# Ramipril for the Treatment of COVID-19: RAMIC, a Randomized, Double-Blind, Placebo-Controlled Clinical Trial

#### **Author list:**

Daniel Q. Huang<sup>1,2,3\*</sup>, Veeral Ajmera<sup>1,4\*</sup>, Christian Tomaszewski<sup>5</sup>, Andrew LaFree<sup>5</sup>, Ricki Bettencourt<sup>1</sup>, Wesley K Thompson<sup>6</sup>, Davey M. Smith<sup>7,8</sup>, Atul Malhotra<sup>9</sup>, Ravindra L Mehta<sup>10</sup>, Vaishal Tolia<sup>11</sup>, Jeffrey Yin<sup>12</sup>, Paul A Insel<sup>13,14</sup>, Stone Leachman<sup>1</sup>, Jinho Jung<sup>1</sup>, Summer Collier<sup>4</sup>, Lisa Richards<sup>1</sup>, Kristin Woods<sup>15</sup>, Maral Amangurbanova<sup>1</sup>, Archana Bhatt<sup>15</sup>, Xinlian Zhang<sup>16</sup>, Oana M. Penciu<sup>17</sup>, Stuart Zarich<sup>18</sup>, Tamrat Retta<sup>19</sup>, Michelle S. Harkins<sup>20</sup>, J. Pedro Teixeira<sup>20</sup>, Brian Chinnock<sup>21</sup>, Netanya S Utay<sup>22</sup>, Jordan E. Lake<sup>23</sup> and Rohit Loomba<sup>1,4,24†</sup>

- 1. NAFLD Research Center, Division of Gastroenterology, University of California at San Diego, La Jolla, CA, United States of America.
- 2. Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.
- 3. Division of Gastroenterology and Hepatology, Department of Medicine, National University Health System, Singapore.
- 4. Division of Gastroenterology, Department of Medicine, University of California San Diego, La Jolla, California, United States of America.
- 5. Department of Emergency Medicine, University of California, San Diego and the El Centro Regional Medical Center, San Diego California, United States of America.
- 6. Division of Biostatistics and Bioinformatics, Department of Family Medicine and Public Health, University of California San Diego, La Jolla, California, United States of America.
- 7. Division of Infectious Diseases and Global Public Health, Department of Medicine, University of California San Diego, La Jolla, California, United States of America
- 8. Veteran Affairs Medical Center, San Diego, California, United States of America.
- 9. Division of Pulmonary, Critical Care & Sleep Medicine, Department of Medicine, University of California San Diego, La Jolla, California, United States of America.
- 10. Division of Nephrology-Hypertension, Department of Medicine, University of California San Diego, La Jolla, California, United States of America.
- 11. Department of Emergency Medicine, University of California San Diego, La Jolla, California, United States of America.
- 12. Department of Pharmacy, University of California San Diego, La Jolla, California, United States of America.
- 13. Department of Pharmacology, University of California San Diego, La Jolla, California, United States of America.
- 14. Division of Endocrinology and Metabolism, University of California San Diego, La Jolla, California, United States of America.
- 15. Clinical Translational Research Institute, University of California at San Diego, San Diego, California, United States of America.
- 16. Division of Biostatistics and Bioinformatics, Herbert Wertheim School of Public Health, University of California San Diego, San Diego, California, United States of America.
- 17. Beverly Hospital, Montebello, California, United States of America.
- 18. Section of Cardiovascular Medicine, Yale New Haven Health Bridgeport Hospital, United States of America.
- 19. Department of Internal Medicine, Howard University, Washington, United States of America.
- 20. Department of Internal Medicine, University of New Mexico, Albuquerque, New Mexico, United States of America.
- 21. Department of Emergency Medicine, University of California San Francisco Fresno, Fresno, California, United States of America.
- 22. Division of Infectious Diseases and Geographic Medicine, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, United States of America.

- 23. Division of Infectious Diseases, Department of Internal Medicine, McGovern Medical School at the University of Texas Health Science Center, Houston, Texas, United States of America.
- 24. Division of Epidemiology, Department of Family Medicine and Public Health, University of California at San Diego, San Diego, CA, United States of America.
- \*These authors share co-first authorship.

#### †Corresponding Author:

Rohit Loomba, MD, MHSc Professor of Medicine Director, NAFLD Research Center University of California at San Diego Altman Clinical and Translational Research Institute 9500 Gilman Drive La Jolla, CA, 92093-0887

## Supplemental Table 1. Scoring of toxicity for discontinuation

Adverse events	1	2	3	4	5
Allergic reaction	Transient flushing or rash, Intervention not indicated	Intervention; Responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); Prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication; Recurrence of symptoms following initial improvement; Hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life threatening consequences;     Urgent intervention indicated	Death
Anaphylaxis			Symptomatic bronchospasm, with or without urticaria; Parenteral intervention indicated; Allergy-related edema/angioedema; Hypotension	Life-threatening consequences; Urgent intervention indicated	Death
Hypotension			SBP < 90 mm hg or DBP < 50 mm hg	Requiring vasopressor support	Death
ALT (U/L)	Baseline-1.5x baseline	>200 and > 1.5x baseline	>400 and > 2x baseline	401-800 and > 3x baseline	>800
AST (U/L)	Baseline-1.5x baseline	>200 and > 1.5x baseline	>400 and > 2x baseline	401-800 and > 3x baseline	>800
Total Bilirubin (mg/dL)	0.1 to 1	1.1 to 2 and direct bilirubin >0.5	2 to 5 and direct bilirubin > 1	5.1 to 10	>10
Potassium (mg/dL)	5.1-5.3	> 5.3-5.5	> 5.5- 6.0 Investigator can assess for possible hemolysis	> 6.0	Death
Creatinine (mg/dL)	Creatinine level increase of >0.3 mg/dL; Creatinine 1- 1.5 x above baseline	Creatinine 1.5 - 2x above baseline	Creatinine >2x baseline or >2.0 mg/dL; Hospitalization indicated	Life-threatening consequences; Dialysis indicated	Death

Scoring of toxicity from the CTC Version 4.0, with modifications

### **Supplemental Table 2.** Concomitant therapy for COVID-19, by treatment allocation

	Ramipril (N=79)	Placebo (N=35)
Concomitant therapy, n (%)		
Azithromycin	25 (32)	8 (23)
Chloroquine	0 (0)	0 (0)
Corticosteroid	20 (25)	5 (14)
Remdesivir	21 (27)	6 (17)
Monoclonal antibody	1(1)	0 (0)