A Randomized, Double-blind, Placebo-controlled Phase 1 Single and Multiple-dose Pharmacokinetic First-in-Human Study of AV-001 in Healthy Subjects for the Treatment of Acute Respiratory Distress Syndrome

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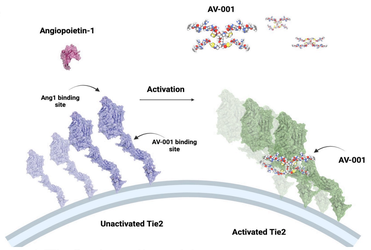
Introduction

Focusing on the host response, strengthening the vasculature through enhanced endothelial stability, and reducing pulmonary vascular leakage represents a promising therapeutic strategy in addressing the underlying pathophysiology of ARDS.

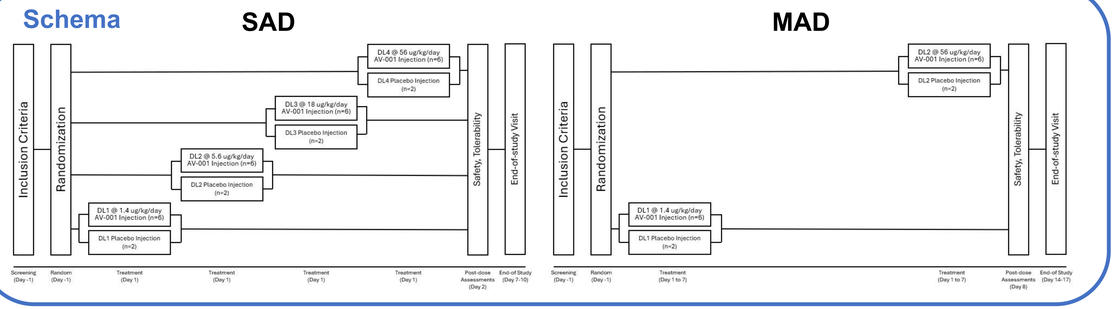
The activation of the Tie2-Angpt-1 signaling cascade is critical for maintaining vascular homeostasis and barrier function and notably, patients with ARDS display a dramatic attenuation of Tie2 signaling. Vasomune Therapeutics Inc. is developing AV-001, a functional mimetic of Angpt-1, as a threat agnostic therapeutic for ARDS and similar conditions.



Methods

In the SAD phase, healthy subjects were divided into cohorts receiving sequential doses of AV-001 or Placebo, with a post-dose follow-up and an end-of-study visit. The MAD phase had subjects take daily doses for a week, with similar follow-up. Sample collection for pharmacokinetics (PK) and pharmacodynamics (PD) analysis were taken. Safety endpoints included adverse events, clinical labs, vital signs, ECG, and physical examinations, aiming to establish AV-001's safety profile through detailed monitoring and assessments.

Schema



Safety and Tolerability

No deaths, no discontinuations, no severe adverse events, no suspected unexpected severe adverse reactions, no adverse events of special interest, no clinically significant abnormal laboratory values, no abnormal ECGs, no hypotension characteristics.

SAD

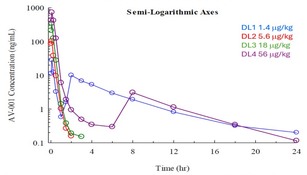
	SAD/MAD 1.4 µg/kg (n=12)			SAD 5.6 µg/kg (n=6)			SAD 18 µg/kg (n=6)			SAD/MAD 56 µg/kg (n=12)			Pooled Placebo (n=12)		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Any treatment-emergent AEs (TEAEs)	2	(16.7)	2	1	(16.7)	1	2	(33.3)	5	5	(41.7)	5	0	(0.0)	0
Mild	2	(16.7)		0	(0.0)		1	(16.7)		4	(33.3)		0	(0.0)	
Moderate	0	(0.0)		1	(16.7)		1	(16.7)		1	(8.3)		0	(0.0)	
Severe	0	(0.0)		0	(0.0)		0	(0.0)		0	(0.0)		0	(0.0)	
Any study drug-related TEAEs	0	(0.0)	0	1	(16.7)	1	2	(33.3)	4	1	(8.3)	1	0	(0.0)	0
Mild	0	(0.0)		0	(0.0)		1	(16.7)		0	(0.0)		0	(0.0)	
Moderate	0	(0.0)		1	(16.7)		1	(16.7)		1	(8.3)		0	(0.0)	
Severe	0	(0.0)		0	(0.0)		0	(0.0)		0	(0.0)		0	(0.0)	
Any TEAEs of special interest	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Mild	0	(0.0)		0	(0.0)		0	(0.0)		0	(0.0)		0	(0.0)	
Moderate	0	(0.0)		0	(0.0)		0	(0.0)		0	(0.0)		0	(0.0)	
Severe	0	(0.0)		0	(0.0)		0	(0.0)		0	(0.0)		0	(0.0)	

MAD

	MAD 1.4 µg/kg (n=6)			MAD 56 µg/kg (n=6)			Pooled Placebo (n=12)		
	n	(%)	e	n	(%)	e	n	(%)	e
Any treatment-emergent AEs (TEAEs)	2	(33.3)	2	3	(50.0)	3	0	(0.0)	0
Mild	2	(33.3)		2	(33.3)		0	(0.0)	
Moderate	0	(0.0)		1	(16.7)		0	(0.0)	
Severe	0	(0.0)		0	(0.0)		0	(0.0)	
Any study drug-related TEAEs	0	(0.0)	0	1	(16.7)	1	0	(0.0)	0
Mild	0	(0.0)		0	(0.0)		0	(0.0)	
Moderate	0	(0.0)		1	(16.7)		0	(0.0)	
Severe	0	(0.0)		0	(0.0)		0	(0.0)	
Any TEAEs of special interest	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Mild	0	(0.0)		0	(0.0)		0	(0.0)	
Moderate	0	(0.0)		0	(0.0)		0	(0.0)	
Severe	0	(0.0)		0	(0.0)		0	(0.0)	

N = 100 x n/N, e = number of events. Note that number of events is not presented for summaries by maximum severity. TEAEs are defined as AEs that started after the first dose of study drug. AEs with the following causality: Related, Probably Related, Possibly Related are considered related to the study drug. All reported terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1.

Pharmacokinetics



Geometric mean plasma concentrations of AV-001 after IV administration of single doses to healthy volunteers; semi-logarithmic axes. All Active Subjects.

SAD

Parameter*	Cohort 1 1.4 µg/kg	Cohort 2 5.6 µg/kg	Cohort 3 18 µg/kg	Cohort 4 56 µg/kg
Cmax (ng/mL)	29.9 [29.7] (6)	109 [9.14] (6)	347 [10.6] (6)	896 [13.8] (6)
Tmax (hr)	0.083 (6) [0.033 – 0.083]	0.083 (6) [0.033 – 0.083]	0.083 (6) [0.033 – 0.083]	0.083 (6) [0.033 – 0.250]
AUC(0-t) (hr×ng/mL)	9.83 [136] (6)	27.5 [23.7] (6)	88.0 [12.6] (6)	304 [54.8] (6)
AUC(inf) (hr×ng/mL)	11.3 [152] (5)	27.5 [23.6] (6)	88.7 [13.9] (5)	304 [54.8] (6)
λz (1/hr)	2.25 [391] (5)	4.26 [25.0] (6)	2.09 [64.5] (5)	0.32 [29.1] (6)
t½ (hr)	0.308 [391] (5)	0.163 [25.0] (6)	0.332 [64.5] (5)	2.19 [29.1] (6)
CL (L/hr)	9.38 [103] (5)	17.4 [33.9] (6)	15.5 [18.4] (5)	15.6 [46.4] (6)
(L/hr/kg)	0.124 [151] (5)	0.203 [23.4] (6)	0.203 [13.7] (5)	0.185 [54.9] (6)
Vz (L)	4.17 [106] (5)	4.09 [35.1] (6)	7.41 [69.9] (5)	49.36 [29.7] (6)
(L/kg)	0.055 [73.8] (5)	0.048 [17.0] (6)	0.097 [80.5] (5)	0.583 [36.6] (6)

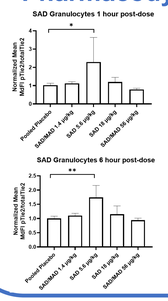
*Geometric mean [geometric %CV] (N) except Tmax for which the median (N) [Range] is reported.

MAD

Parameter*	Cohort 1 – 1.4 µg/kg Day 1	Cohort 1 – 1.4 µg/kg Day 7	Cohort 2 – 56 µg/kg Day 1	Cohort 2 – 56 µg/kg Day 7
Cmax (ng/mL)	28.5 [17.9] (6)	28.2 [19.8] (6)	1.041 [10.9] (6)	1.106 [14.1] (6)
Tmax (hr)	0.058 (6) [0.033 – 0.083]	0.083 (6) [0.033 – 0.117]	0.083 (6) [0.033 – 0.083]	0.083 (6) [0.033 – 0.083]
AUC(0-t) (hr×ng/mL)	7.66 [18.5] (6)	7.61 [20.4] (6)	250 [19.8] (6)	241 [8.50] (6)
AUC(inf) (hr×ng/mL)	7.71 [18.3] (6)	7.66 [20.3] (6)	289 [20.9] (2)	245 [8.56] (5)
λz (1/hr)	4.15 [16.2] (6)	4.35 [18.4] (6)	0.318 [137] (2)	0.110 [28.0] (5)
t½ (hr)	0.167 [16.2] (6)	0.159 [18.4] (6)	2.18 [137] (2)	6.29 [28.0] (5)
CL (L/hr)	15.3 [22.0] (6)	15.4 [26.2] (6)	15.0 [6.01] (2)	17.2 [26.5] (5)
(L/hr/kg)	0.182 [18.7] (6)	0.183 [20.5] (6)	0.192 [20.8] (2)	0.227 [9.24] (5)
Vz (L)	3.69 [16.2] (6)	3.55 [11.4] (6)	47.0 [150] (2)	156 [51.2] (5)
(L/kg)	0.044 [17.7] (6)	0.042 [10.0] (6)	0.604 [189] (2)	2.06 [37.8] (5)

*Geometric mean [geometric %CV] (N) except Tmax for which the median (N) [Range] is reported.

Pharmacodynamics: Tie2 Activation



Tie2 Phosphorylation on Granulocytes.

1-hour post-drug: Tie2 phosphorylation on granulocytes. Peak granulocyte top activation is 229% above placebo at 5.6 µg/kg.

6-hours post-drug: Tie2 phosphorylation on granulocytes. Peak granulocyte activation is 174% at 5.6 µg/kg.

6 hours is within the elimination phase of our drug based on MAD $t_{1/2}$.

One way ANOVA post hoc Fisher's LSD relative to Placebo. Baseline T0 normalized. Doses relative to Placebo.

Conclusions

- Dose-proportional increases in geometric mean AV-001 plasma concentrations and Cmax, AUC(0-t), and AUC(inf) for SAD and MAD QDx7 from 1.4 µg/kg to 56 µg/kg.
- Geometric mean t½ increased as dose increased, from 0.147 hours at 1.4 µg/kg to 2.19 hours at 56 µg/kg, a consequence of longer tracking of plasma concentrations over time.
- Geometric mean CL values consistent across the 4 doses.
- No evidence of accumulation with once-daily dosing; geometric mean plasma concentrations and values for Cmax and AUC(inf) on Days 1 and 7.
- PK linear with doses ranging from 1.4 µg/kg to 56 µg/kg.
- CL correlated with increased body size; the µg/kg dosing used in this study was appropriate.
- No deaths, no discontinuations, no SAEs, no SUSARs, no AESIs, no clinically significant abnormal laboratory values, abnormal ECGs, or hypotension characteristics.
- On-target activation of Tie2 measured by TEL assay.

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