	51.8	69.0
	1 Min	19	42.6	23.1	3	47.0	77	31.5	53.8
	2 Min	19	41.0	23.0	0	47.0	72	29.9	52.1
	3 Min	19	38.5	22.0	2	39.0	72	27.9	49.1
	4 Min	19	36.9	21.1	2	37.0	68	26.7	47.1
	5 Min	19	33.4	20.2	2	30.0	68	23.7	43.1
	10 Min	19	33.7	22.8	1	35.0	68	22.7	44.7
	15 Min	19	28.5	21.8	0	26.0	70	18.0	39.0
	30 Min	19	19.5	25.9	0	6.0	73	7.1	32.0
IMD									
	Baseline	19	67.6	17.9	32	69.0	94	59.0	76.3
	1 Min	19	45.5	25.2	6	53.0	83	33.3	57.6
	2 Min	19	40.7	24.6	5	42.0	82	28.9	52.6
	3 Min	19	35.5	24.5	2	33.0	88	23.7	47.3
	4 Min	19	32.1	23.5	1	27.0	85	20.7	43.4
	5 Min	19	30.1	23.5	2	24.0	89	18.8	41.4
	10 Min	19	25.8	20.9	1	25.0	83	15.8	35.9
	15 Min	19	21.3	20.5	1	16.0	90	11.4	31.1
	30 Min	19	11.5	20.0	1	6.0	90	1.9	21.2

CI = Confidence Interval; IMD = Investigational Medical Device; N/n = Number of subjects; PD = Placebo medical device; PP = per-Protocol Population.

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SDC, Table S2

Descriptive statistics for differences to baseline and area under the curve based on differences to baseline over time of the visual analog scale [mm] of itching (per-protocol population)

		PP N=19								
		Descriptive statistics						95% CI		
		n	Mean	Standard deviation	Minimum	Median	Maximum	Lower limit	Upper limit	
AUC of PD		AUC	19	914.61	653.79	-12.5	744.50	2245.5	599.49	1229.72
AUC of IMD		AUC	19	1311.71	723.56	-377.0	1252.50	2586.0	962.97	1660.45
PD		1 Min	19	17.79	22.97	-14.0	8.00	75.0	6.72	28.86
	2 Min	19	19.42	22.78	-13.0	12.00	78.0	8.44	30.40	
	3 Min	19	21.89	21.62	-5.0	16.00	76.0	11.48	32.31	
	4 Min	19	23.53	21.40	-3.0	16.00	76.0	13.21	33.84	
	5 Min	19	27.00	22.48	-3.0	20.00	76.0	16.17	37.83	
	10 Min	19	26.74	24.58	-5.0	20.00	77.0	14.89	38.58	
	15 Min	19	31.95	24.07	0.0	23.00	78.0	20.34	43.55	
	30 Min	19	40.89	26.97	-3.0	40.00	78.0	27.89	53.90	
IMD		1 Min	19	22.16	25.18	-15.0	13.00	77.0	10.02	34.29
	2 Min	19	26.89	26.73	-15.0	21.00	81.0	14.01	39.78	
	3 Min	19	32.16	27.89	-13.0	30.00	82.0	18.72	45.60	
	4 Min	19	35.58	28.56	-16.0	33.00	79.0	21.81	49.34	
	5 Min	19	37.53	29.07	-14.0	39.00	77.0	23.52	51.54	
	10 Min	19	41.79	26.76	-8.0	44.00	90.0	28.89	54.69	
	15 Min	19	46.37	25.54	-15.0	48.00	93.0	34.06	58.68	
	30 Min	19	56.11	25.57	-15.0	59.00	93.0	43.78	68.43	

AUC = Area Under the Curve; CI = Confidence Interval; IMD = Investigational Medical Device; N/n = Number of subjects;
 PD = Placebo medical device ; PP = per-Protocol Population.

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SDC, Table S3

Results of the Shapiro-Wilk test for normality on the area under the curve based on differences to baseline over time of the visual analogue scale [mm] of itching (per-protocol population)

Analysis set (PP)		Shapiro-Wilk test for normal distribution assumption on AUC - (N=19)			
Test device		n	Test statistic	p-Value	Result
AUC PD		19	0.957	0.5194	n.s.
IMD		19	0.980	0.9428	n.s.

Note on the result *: significant ($p \leq 0.01$), n.s.: not significant ($p > 0.01$)

AUC = Area Under the Curve; IMD = Investigational Medical Device; N/n = Number of subjects; PD = Placebo medical device; PP = per-Protocol Population.

SDC, Table S4

Results of paired t-test (one-sided) for comparisons of treatments on the area under the curve based on differences to baseline over time of the visual analogue scale [mm] of itching (per-protocol population)

Analysis set (PP)		Results of paired t-test for comparisons of treatments on AUC (N=19)					
Comparison		Mean difference	SD	DF	t-Value	p-Value	Result
AUC	PD vs. IMD	397.11	710.52	18	2.44	0.0127	*

Note on the result *: significant ($p \leq 0.025$), n.s.: not significant ($p > 0.025$)

AUC = Area Under the Curve; DF = Degrees of Freedom; IMD = Investigational Medical Device; N/n = Number of subjects;
PD = Placebo medical device ; PP = per-Protocol Population; SD = Standard Deviation.

SDC, Table S5

Descriptive statistics for raw data of the visual analogue scale [mm] of itching (post-hoc analysis)

		Post-hoc analysis N=18							
		Descriptive statistics						95% CI	
		n	Mean	Standard deviation	Minimum	Median	Maximum	Lower limit	Upper limit
PD									
	Baseline	18	59.4	17.8	31	67.5	84	50.6	68.3
	1 Min	18	44.8	21.6	10	47.5	77	34.1	55.6
	2 Min	18	43.3	21.3	10	47.0	72	32.7	53.9
	3 Min	18	40.6	20.7	5	41.5	72	30.2	50.9
	4 Min	18	38.8	19.9	2	40.5	68	28.9	48.7
	5 Min	18	35.2	19.2	2	30.5	68	25.6	44.7
	10 Min	18	35.5	22.0	2	35.5	68	24.6	46.4
	15 Min	18	30.1	21.3	2	26.5	70	19.5	40.6
	30 Min	18	20.6	26.2	1	7.5	73	7.6	33.6
IMD									
	Baseline	18	68.4	18.1	32	70.0	94	59.4	77.4
	1 Min	18	44.2	25.3	6	50.5	83	31.6	56.7
	2 Min	18	39.2	24.3	5	38.5	82	27.1	51.3
	3 Min	18	33.7	23.9	2	30.5	88	21.8	45.6
	4 Min	18	29.9	22.2	1	25.5	85	18.9	41.0
	5 Min	18	28.1	22.3	2	21.0	89	17.0	39.2
	10 Min	18	24.5	20.7	1	25.0	83	14.2	34.8
	15 Min	18	21.7	21.0	1	16.0	90	11.3	32.2
	30 Min	18	12.1	20.4	1	6.5	90	1.9	22.3
CI = Confidence Interval; IMD = Investigational Medical Device; N/n = Number of subjects; PD = Placebo medical device.									

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SDC, Table S6

Descriptive statistics for differences to baseline and area under the curve based on differences to baseline over time of the visual analogue scale [mm] of itching (post-hoc analysis)

Post-hoc analysis N=18									
		Descriptive statistics						95% CI	
		n	Mean	Standard deviation	Minimum	Median	Maximum	Lower limit	Upper limit
AUC of PD									
	AUC	18	840.67	585.32	-12.5	718.25	1856.5	549.59	1131.74
AUC of IMD									
	AUC	18	1343.64	730.63	-377.0	1357.25	2586.0	980.30	1706.97
PD									
	1 Min	18	14.61	18.85	-14.0	7.50	57.0	5.24	23.98
	2 Min	18	16.17	18.34	-13.0	12.00	53.0	7.04	25.29
	3 Min	18	18.89	17.69	-5.0	15.50	55.0	10.09	27.69
	4 Min	18	20.61	17.72	-3.0	16.00	58.0	11.80	29.42
	5 Min	18	24.28	19.64	-3.0	19.00	58.0	14.51	34.05
	10 Min	18	23.94	21.97	-5.0	19.50	68.0	13.02	34.87
	15 Min	18	29.39	21.95	0.0	22.00	68.0	18.47	40.31
	30 Min	18	38.83	26.17	-3.0	39.00	76.0	25.82	51.85
IMD									
	1 Min	18	24.22	24.20	-5.0	14.50	77.0	12.19	36.26
	2 Min	18	29.22	25.45	-7.0	24.00	81.0	16.57	41.88
	3 Min	18	34.67	26.40	-13.0	32.00	82.0	21.54	47.79
	4 Min	18	38.44	26.43	-10.0	40.00	79.0	25.30	51.59
	5 Min	18	40.33	27.13	-14.0	44.00	77.0	26.84	53.83
	10 Min	18	43.89	25.88	-8.0	45.50	90.0	31.02	56.76
	15 Min	18	46.67	26.24	-15.0	48.50	93.0	33.62	59.72
	30 Min	18	56.28	26.30	-15.0	60.00	93.0	43.20	69.36
AUC = Area Under the Curve; CI = Confidence Interval; IMD = Investigational Medical Device; N/n = Number of subjects; PD = Placebo medical device .									

D. Wilhelm: Symptomatic treatment of mosquito bites with a thermo-therapeutic medical device: a prospective, intra-individually compared, placebo-controlled, randomised clinical trial

SDC, Table S7

Results of the Shapiro-Wilk test for normality on the area under the curve based on differences to baseline over time of the visual analogue scale [mm] of itching (post-hoc analysis)

Post-hoc analysis set		Shapiro-Wilk test for normal distribution assumption on AUC - (N=18)			
Test device		n	Test statistic	p-Value	Result
AUC PD		18	0.952	0.4504	n.s.
IMD		18	0.972	0.8319	n.s.

Note on the result *: significant ($p \leq 0.01$), n.s.: not significant ($p > 0.01$)

AUC = Area Under the Curve; IMD = Investigational Medical Device; N/n = Number of subjects; PD = Placebo medical device

SDC, Table S8

Results of paired t-test (one-sided) for comparisons of treatments on area under the curve based on differences to baseline over time of the visual analogue scale [mm] of itching (post-hoc analysis)

Post-hoc analysis set		Results of paired t-test for comparisons of treatments on AUC (N=18)					
Comparison		Mean difference	SD	DF	t-Value	p-Value	Result
AUC	PD vs. IMD	502.97	555.94	17	3.84	0.0007	*

Note on the result *: significant ($p \leq 0.025$), n.s.: not significant ($p > 0.025$)

AUC = Area Under the Curve; DF = Degrees of Freedom; IMD = Investigational Medical Device; N/n = Number of subjects;
PD = Placebo medical device ; SD = Standard Deviation.

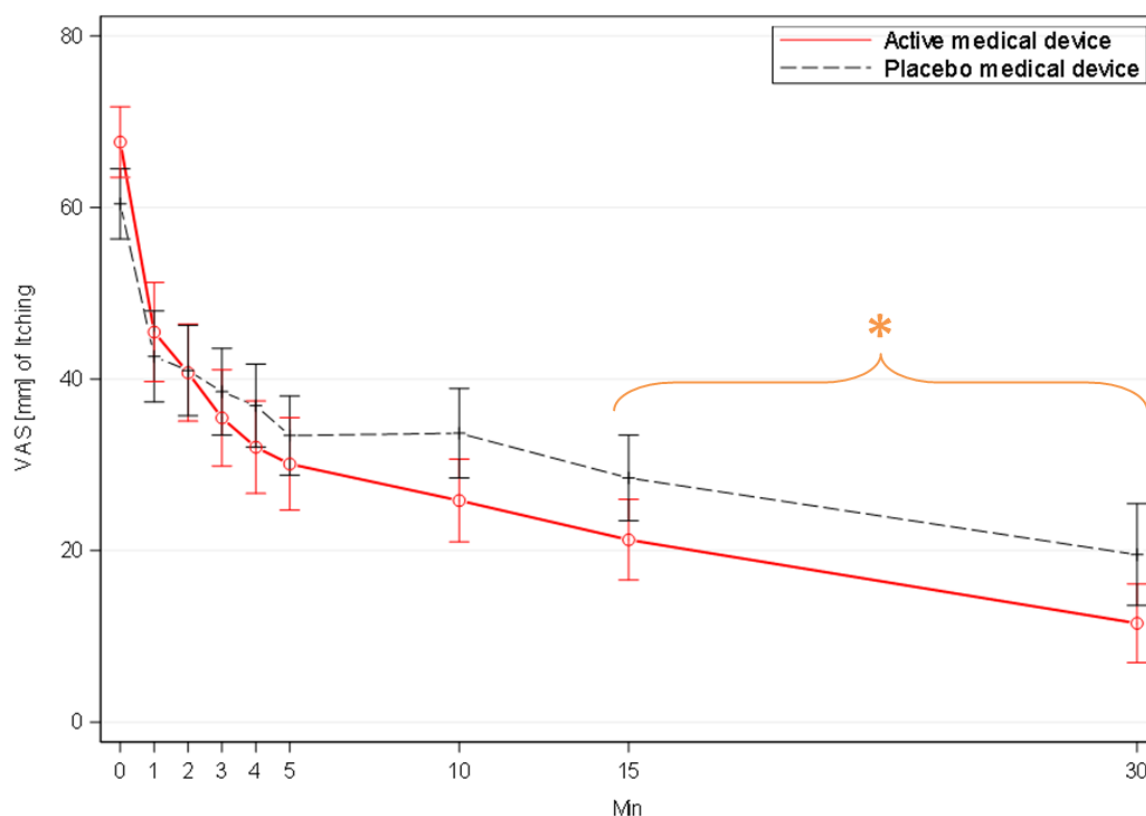
SDC, Table S9

Baseline demographic and clinical characteristics.

Baseline demographic and clinical characteristics	SP (N=25)
	Mean $\pm$ SD or N (%)
Age [years]	53.5 $\pm$ 15.7
Height [cm]	168.5 $\pm$ 8.3
Weight [kg]	76.1 $\pm$ 18.3
Female sex	18 (72%)
Lower volar forearm condition = normal	25 (100%)
Systolic blood pressure [mmHg]	136.4 $\pm$ 17.7
Diastolic blood pressure [mmHg]	88.0 $\pm$ 9.5
Pulse [b/min]	78.4 $\pm$ 12.2

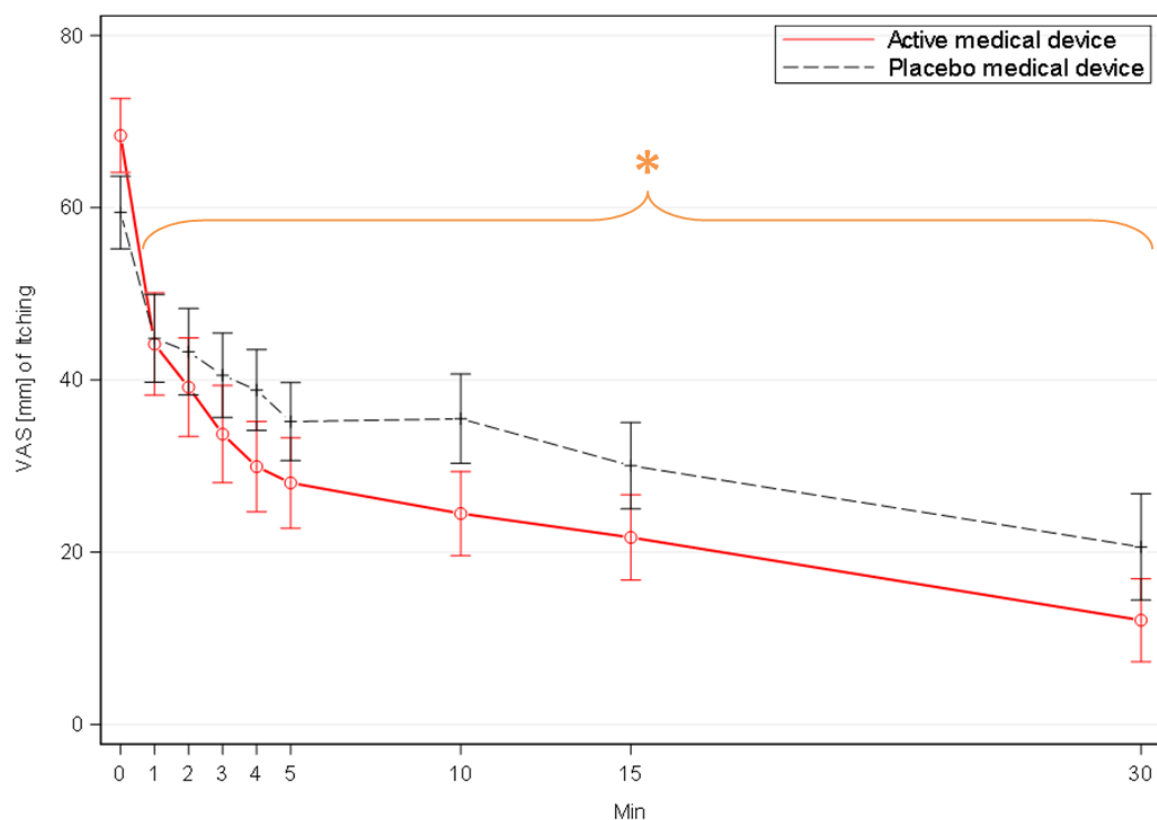
Abbreviations: SP = Safety Population; SD = Standard Deviation, N = number of subjects.

SDC, Figure S1



SDC, Figure S1 Line plot of mean VAS of itching (mm $\pm$ SD) over assessment times (in minutes) per device (PP population, N = 19). N = number of subjects; VAS = Visual Analogue Scale; PP = per-Protocol Population;

SDC, Figure S2



SDC, Figure S2. Line plot of mean VAS of itching (mm $\pm$ SD) over assessment times (in minutes) per device (post-hoc analysis, N = 18). N = number of subjects; VAS = Visual Analogue Scale.