Statistical Report

Protocol title	A double blind placebo control study to evaluate the efficacy of BioStick (BS) phototherapeutic device in the treatment of Aphthous Stomatitis.
Name of medical device	BioStick™
Study number	Protocol Number: BS-01

Version:	Version 1.2
Version date:	26/06/2009

Approved by:

For the sponsor – SyroLight

Yoav Barak, BSc, MBA – Managing Director

Signature: SYROLIGHT LTD. Date: 28-6-09

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Biostatistician

Zmira Silman, M.A.

Signature: Date: 26.06.2009

Study description

Study design:	A double blind placebo control study
Number of centers:	1
Blinding:	Double blind
Randomization:	Block randomization
Name of medical device:	BioStick(BS)
Comparator:	BioStick(BS) with low light

Aim of study (main hypothesis)

This study compares the efficacy of SyroLight BioStick device with active light to control with low light density.

Objectives:

The primary objectives of this study are to:

- Compare time to healing between the active device and the placebo control

The secondary objectives of this study are to:

- Compare the reduction in pain, ability to speak, eat and drink between the active and placebo treatment.
- Evaluate patients' satisfactory of the products.

Randomization

Block randomization

Study endpoints

Primary endpoint:

Efficacy:

Compare the time to cure in days

Compare the response grade for each group.

Secondary endpoints:

Safety:

Evaluation of adverse events.

Sample size

Forty (40) subjects partitioned into 2 groups.

Twenty allocated randomly to receive active treatment and 20 allocated to receive control treatment.

The primary end point of this study is time to cure (number of days to obtain total cure).

The expected difference between the active and placebo groups is anticipated to be at least two days (with standard deviation of two).

A total of 40 enrolled patients (20 in each group) will provide 80% power at a 5% significance level and 95% Confidence Interval of Difference taking into account a 15% drop out rate.

Analysis set

The full analysis set including all enrolled subjects in the study (ITT) was the primary analysis set.

Due to one subject that was lost to follow-up and one subject that used additional medications during treatment the modified ITT served as the primary analysis set.

Analysis method

Data was analyzed using the SPSS software (version 17.00, SPSS Inc.).

Baseline characteristics are presented as descriptive statistics (frequency (%) or mean, standard deviation (SD), standard error (SE) minimum, median and maximum).

Comparison between treatment arms of time to cure, number of treatments and lesion size is based on independent t-test.

Comparison of grade at baseline level is based on Mann Whitney test.

Safety is assessed descriptively.

Significance level was defined as α=0.05.

Missing data

No imputation for missing values was applied.

Executive summary

Forty subjects with Aphthous Stomatitis participated in double blind placebo control study to evaluate the efficacy of BioStick (BS) phototherapeutic device in the treatment of Aphthous Stomatitis.

Compliance: 90% of placebo group and 100% of treated group complied with the study.

Demographic characteristics:

No significant differences between groups.

All subjects are Caucasian, the majority male, age of 36.8 ±11.9.

Baseline characteristics:

Subjects suffer from 1 to 3 lesions. The average lesion size of the placebo group was significantly smaller than in the treated group 13.56± 9.3 vs. 21.80±12.88, meaning that the treated group started the study in inferior condition.

The majority of both groups suffer from severe pain, burning sensation, speech and eating difficulties.

Most of the lesions were located in the lower lip.

Efficacy:

All subjects archived complete cure, as noted as complete recovery in all measurements and size of lesion equal to 0.

There are significant differences in the days to total cure, the treat group had significantly shorter time to cure than the placebo group (3.95±2.82 compared to 5.89±2.95, p=0.046)

There are significant differences in the number of treatments used until total cure, the treat group had significantly less treatments than the placebo group (12.56±7.30 compared to 20.00±8.94, p=0.010).

Subjective evaluation of efficacy

In the treated group the majority (60% to 73.3%) stated good to total cure in all measurements (pain, burning sensations, eating & speech difficulties) compared to approximately 29% to 35% in the placebo group.

Continence of use

80% of subjects from treated group grade the device better to much better then comparative treatments while only 16.7% from placebo group grade the device as much better.

The majority of both groups would like to use the device again (above 80%)

86.7% of the subjects in the treated group would like to buy the device compared to only 60% of subjects in the placebo group.

Safety:

No adverse events were recorded.

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Tables:

14.1 General and baseline characteristics

Table 14.1.1: Study dates

	Placebo	Treat
N	18	20
Date first subject screened	05.7.2007	13.6.2007
Date last subject - screened	31.5.2009	05.6.2009
Date last subject – Final visit	03.6.2009	14.6.2009

Table 14.1.3: Demographic characteristics

		Placebo		Treat		P value
		N	%	N	%	
Gender	Male	11	61.1%	11	55.0%	0.752*
	Female	7	38.9%	9	45.0%	
Race	Caucasian	18	100.0%	20	100.0%	1.000*
Age (years)	N	18		20		0.713**
	Mean	36.0		37.5		
	Median	30.0		38.0		
	SD	12.8		11.3		
	Minimum	21.0		20.0		
	Maximum	61.0		56.0		

The majority in both groups are male, all from Caucasian origin.
The average age was 36 for placebo group and 37.5 for treated group.
No significant differences in the demographic characteristics.

Table 14.1.4: Aphthous stomatitis condition at baseline

		Placebo		Treat		P value
Time from diagnosis *(Days)*	N		18		20	0.601
	Mean		1.39		1.20	
	Median		1.00		1.00	
	SD		.61		.70	
	Minimum		.00		.00	
	Maximum		2.00		2.00	
Suffered in the past	N %	15	83.3%	19	95.0%	0.328
Treated in the past	N %	13	72.2%	14	70.0%	1.000

Days from diagnosis: 50% of subject arrived to the clinic within 1 day.
The majority suffered in the past (above 83%) and 70% of both groups were treated in the past.

Table 14.1.4.1: Past Medication

No past medication recoded

Table 14.1.5: Enrollment status

Table 14.1.5.1: Number of lesions:

Number of lesions	Placebo		Treat		P value
	N	%	N	%	
One lesion	13	72.2%	14	70.0%	0.979
Two lesions	4	22.2%	5	25.0%	
Three lesions	1	5.6%	1	5.0%	

The majority of subjects in both groups (70%) had one lesion.

Table 14.1.5.2: Location of lesions:

	Lesion 1				***Lesion2***				***Lesion 3***			
	Placebo		**Treat**		**Placebo**		**Treat**		**Placebo**		**Treat**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
1 Gingival Mucosa	3	16.7	6	30.0	3	50.0	2	33.3				
2 Tongue	6	33.3	2	10.0	1	16.7	2	33.3				
3 Upper Lip	1	5.6	1	5.0	1	16.7	1	16.7				
4 Lower Lip	**7**	**38.9**	**8**	**40.0**	1	16.7	1	16.7			1	100%
5 Hard palate	1	5.6										
6 Soft palate			3	15.0					1	100%		
Total	18	100.0	20	100.0								

The majority of lesions are in the lower lip for both groups.

Table 14.1.5.3: Size of lesions (mm2):

		Treatment		
		Placebo	**Treat**	**P value**
Lesion 1 Size (mm^2)	N	18	20	0.031
	Mean	13.56	21.80	
	Median	12.00	16.00	
	SD	9.30	12.88	
	Minimum	2.00	9.00	
	Maximum	30.00	48.00	
Lesion 2 Size (mm^2)	N	6	6	0.421
	Mean	7.50	11.17	
	Median	6.00	9.00	
	SD	4.72	9.60	
	Minimum	2.00	2.00	
	Maximum	16.00	28.00	
Lesion 3 Size (mm^2)	N	1	1	
	Mean	9.00	6.00	
	Median	9.00	6.00	
	SD	.	.	
	Minimum	9.00	6.00	
	Maximum	9.00	6.00	

Lesion 1: at baseline there are significant differences in the first lesion size, the treatment group has significantly bigger lesions compared to the placebo 21.80 mm^2 vs. 13.56 mm^2 respectively (p=0.031)
Lesion 2: same trend but not statistically significant.

Table 14.1.5.4: Condition of lesion at baseline

		Placebo		*Treat*		*P value*
		N	**%**	**N**	**%**	
Pain	None	1	5.6%	0	.0%	0.806
	Moderate	5	27.8%	6	30.0%	
	Severe	**12**	**66.7%**	**14**	**70.0%**	
Burning Sensation	None	1	5.6%	1	5.0%	0.874
	Mild	2	11.1%	0	.0%	
	Moderate	4	22.2%	7	35.0%	
	Severe	**11**	**61.1%**	**12**	**60.0%**	
Speech Difficulties	None	3	16.7%	2	10.0%	0.613
	Mild	1	5.6%	2	10.0%	
	Moderate	5	27.8%	4	20.0%	
	Severe	**9**	**50.0%**	**12**	**60.0%**	
Eating Drinking Difficulties	None	1	5.6%	0	.0%	0.919
	Mild	0	.0%	1	5.0%	
	Moderate	3	16.7%	4	20.0%	
	Severe	**14**	**77.8%**	**15**	**75.0%**	

The majority of both groups suffer from sever pain, burning sensation, speech and eating difficulties.

Table 14.1.6: Medical History

	Placebo		*Treat*		*P value*
	N	%	N	%	
Number of subjects	3	16.67%	0	0%	
Description of findings					
Hypercholesterolemia + hypertension	1	5.6%	0	0%	
Hypothyroidism	1	5.6%	0	0%	
Penicillin allergy	1	5.6%	0	0%	

Three subjects from the placebo group had some non related medical history.

Table 14.1.7: Medication History

No Medications were stopped within the last 14 days.

Table 14.1.8: Subject validity status for analysis

	Placebo		***Treat***	
	N	%	N	%
Number of subjects	20	100%	20	100%
Complete study	18	90%	20	100%
Reasons for incomplete				
Lost to Follow up	1	5.0%		
Protocol violation use of other medication	1	5.0%		

There were two subjects that didn't complete the study, both from the Placebo group.

14.2 Efficacy – Objective evaluation

Table 14.2.1: Time to total cure

		Treatment		*P value
		Placebo	Treat	
Days To Total Cure	N	18	20	0.046
	Mean	5.89	3.95	
	Median	5.50	3.00	
	SD	2.95	2.82	
	Minimum	2.00	1.00	
	Maximum	12.00	10.00	
Number of treatments during period	N	18	18	0.010
	Mean	20.00	12.56	
	Median	19.50	9.50	
	SD	8.94	7.30	
	Minimum	7.00	5.00	
	Maximum	39.00	30.00	
Total days in treatment	N	18	20	0.041
	Mean	6.89	4.90	
	Median	6.50	4.00	
	SD	2.95	2.83	
	Minimum	3.00	2.00	
	Maximum	13.00	11.00	
Rate of use *(number of treatments/days)*	N	18	18	0.724
	Mean	2.87	2.84	
	Median	3.00	3.00	
	SD	.23	.28	
	Minimum	2.33	2.00	
	Maximum	3.00	3.00	

*p value based on independent t-test

There are significant differences in the days to total cure, the treat group had significantly shorter time to cure than the placebo group (3.95±2.82 compared to 5.89±2.95, p=0.046)
There are significant differences in the number of treatments used until total cure, the treat group had significantly less treatments than the placebo group (12.56±7.30 compared to 20.00±8.94, p=0.010)
There are no significant differences between groups in the rate of use (2.84±0.28 compared to 2.87±0.23, p=0.724)

Fig 1: Number of days to total cure

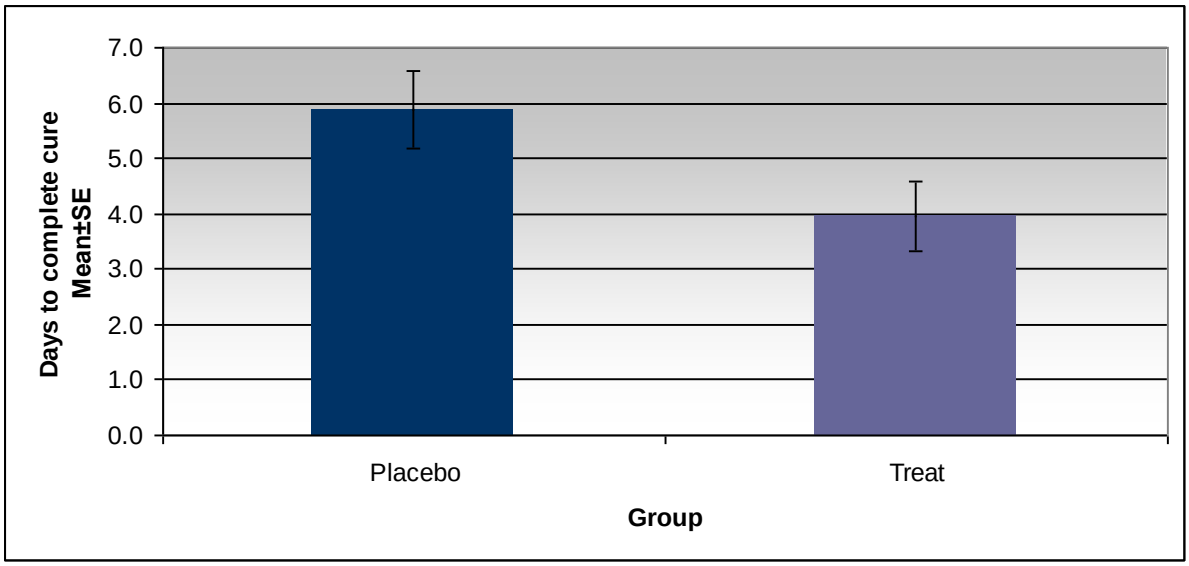


Fig 2: Number of treatments until total cure

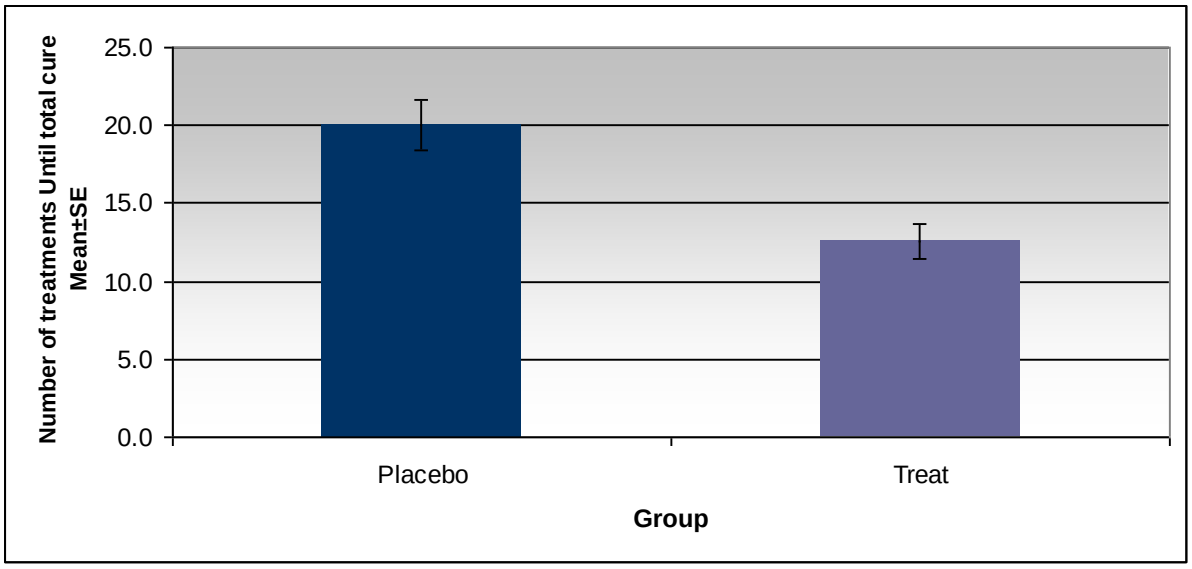


Table 14.2.2: Improvement in lesion condition at the end of follow up

	Placebo		*Treat*	
	N	***%***	***N***	***%***
Number of subjects	20	100%	20	100%
Complete study	18	90%	20	100%
Complete recovery				
Pain	18	100%	20	100%
Burning sensation	18	100%	20	100%
Speech difficulty	18	100%	20	100%
Eating/Drinking difficulty	18	100%	20	100%
General status of lesions	18	100%	20	100%

All subjects in both groups demonstrated complete recovery

Table 14.2.3: Lesion size at end of follow-up

		Treatment	
		Placebo	**Treat**
Lesion 1 Size (mm^2)	N	18	20
	Mean	0	0
	Median	0	0
	SD	0	0
	Minimum	0	0
	Maximum	0	0
Lesion 2 Size (mm^2)	N	6	6
	Mean	0	0
	Median	0	0
	SD	0	0
	Minimum	0	0
	Maximum	0	0
Lesion 3 Size (mm^2)	N	1	1
	Mean	0	0
	Median	0	0
	SD	.	.
	Minimum	0	0
	Maximum	0	0

All subjects in both groups demonstrated no lesions at the end of follow-up, therefore size equal to 0.

14.3 Efficacy – Subjective evaluation

Table 14.3.1: Time to total cure by home diary

		Placebo	*Treat*	*P value*
Days to Cure (based on Diary)	N	14	14	0.046
	Mean	5.86	3.64	
	Median	5.50	2.00	
	SD	2.82	2.76	
	Minimum	2.00	1.00	
	Maximum	12.00	9.00	

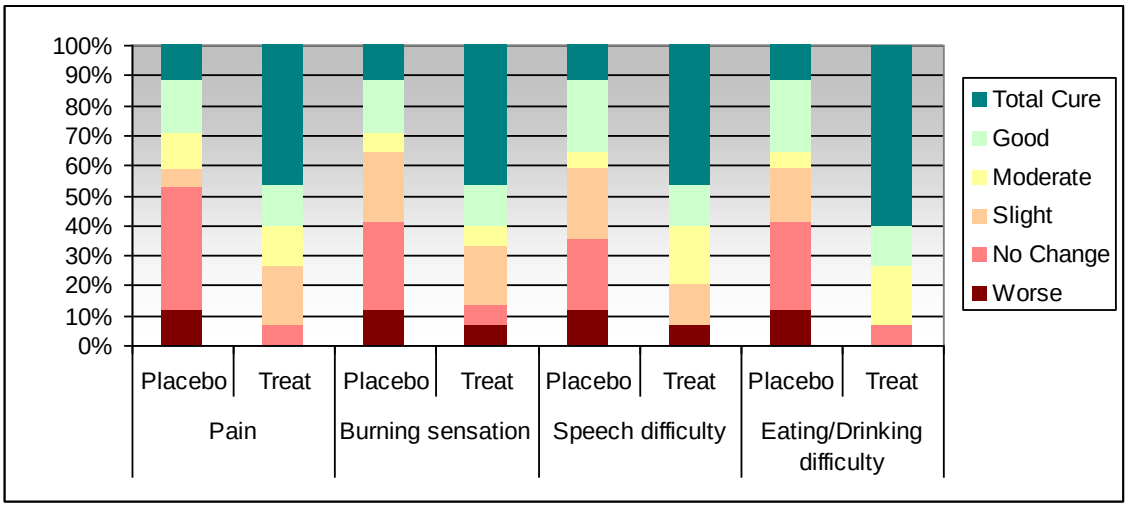
There is a significant difference in the number of days until total cure, the treated group has significantly less days until cure (3.64±2.76 vs. 5.85±2.82 p=0.046)

Table 14.3.2: Stage of cure after two days of treatments

Good to total cure		***Total cure***		***Good***		***Moderate***		***Mild***		***No change***		***Worse***		***Total***		
29.4%	5	11.8%	2	17.6%	3	11.8%	2	5.9%	1	41.2%	7	11.8%	2	17	Pain	Placebo
29.4%	5	11.8%	2	17.6%	3	5.9%	1	23.5%	4	29.4%	5	11.8%	2	17	Burning sensation	
35.3%	6	11.8%	2	23.5%	4	5.9%	1	23.5%	4	23.5%	4	11.8%	2	17	Speech difficulty	
35.3%	6	11.8%	2	23.5%	4	5.9%	1	17.6%	3	29.4%	5	11.8%	2	17	Eating/Drinking difficulty	
60.0%	9	46.7%	7	13.3%	2	13.3%	2	20.0%	3	6.7%	1	0.0%	0	15	Pain	Treat
60.0%	9	46.7%	7	13.3%	2	6.7%	1	20.0%	3	6.7%	1	6.7%	1	15	Burning sensation	
60.0%	9	46.7%	7	13.3%	2	20.0%	3	13.3%	2	0.0%	0	6.7%	1	15	Speech difficulty	
73.3%	11	60.0%	9	13.3%	2	20.0%	3	0.0%	0	6.7%	1	0.0%	0	15	Eating/Drinking difficulty	

After two days of treatment, in the treated group the majority (60% to 73.3%) stated good to total cure in all measurements compared to approximately 29% to 35% in the placebo group.

Fig2: Stage of cure after two days of treatments



14.4 Convenience of use – Subjective evaluation

Table 14.4.1: Previous treatments

P value	*Total*	*Treat*		*Placebo*		
	N	%	N	%	N	
	33	100%	16	100%	17	Number of subjects
0.721	22	62.5%	10	70.6%	12	Used previous treatments
		20.0%	2	50.0%	6	Aphtagon
		50.0%	5	8.3%	1	Kanka
		30.0%	3	25.0%	3	Oracorte
		30.0%	3	33.3%	4	Other

The majority of the placebo group used Aphtagon in the past,
The majority of the treat group used Kanka in the past.

Table 14.4.2: Comparing the device to previous treatments

P value	*Total*	*Treat*		*Placebo*		
	N	%	N	%	N	
	24	100%	11	100%	14	Number of subjects
0.721	22	62.5%	10	70.6%	12	Used previous treatments
0.314						Grade effectiveness of device
		20.0%	2	16.7%	2	Less effective
		.0%	0	25.0%	3	Similar
		40.0%	4	41.7%	5	Better
		40.0%	4	16.7%	2	Much better

80% of subjects from treated group grade the device better to much better that comparative treatments.
Only 16.7% from placebo group grade the device as much better,

Table 14.4.3: Comfort of use

Treat		***Placebo***		
%	N	%	N	
100.0%	13	100.0%	14	Comfort for use
				Comments
	8		8	Comfortable
			1	Complicated to clean after each use
	1		1	Comfortable but not effective
			1	If it was smaller it wouldl be better
	1			Depends on location
			1	Too long
			1	Not greasy or sandy fill in mouth

All subjects stated that the device is comfort for use

Table 14.4.4: Side Effects

Treat		*Placebo*		
%	N	%	N	
100.0%	16	100.0%	16	No side effects

No side effects were recorded

Table 14.4.5: Prefer to use the device again on the occurrence of aphta

Treat		*Placebo*		
%	N	%	N	
86.7%	13	80.0%	12	Use again

The majority of both groups would like to use the device again (above 80%)

Table 14.4.6: Will you buy the device if exist in the market

Treat		*Placebo*		
%	N	%	N	
86.7%	13	60.0%	9	Buy the device

86.7% of the subjects in the treated group would like to buy the device compared to only 60% of subjects in the placebo group.

14.5 Safety

Table 14.5.1: Concomitant medications

Related AE	Indication	Ongoing	Start date	Route	Daily Dose	Units	Drug Name	ID	Group
No	hypothyroidism	Yes	01.1.2002	PO	100	mg	elthroxin	3	Placebo
No	hypercholesterolemia	Yes	01.4.2007	PO	40	mg	t.simvastatin	21	Placebo

Table14.5.2: Treatment-emergent adverse events

No adverse events were recorded.

Table 14.5.3: Reasons for study termination

Treat		***Placebo***		
%	***N***	***%***	***N***	
100	20	100	20	Number of subjects N
				Study completed
100	20	90	18	Yes
0	0	10%	2	No
				Reasons for premature termination
0	0	5	1	Lost to follow-up
0	0	5	1	Protocol violation (use additional medications)