

## **SUPPLEMENTAL MATERIAL**

### **THE ALBUMIN IN SUBARACHNOID HEMORRHAGE (ALISAH) MULTICENTER PILOT CLINICAL TRIAL: SAFETY AND NEUROLOGIC OUTCOMES**

Jose I Suarez, MD<sup>1</sup>, Renee H. Martin, PhD<sup>2</sup>, Eusebia Calvillo, RN<sup>1</sup>, Eric M Bershad, MD<sup>1</sup>, R Loch MacDonald, MD<sup>3</sup>, John Wong,  
MD<sup>4</sup>, Robert Harbaugh, MD<sup>5</sup>, for the ALISAH Investigators<sup>6</sup>

1 Department of Neurology, Baylor College of Medicine, Houston, Tx; 2 Division of Biometry and Biostatistics, Medical University of South Carolina, Charleston, SC; 3 Department of Neurosurgery, University of Toronto, Toronto, ON, Canada; 4 University of Calgary, Calgary, AB, Canada; 5 Penn State University, Hershey, PA; 6 the complete list of investigators is provided in the appendix

#### **Corresponding author:**

Jose I Suarez, MD

Department of Neurology

Baylor College of Medicine

6501 Fannin St, NB 302

Houston, TX 77030

Tel. 713-798-8472

FAX: 713-798-3091

E-mail: [jisuarez@bcm.edu](mailto:jisuarez@bcm.edu)

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**Tables:8**

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**Subject code:** [50] Cerebral Aneurysm, AVM, & Subarachnoid hemorrhage

Clinical Trial Registration: <http://clinicaltrials.gov/ct2/show/NCT00283400?term=subarachnoid+hemorrhage+houston&rank=1>

## **Table S1. ALISAH Investigators**

### **Executive Committee**

Jose I Suarez, MD, Baylor College of Medicine, Houston, TX (PI); Renee' Martin, PhD, Medical University of South Carolina, Charleston, SC (Statistician); Catherine Dillon, Medical University of South Carolina, Charleston, SC (Data Manager); Eusebia Calvillo, RN, Baylor College of Medicine, Houston, TX (Project Manager); Claudia S. Moy, PhD, NINDS, NIH, Rockville, MD (NINDS Project Officer)

### **External Safety Monitor**

Gene Sung, MD, University of Southern California, Los Angeles, CA (neurointensivist)

### **Data and Safety Monitoring Board (DSMB)**

Paul Muizelaar, MD, PhD, UC Davis, DSMB chairman; William Clarke, MS, PhD, University of Iowa; Steven M Greenberg, MD, PhD, Harvard School of Medicine; Leslie McClure, PhD, University of Alabama at Birmingham; Emmy Miller, RN, PhD, Baylor College of Medicine; Julie Swain, MD, Fallbrook, CA; Howard Yonas, MD University of New Mexico; Peter Gilbert, PhD, NINDS DSMB Liaison.

**Participating clinical sites (with numbers of subjects contributed):** Penn State University, Hershey, Pennsylvania, USA (15):

Robert Harbaugh, MD (PI), Deborah Hoffman, RN (coordinator); Baylor College of Medicine, Houston, Texas, USA (12): Jose I Suarez, MD (PI), Eric M Bershad, MD (sub-PI), Eusebia Calvillo, RN (coordinator), Jose G Diez, MD, Baylor College of Medicine, Houston, TX (Study Cardiologist), Edward Duckworth, MD, Baylor College of Medicine, Houston, TX (Study Neurosurgeon), Michel Mawad, MD (Study Neuroradiologist); University of Toronto, Toronto, Ontario, Canada (9): R Loch Macdonald, MD (PI), Yangmei Li,

PhD (coordinator); University of Calgary, Calgary, Alberta, Canada (7): John Wong, MD (PI), Michael D Hill, MD (sub-PI), Karla Ryckborst, BA, RN (coordinator); Johns Hopkins University, Baltimore, Maryland, USA (3): Judy Huang, MD (PI), Shannon Ledroux (coordinator); Case Western Reserve University, Cleveland, Ohio, USA (1): Jose I Suarez, MD (PI), Christopher Murphy, RN (coordinator).

**Table S2.** Inclusion and Exclusion Criteria

<p><b><i>Inclusions</i></b></p> <ul style="list-style-type: none"><li>• At least 18 but younger than 80 years of age.</li><li>• Onset of new neurological signs of subarachnoid hemorrhage within 72 hours at the time of evaluation and initiation of treatment with 25% human albumin.</li><li>• Clinical signs consistent with the diagnosis of subarachnoid hemorrhage including severe thunderclap headache, cranial nerve abnormalities, decreased level of consciousness, meningismus and focal neurological deficits.</li><li>• Head computed tomography demonstrates subarachnoid hemorrhage (rating scale 2-4).</li><li>• Cerebral angiography reveals the presence of saccular aneurysm(s) in a location that explains the subarachnoid hemorrhage.</li><li>• Treatment of cerebral aneurysm must be carried out prior to treatment initiation but within 72 hours of symptom onset. Accepted treatments of aneurysms include surgical clipping or endovascular embolization.</li><li>• Signed and dated informed written consent by the subject or his/her legally authorized representative.</li></ul>
<p><b><i>Exclusions</i></b></p> <ul style="list-style-type: none"><li>• Time of symptom onset cannot be reliably assessed.</li><li>• No demonstrable aneurysm by cerebral angiography.</li><li>• Evidence of traumatic, mycotic, or fusiform aneurysm by cerebral angiography.</li><li>• World Federation of Neurological Surgeons scale of IV and V</li><li>• Head computed tomography rating scale of 0 – 1</li><li>• History within the past 6 months, and/or physical findings on admission of decompensated heart failure (NYHA Class III and IV or heart failure requiring hospitalization). (162)</li><li>• Patient has received albumin prior to treatment assignment during the present admission.</li><li>• Hospitalization for or diagnosis of acute myocardial infarction within the preceding 3</li></ul>

months.

- Symptoms or electrocardiographic signs indicative of acute MI on admission.
- Electrocardiographic evidence and/or physical findings compatible with second- or third-degree heart block, or of cardiac arrhythmia associated with hemodynamic instability.
- Echocardiogram performed before treatment revealing a left ventricular ejection fraction  $\leq 40\%$  (if available).
- Serum creatinine  $> 2.0$  mg/dl or creatinine clearance  $< 50$  ml/min.
- Pregnancy, lactation or parturition within previous 30 days.
- Known allergy to albumin.
- Severe prior physical disability (Rankin Scale  $> 2$ ) that precludes evaluation of clinical outcome measures.
- History of severe chronic obstructive lung disease ( $FEV_1 < 50\%$  predicted, increased shortness of breath, and repeated exacerbations which have an impact on patients' QOL
- History of confirmed or suspected liver failure (increased prothrombin time, elevated liver enzymes, hypoalbuminemia, and hyperbilirubinemia with or without peripheral edema and encephalopathy)
- Current participation in another drug treatment protocol.
- Severe terminal disease with life expectancy less than 6 months.

**Table S3.** Serum albumin concentration up to 15 days after ALB treatment initiation.

SERUM ALBUMIN (G/DL)		DAY															
		BASELINE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
TIER 1	TOTAL_N	16	16	18	14	18	17	16	17	13	10	8	9	6	8	4	4
	Mean	3.51	3.51	3.99	4.28	4.53	4.61	4.73	4.82	4.89	4.43	4.13	4.16	4.05	3.80	4.07	4.12
	SD	0.43	0.35	0.36	0.43	0.58	0.54	0.64	0.60	0.55	0.48	0.47	0.67	0.32	0.42	0.63	0.75
	Median	3	3	4	4	4	5	5	5	5	5	4	4	4	4	4	4
	Min	3	3	3	4	4	4	3	4	4	3	3	3	4	3	3	3
	Max	5	4	5	5	6	6	6	6	6	5	5	6	5	4	5	5
TIER 2	TOTAL_N	15	14	17	19	19	19	15	16	15	13	10	7	8	6	6	5
	Mean	3.67	3.91	4.56	4.65	4.90	4.92	4.89	5.19	5.51	4.98	4.60	4.31	4.27	4.12	4.20	4.06
	SD	0.73	0.75	1.75	0.82	0.78	0.84	0.84	0.82	0.74	0.84	0.68	0.47	0.53	0.55	0.37	0.73
	Median	4	4	4	5	5	5	5	5	6	5	5	4	4	4	4	4
	Min	3	3	3	3	3	3	3	3	4	3	3	3	3	3	4	4
	Max	5	5	11	6	7	6	6	6	7	6	6	5	5	5	5	5
TIER 3	TOTAL_N	7	7	6	6	5	5	5	5	5	5	4	4	3	3	2	2
	Mean	3.26	3.13	4.22	4.57	4.86	4.40	4.64	4.72	4.68	4.76	4.62	4.68	4.30	4.23	3.20	3.55
	SD	0.44	0.35	0.25	0.54	0.83	1.19	1.29	1.57	1.54	1.68	1.68	1.75	2.07	1.91	1.56	2.19
	Median	3	3	4	5	5	4	5	5	6	5	5	5	5	5	3	4
	Min	3	3	4	4	4	3	3	3	3	2	2	2	2	2	2	2
	Max	4	4	5	5	6	6	6	6	6	7	6	6	6	6	4	5

Definitions: ALB: 25% human albumin; Tier 1: 0.625 g/Kg/d x 7 days; Tier 2: 1.25 g/Kg/d x 7 days; Tier 3: 1.875 g/Kg/d x 7 days; SD: standard deviation; Min: minimum; Max: maximum.

**Table S4.** Maximum Mean Arterial Blood Pressure in mmHg up to 15 days after ALB treatment initiation.

MAX MEAN ARTERIAL PRESSURE		DAY															
		BASELINE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
TIER 1	TOTAL_N	20	20	20	20	20	20	20	19	18	16	15	13	11	9	7	4
	Mean	106.75	109.80	108.90	117.65	118.80	119.40	119.10	115.32	114.61	118.63	114.47	115.85	123.55	117.44	113.29	119.75
	SD	8.23	16.8	17.5	14.8	13.5	16.7	14.8	18.5	17.4	20.3	25.6	21.4	19.6	16.6	21.9	21.8
	Median	108	108	115	118	121	116	119	115	114	118	109	118	119	115	111	116
	Min	90	89	52	82	94	82	94	68	86	87	79	84	87	94	78	98
	Max	126	167	126	140	141	160	143	154	162	165	182	165	157	152	151	149
TIER 2	TOTAL_N	19	19	20	20	20	20	19	19	18	17	15	14	11	11	11	9
	Mean	117.58	115.26	120.00	118.95	122.70	125.20	122.58	118.79	125.22	118.41	117.27	113.57	118.91	123.91	116.91	111.44
	SD	37.6	11.1	20.0	11.4	13.3	18.1	13.6	16.0	16.1	15.8	16.1	14.2	16.5	18.8	14.1	17.2
	Median	112	118	120	122	122	126	126	120	124	124	118	111	123	121	117	114
	Min	87	87	75	89	94	83	93	84	90	82	86	93	96	98	94	86
	Max	261	133	170	135	145	151	142	148	159	146	143	136	146	160	138	142
TIER 3	TOTAL_N	7	7	7	7	7	7	7	6	6	6	5	5	4	4	3	3
	Mean	106.43	108.71	115.00	114.57	112.43	112.43	116.86	112.67	117.50	111.33	116.80	109.40	113.00	109.75	105.67	113.33
	SD	9.66	13.2	11.1	15.6	14.0	10.8	12.9	11.7	13.6	13.4	11.5	7.64	8.76	8.66	7.37	24.0
	Median	105	107	115	115	115	113	116	118	122	116	118	110	110	109	103	100
	Min	95	95	98	95	98	94	96	96	94	86	101	99	107	100	100	99
	Max	124	135	135	142	136	125	135	124	131	122	128	118	126	121	114	141

Definitions: ALB: 25% human albumin; Tier 1: 0.625 g/Kg/d x 7 days; Tier 2: 1.25 g/Kg/d x 7 days; Tier 3: 1.875 g/Kg/d x 7days; SD: standard deviation; Min: minimum; Max: maximum.



**Table S5.** Serum Osmolality (mOsm/L) up to 15 days after ALB treatment initiation.

PLASMA OSMOLALITY (MOSM/L)		DAY															
		BASELINE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
<b>TIER 1</b>	<b>TOTAL_N</b>	6	10	13	14	14	13	12	9	7	7	4	4	2	3	2	0
	<b>Mean</b>	291.17	293.20	294.38	293.00	293.57	291.00	290.25	291.56	290.86	285.29	280.00	279.50	283.50	278.33	286.00	
	<b>SD</b>	9.83	8.07	6.37	8.53	10.4	6.93	10.2	12.4	9.41	13.6	6.38	11.8	4.95	8.62	19.8	
	<b>Median</b>	288	290	297	293	295	290	291	291	291	283	282	276	284	280	286	
	<b>Min</b>	283	285	284	278	273	280	273	276	276	271	271	270	280	269	272	
	<b>Max</b>	310	310	301	308	309	307	309	313	305	309	285	296	287	286	300	
<b>TIER 2</b>	<b>TOTAL_N</b>	11	14	15	14	14	14	17	13	11	11	8	6	6	4	3	3
	<b>Mean</b>	289.82	286.79	287.80	291.36	290.50	288.93	291.41	302.23	298.45	290.64	289.50	294.67	289.83	288.50	288.00	287.33
	<b>SD</b>	7.33	8.29	8.12	9.20	10.5	10.2	11.9	29.8	21.7	22.9	10.1	9.89	9.81	7.14	9.17	2.31
	<b>Median</b>	290	287	285	288	290	287	288	293	293	288	288	298	288	286	286	286
	<b>Min</b>	276	268	275	275	276	278	279	275	274	254	278	280	280	283	280	286
	<b>Max</b>	300	300	306	314	316	317	328	385	358	347	307	304	306	299	298	290
<b>TIER 3</b>	<b>TOTAL_N</b>	5	6	6	6	6	6	5	6	5	5	4	3	3	2	1	1
	<b>Mean</b>	287.80	283.33	290.17	303.00	289.83	289.50	295.00	294.17	287.00	286.00	290.75	282.33	298.67	282.50	283.00	277.00
	<b>SD</b>	6.30	5.99	11.5	36.1	10.1	17.1	18.7	17.2	15.9	8.97	22.0	2.52	26.3	0.71	.	.
	<b>Median</b>	288	283	287	285	285	285	287	287	283	285	283	282	284	283	283	277
	<b>Min</b>	278	278	280	277	281	270	276	277	270	275	274	280	283	282	283	277
	<b>Max</b>	295	291	309	370	307	320	317	320	313	300	323	285	329	283	283	277

Definitions: ALB: 25% human albumin; Tier 1: 0.625 g/Kg/d x 7 days; Tier 2: 1.25 g/Kg/d x 7 days; Tier 3: 1.875 g/Kg/d x 7days; SD: standard deviation; Min: minimum; Max: maximum.

**Table S6.** Serum creatinine up to 15 days after ALB treatment initiation.

SERUM CREATININE (MG/DL)		DAY															
		BASELINE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
TIER 1	TOTAL_N	20	20	19	19	20	20	20	18	18	13	13	13	11	9	7	5
	Mean	0.69	0.70	0.67	0.68	0.65	0.65	0.69	0.67	0.68	0.66	0.69	0.68	0.69	0.65	0.65	0.62
	SD	0.11	0.10	0.13	0.13	0.12	0.14	0.14	0.13	0.13	0.09	0.16	0.18	0.22	0.18	0.17	0.13
	Median	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Min	1	1	1	0	0	0	0	0	0	1	1	0	0	1	0	1
	Max	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
TIER 2	TOTAL_N	20	19	20	20	20	20	19	19	18	16	14	13	10	8	10	8
	Mean	0.68	0.67	0.64	0.65	0.66	0.65	0.63	0.63	0.65	0.64	0.61	0.63	0.55	0.61	0.63	0.57
	SD	0.13	0.16	0.18	0.16	0.18	0.15	0.17	0.16	0.16	0.14	0.16	0.17	0.14	0.18	0.15	0.12
	Median	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Min	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Max	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
TIER 3	TOTAL_N	6	6	7	7	7	6	7	6	5	6	5	5	4	4	3	3
	Mean	0.55	0.52	0.56	0.58	0.65	0.69	0.72	0.69	0.71	0.70	0.76	0.77	0.79	0.72	0.73	0.72
	SD	0.17	0.11	0.11	0.12	0.27	0.28	0.31	0.30	0.29	0.26	0.39	0.31	0.28	0.23	0.23	0.24
	Median	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Min	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1
	Max	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Definitions: ALB: 25% human albumin; Tier 1: 0.625 g/Kg/d x 7 days; Tier 2: 1.25 g/Kg/d x 7 days; Tier 3: 1.875 g/Kg/d x 7days; SD: standard deviation; Min: minimum; Max: maximum.

**Table S7.** Daily fluid balance up to 15 days after ALB treatment initiation.

FLUID BALANCE		DAY															
		BASELINE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
TIER 1	TOTAL_N	20	20	20	19	20	20	20	16	17	13	12	11	9	9	6	4
	Mean	-378.9	-414.1	-630.3	-524.8	-130.8	-27.05	93.20	394.06	134.29	334.23	-235.4	139.09	168.56	311.44	1360.8	903.50
	SD	1198	1143	1247	1278	1428	967	1004	784	785	1595	833	1201	809	1127	649	1195
	Median	-273	-273	-303	-338	-177	-25	73	468	133	-132	-262	-364	175	212	1514	528
	Min	-2498	-2498	-4036	-3155	-3011	-1307	-2332	-1224	-1730	-2559	-1369	-1380	-1340	-1510	142	0
	Max	1878	1378	1280	1298	2493	2042	1619	1658	1270	3150	1648	3011	1356	2120	2041	2558
TIER 2	TOTAL_N	19	18	20	20	20	19	18	18	18	12	12	12	9	8	8	8
	Mean	516.11	478.33	-145.3	72.10	-81.05	586.84	-42.43	28.28	-281.5	207.67	385.50	165.50	73.89	-513.8	170.88	209.88
	SD	1505	1326	1385	1298	1412	1716	1510	1279	1216	1147	1085	1096	861	1227	1185	1071
	Median	858	461	-138	150	-210	165	-23	-258	-96	193	301	73	172	-553	318	55
	Min	-4100	-1501	-3960	-2325	-2333	-1447	-4377	-1889	-3062	-1000	-1889	-2000	-1440	-1870	-2304	-1513
	Max	2045	3500	2164	2217	3932	5111	2411	2730	1700	3050	2600	2372	1200	1350	1770	2220
TIER 3	TOTAL_N	7	7	7	7	7	7	6	5	4	4	4	4	3	3	3	3
	Mean	360.86	-623.1	-1291	-134.6	166.43	120.57	532.50	1321.8	1136.8	329.00	-539.8	149.50	-383.3	-200.3	258.67	-76.67
	SD	1212	1788	1341	1470	1334	987	817	534	818	867	1161	1538	953	1321	1498	1091
	Median	181	-185	-1755	385	-334	-300	410	1565	1125	553	-752	-571	-65	40	1066	-635
	Min	-1320	-3978	-3201	-2220	-1375	-1015	-515	725	197	-864	-1705	-710	-1455	-1625	-1470	-775
	Max	2119	1495	705	1215	2119	1869	1764	1933	2100	1075	1050	2450	370	984	1180	1180

**Table S8.** Daily weights up to 15 days after ALB treatment initiation.

WEIGHT		DAY															
		BASELINE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
TIER 1	TOTAL_N	18	20	20	19	20	20	20	19	9	7	11	8	4	6	4	3
	Mean	73.17	73.45	73.45	72.31	73.06	73.11	73.06	72.69	67.33	64.13	71.75	73.85	68.82	62.52	64.40	71.37
	SD	13.6	14.0	14.0	13.6	13.7	13.7	13.7	14.0	11.6	18.3	15.5	14.7	16.4	13.0	15.6	15.9
	Median	74	74	74	72	74	74	74	72	67	67	67	72	66	59	63	81
	Min	53	53	53	53	53	53	53	53	53	36	53	53	53	49	50	53
	Max	92	98	98	98	98	98	98	98	98	90	90	101	96	90	83	82
TIER 2	TOTAL_N	17	20	20	20	20	20	19	19	16	12	11	10	7	5	5	4
	Mean	72.31	72.65	72.59	72.74	72.64	72.67	72.71	72.65	73.72	74.14	73.48	73.53	73.39	66.82	66.90	69.30
	SD	10.0	9.87	10.4	9.98	9.98	9.96	10.3	10.3	12.0	11.6	11.2	11.5	12.1	8.66	8.63	8.32
	Median	70	70	69	73	72	72	70	70	72	75	75	74	75	64	65	71
	Min	59	59	59	59	59	59	59	59	59	59	59	59	59	59	59	59
	Max	90	90	94	90	90	90	90	90	95	95	90	89	90	77	77	77
TIER 3	TOTAL_N	7	7	7	7	5	5	3	3	2	2	2	2	2	1	0	1
	Mean	67.61	67.63	68.30	68.19	70.40	71.28	66.67	66.67	69.95	71.50	69.95	69.30	69.95	87.80	.	87.00
	SD	15.0	15.0	15.5	15.3	13.9	14.3	18.2	18.2	25.4	27.6	25.4	24.5	25.4	.	.	.
	Median	74	74	74	74	74	78	61	61	70	72	70	69	70	88	.	87
	Min	46	46	46	46	52	52	52	52	52	52	52	52	52	88	.	87
	Max	87	87	87	87	87	87	87	87	87	88	91	88	87	88	88	.

Definitions: ALB: 25% human albumin; Tier 1: 0.625 g/Kg/d x 7 days; Tier 2: 1.25 g/Kg/d x 7 days; Tier 3: 1.875 g/Kg/d x 7days; SD: standard deviation; Min: minimum; Max: maximum.