8. Safety Evaluation

8.1 Extent of Exposure

In both SeraSeal treatment groups, all of the patients were exposed to the hemostatic agent for only 1-2 minutes with each application throughout the surgical procedure. Once hemostasis had occurred the investigational product was removed through irrigation and suction. The number of applications in the SeraSeal syringe treatment group had a range of 1-6 applications, with a mean of 3.64 (± 1.42), while the spray treatment group had a range of 1-8 applications and a mean of 2.83 (± 1.92).

The mean dose/application was 2640 IU (± 1170 IU) and 4380 IU (± 3300 IU) for the SeraSeal syringe and spray delivery systems, respectively, with an overall mean dose exposure of 3870 IU (± 2940 IU) for each application throughout the surgical procedure.

The drug concentration is directly linked to the dose level with each application and it does not accumulate on the surface of the wound, since it is removed a few minutes after each application; nor is it accumulated in the plasma, because SeraSeal does not enter the systemic system.

8.2 Adverse Events

8.2.1 Brief Summary of Adverse Events

Only 1 patient (1.1%) from the SeraSeal spray treatment group, and no patients in the syringe treatment group, had treatment-emergent adverse exposure, with an overall < 0.001% episode.

Table 14 details the emergent adverse exposure from the two SeraSeal treatment groups.

9. Discussion and Overall Conclusions

The results of this unblinded controlled trial supports that SeraSeal is an effective hemostatic agent to control bleeding in a wide range of hemorrhages throughout the entire surgical procedure, using a single delivery system, without the use of another surgical modality. There were only 3 therapeutic breaks with the SeraSeal spray delivery system and none in the SeraSeal syringe treatment group, achieving 97.5% effectiveness, a level above the 95% parameter established in the protocol.

Table 19 Summary of Patient Distribution by Treatment Intent-to-Treat Population

	Treatment Group		
Study Center	**SeraSeal Syringe**	**SeraSeal Spray**	**Total**
Joaquin Albarran Hospital	26	63	89
Salvador Allende Hospital	4	6	10
National Institute for Cardio-Vascular Surgery	6	15	21
Total	36	84	120

Ref: Individual Patient Data Listing, appendix 12.4.

Table 20 Summary of Demographic Data Intent-to-Treat Population

		Treatment Group					
		SeraSeal Syringe		**SeraSeal Spray**		**Total Patients**	
		N	**%**	**N**	**%**	**N**	**%**
Race	Hispanic	36	30.0	84	70.0	120	100.0
Sex	Male	15	41.7	33	39.3	48	40.0
	Female	21	58.3	51	60.7	72	60.0
Age	18-19	1	2.8	2	2.4	3	2.5
	20-29	1	2.8	11	13.1	12	10.0
	30-39	7	19.4	15	17.9	22	18.3
	40-49	8	22.2	17	20.2	25	20.8
	50-59	6	16.7	16	19.0	22	18.3
	60-69	8	22.2	14	16.7	22	18.3
	70-79	4	11.1	6	7.1	10	8.3
	80-86	1	2.8	3	3.6	4	3.3
Total Patients		36	100.0	84	100.0	120	100.0

Ref. Individual Patient Data Listing, appendix 12.4.

Table 21 Summary of Demographic Mean (+/-) Data Intent-to-Treat Population

		Treatment Group		
		SeraSeal Syringe	SeraSeal Spray	Total Patients
Age (yrs)	mean	47.4	43.9	45.6
	minimum	19.0	18.0	18.0
	maximum	86.0	86.0	86.0
	Std Dev	15.7	16.6	15.9

Ref. Individual Patient Data Listing, appendix 12.4.

Table 22 Summary of Height and Weight at Baseline Intent-to-Treat Population

	Treatment Group									
	SeraSeal Syringe					SeraSeal Spray				
	n	mean	SD	min	max	n	mean	SD	min	max
Height (in)	36	65.5	2.9	62	72	84	65.5	2.7	60	71
Weight (lbs)	36	152.1	14.1	125	182	84	148.9	12.5	118	179

Ref. Individual Patient Data Listing, appendix 12.4.

Table 23 Summary of Comparing Time to Hemostasis Between Normal to Warfarin Patients

	Treatment Groups							
	Normal Patients				Warfarin Patients			
Hemostasis (sec)	SeraSeal Syringe	n	SeraSeal Spray	n	SeraSeal Syringe	n	SeraSeal Spray	n
mean	1.00	15	1.64	79	1.00	21	1.80	5
minimum (min)	1.00		1.0		1.00		1.00	
maximum (max)	1.00		7.0		1.00		3.00	
Std Dev	0.00		2.25		0.00		0.84	

Ref. Individual Patient Data Listing, appendix 12.4.

Table 24 Summary of Time to Hemostasis Between Normal and Warfarin Patients

Hemostasis (sec)	Normal Patients (n=94)	Warfarin Patients (n=26)
mean	1.47	1.14
minimum (min)	1.00	1.00
maximum (max)	7.00	3.00
Std Dev	1.20	0.45

Ref. Efficacy Response Data Listing, appendix 12.2.4

Table 25 Summary of the Number of SeraSeal Applications Between Normal and Warfarin Patients

Hemostasis (sec)	Normal Patients				Warfarin Patients			
	SeraSeal Syringe	n	SeraSeal Spray	n	SeraSeal Syringe	n	SeraSeal Spray	n
mean	3.33	12	2.76	79	3.79	24	4.0	5
minimum (min)	1		1		1.0		2.0	
maximum (max)	6		8		6.0		6.0	
Std Dev	1.67		1.93		1.28		1.58	

Ref. Individual Patient Data Listing, appendix 12.4.

Table 26 Summary of the Mean (+/-) Applications of SeraSeal Between Normal and Warfarin Patients

Application	Normal Patients (n=94)	Warfarin Patients (n=26)
mean	2.84	4.58
minimum (min)	1.0	1.0
maximum (max)	8.0	6.0
Std Dev	1.90	4.32

Ref. Efficacy Response Data Listing, appendix 12.2.4.

Table 27 Summary of Dosage Between SeraSeal Treatment Groups of Normal and Warfarin Patients

Dosage (IU)	Normal Patients				Warfarin Patients			
	SeraSeal Syringe	n	SeraSeal Spray	n	SeraSeal Syringe	n	SeraSeal Spray	n
mean	2953.8	15	4234.2	79	2478.0	21	7800	5
minimum (min)	1500		1500		1500		4500	
maximum (max)	6000		15000		6000		12000	
Std Dev	1289.4		3202.4		1104.0		2885.3	

Ref. Individual Patient Data Listing, appendix 12.4.

Table 28 Summary of Dosage Between Normal and Warfarin Patients

Dosage (IU)	Normal Patients (n=94)	Warfarin Patients (n=26)
mean	4780.8	3403.8
minimum (min)	1500	1500
maximum (max)	15000	12000
Std Dev	7909.5	2654.9

Ref. Efficacy Response Data Listing, appendix 12.2.4.

Table 29 Summary of Vital Signs

Systolic (BP (mmHg) (n=120)		Pre-Op	Post-Op	Change
Baseline	mean	125.18	131.30	-0.76
	SD	7.91	9.60	2.82
Distolic BP (mmHg) (n=120)				
Baseline	mean	81.38	79.78	-0.55
	SD	7.89	9.99	8.63
Pulse (bpm) (n=120)				
Baseline	mean	81.61	81.24	-1.07
	SD	7.86	2.88	3.16

Ref. Demographic Data Listing, appendix 12.2.3

Table 30 Safety Summary of Laboratory Results Intent-to-Treat Population

Seraseal Syringe	Pre-Op			Post-Op			Change		
	n	mean	SD	n	mean	SD	n	mean	SD
HGB	36	12.4	2.3	36	13.2	4.1	36	30.1	0.9
HCT	36	37.1	3.3	36	35.8	3.4	36	-1.4	1.8
PT	36	13.6	1.8	36	13.3	1.1	36	-0.2	1.2
PTT	36	27.5	3.2	36	27.6	5.2	36	0.6	1.5
SeraSeal Spray	**Pre-Op**			**Post-Op**			**Change**		
	n	**mean**	**SD**	**n**	**mean**	**SD**	**n**	**mean**	**SD**
HGB	84	12.7	1.4	84	12.4	1.5	84	-0.3	0.4
HCT	84	39.4	6.9	84	37.2	6.9	84	-2.2	1.2
PT	84	11.9	0.4	84	11.8	1.7	84	> 0.1	0.3
PTT	84	30.3	2.5	84	31.9	2.3	84	1.7	2.2

Ref. Individual Patient Data Listing, appendix 12.4.

12.2.6 Adverse Event Listing

Adverse Event Listing

In the SeraSeal spray treatment group, there was one reported adverse event (1.19%) and none in the SeraSeal syringe treatment group, with an overall (0.8%) reported adverse event in this study.

SeraSeal Spray Treatment Group									
	Mild		Moderate		Some		Total		Total
Nervous System	Related	NR	Related	NR	Related	NR	Related	NR	Related + NR
Dizziness [a]	1 (1.19%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.19%)	0 (0.00%)	1 (1.19%)
Insomnia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervousness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
[a] Patient CV07 experienced dizziness within 24 hours after surgery.									

VI

MINISTERIO DE SALUD PUBLICA
CENTRO PARA EL DESARROLLO DE LA FARMACOEPIDEMIOLOGIA

Havana, Cuba
December 10, 2004

Dear Dr. Leon Wortham,

The evaluation of the hemostatic agent, FastAct, was quite an ambitious study, requiring the product to control bleeding throughout the surgical procedure without the use of other modalities, with at least a 90% success rate of achieving a collective hemostatic time of less than 5 minutes.

FastAct demonstrated its ability to control bleeding in tissues difficult to manage by other methods. As a result, substantial savings in valuable resources, such as blood transfusions, surgical disposables, hospital stay, were seen in this study.

It is the recommendation of the members of the Scientific Committee, along with this department, to approve FastAct as a safe and effective hemostatic agent.

Dr Julian Pérez Peña
Republica De Cuba
Ministerio De Salud Publica
Centro Para El Desarrollo De La
Farmacoepidemiologica (CDF)

Dr. Ignacio A. Morales Diaz
Hospital Clínico Quirúrgico Joaquín Albarrán

Dr. Danilo Ducongé
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