Pulmonary and Critical Care Medicine
University of North Carolina at Chapel Hill

A Phase II, Placebo-Controlled, Multicenter Pilot Study to Evaluate the Safety and Efficacy of BIO-11006 Inhalation Solution in Patients with Acute Respiratory Distress Syndrome

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Study Rationale and Overview

- Bio-11006 is a peptide inhibitor of Myristoylated Alanine-Rich C-Kinase Substrate (MARCKS). MARCKS is required for degranulation, and secretion of inflammatory modulators from neutrophils. BIO-11006 prevented and reversed the development of ARDS in animal models of (LPS and *S. pneumoniae*).
- This randomized, double-blind, parallel group, placebo-controlled clinical study was designed to evaluate the safety and efficacy of BIO-11006 in sepsis-derived ARDS.
- BIO-11006 (125 mg/3 ml) was administered BID by the Aeroneb Pro nebulizer. Placebo was .45 normal saline.
- Adverse events was the primary safety endpoint. Mortality was the primary efficacy endpoint. Other secondary endpoints included oxygenation, VFDs, and ICU-free days.

Study Overview: Inclusion/Exclusion Criteria

- **Inclusion Criteria**: Clinical diagnosis of sepsis or septic shock defined as: Known or suspected infection and at least 2 of 3 criteria for SIRS,
- enrollment must have occurred within 72 hours of first meeting the Berlin ARDS criteria and no more than 96 hours from the initiation of mechanical ventilation,
- lung injury of acute onset (within 1 week of an apparent clinical insult),
- bilateral opacities on chest imaging not fully explained by effusions, lobar/lung collapse, or nodules,
- respiratory failure not fully explained by cardiac failure or fluid overload,
- decreased arterial PaO_2/FiO_2 ratio (<300) while on a minimum positive end-expiratory pressure (PEEP) of 5 cm H_2O

- **Exclusion Criteria:** Age < 18 years or >90 years old,
- pregnant or breastfeeding,
- any irreversible disease or condition for which 6-month mortality was estimated to be > 50%,
- moderate to severe liver failure (Child-Pugh Score > 9),
- Severe chronic respiratory disease with a $PaCO_2$ > 50 mmHg or the use of home oxygen,
- major trauma in the prior 5 days,
- lung transplant patient,
- moribund patient not expected to survive 24 hours,
- World Health Organization (WHO) Functional Class III or IV pulmonary hypertension,
- currently receiving extracorporeal life support or high-frequency oscillatory ventilation,
- burn victims >20% total body surface area or with known airway inhalation injury,
- neutropenic and/or bone marrow transplant patient

Baseline Demographics and Severity

Variable	All Patients	Placebo	BIO-11006
N	38	19	19
Age in years; Mean ± SD	55.8 ± 15.2	53.2 ± 13.0	58.4 ± 17.1
Gender, n (%)			
Female	19 (50%)	9 (47%)	10 (53%)
Male	19 (50%)	10 (53%)	9 (47%)
Race, n (%)			
White/Caucasian	32 (84%)	17 (89%)	15 (79%)
Black/AA	6 (16%)	2 (11%)	4 (21%)
Smoking Status, n (%)			
Ever smoker (Yes)[a]	22 (59%)	10 (56%)	12 (63%)
Current Smoker (Yes)	14 (64%)	9 (90%)	5 (42%)
Current Smoker (No)	8 (36%)	1 (10%)	7 (58%)
BMI (kg/m^2); Mean ± SD	32.7 ± 9.3	33.5 ± 9.7	32.7 ± 9.3
SOFA Score; Mean ± SD	11.8 ± 3.9	11.9 ± 3.8	11.7 ± 4.0
PaO2/FiO2 Ratio; Mean ± SD	112.3 ± 48.7	105.6 ± 46.3	119.0 ± 51.4

a) Ever smoker is >100 cigarettes in a lifetime

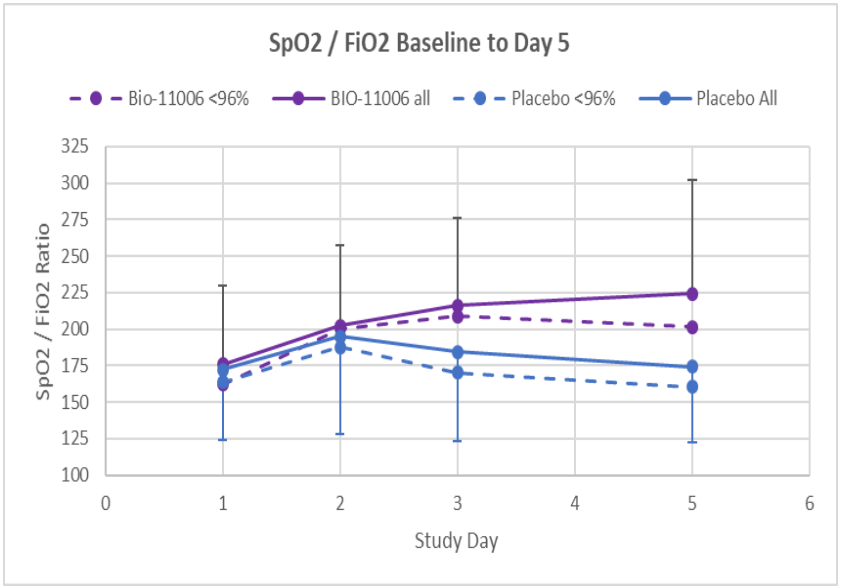
Adverse Events

All patients	Total N = 38	Placebo N = 19	BioMarck 11006 N = 19
Number of Adverse Events by Category, **All severities**	35	12	23
Cardiac	7	3	4
Dermatologic	2	1	1
GI	3	2	1
Hematologic	1	0	1
Hepatobiliary	5	1	4
Metabolic	3	1	2
Pulmonary	9	3	6
Renal	3	0	3
Vascular	2	1	1

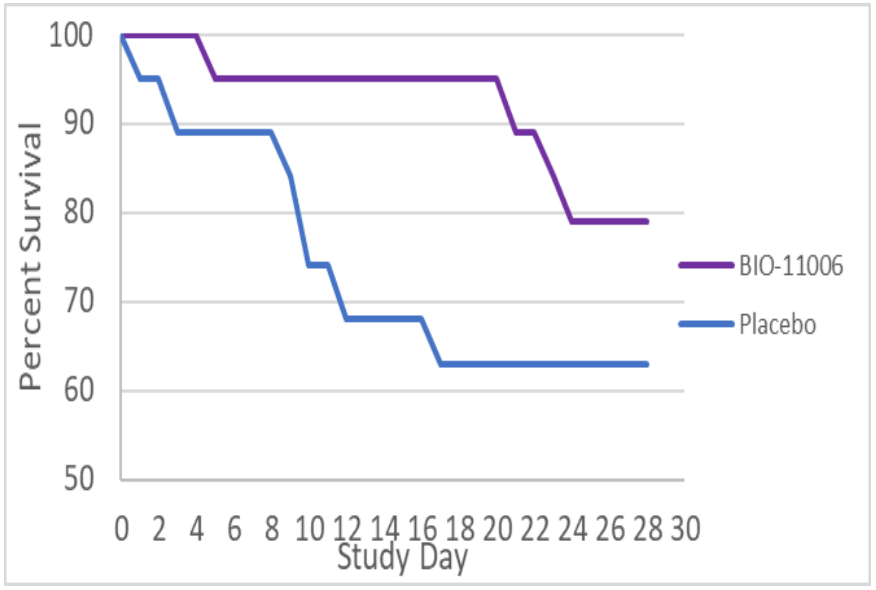
- Only one SAE was judged possibly drug related in the BIO-11006 arm
- No AEs resulted in removal of the patient from the study.

Study Overview: Results

Oxygenation Response



Kaplan-Meier Survival



Secondary Efficacy Endpoints

Variable	All patients	Placebo	BIO-11006
Days on study drug (at least 1 dose study drug given)	Median: 7 [4,16] Mean: 10 ± 8	Median: 4 [3,11] Mean: 7 ± 7	Median: 9 [6,20] Mean: 13 ± 9
All cause 28-day mortality[c]	11 (29%)	7 (37%)	4 (21%)
28-day VFDs[a]	Median: 10.5 [0, 23] Mean: 11 ± 11	Median: 12 [0, 24] Mean: 12.2 ± 11.56	Median: 1 [0, 23] Mean: 10.4 ± 11.3
28-day ICU Free Days[b]	Median: 7 [0,20] Mean: 9.5 ± 10	Median: 12 [0, 22] Mean: 11 ± 11	Median: 7 [0, 16] Mean: 8 ± 9
Days on ventilator for patients who died	Median: 11 [4,12] Mean: 10 ±7	Median: 10 [2,11] Mean: 7 ± 5	Median: 16.5 [8.5,22.5] Mean: 15.5 ± 9

Conclusion

- A randomized, double blind placebo-controlled trial with BIO-11006 is feasible and safe.
  - There were few SAE's that were felt to be possibly related to the Active drug, and none led to discontinuation of the Active drug.

- Although study numbers are small and conclusions about clinical outcomes are not possible, there may be faster improvement in oxygenation and reduced mortality observed with the BIO-11006 compared to placebo