UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of The Securities Exchange Act of 1934

Date of Report (Date of Earliest Event Reported): May 27, 2020

AERPIO PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

Delaware	**001-38560**	**61-1547850**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

9987 Carver Road **Cincinnati, OH**	**45242**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code (513) 985-1920

Not Applicable
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common stock, $0.0001 par value per share	ARPO	Nasdaq Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 or Rule 12b-2 of the Securities Exchange Act of 1934.

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Item 7.01. Regulation FD Disclosure.

Aerpio Pharmaceuticals, Inc. (the "Company", "we" or "us") is furnishing a corporate presentation, attached as Exhibit 99.2 to this Current Report on Form 8-K, which we intend to use from time to time in meetings with investors and others beginning on May 28, 2020. The corporate presentation will also be available in the investor relations section of the Company's website at http://aerpio.com.

The information in this Item 7.01 and Exhibit 99.2 attached hereto shall not be deemed "filed" for purposes of Section 18 of the Securities and Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that section, nor shall they be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, except as expressly set forth by specific reference in such filing.

Item 8.01 Other Events

On May 27, 2020, we issued a press release announcing the selection of razuprotafib in the I-SPY COVID-19 study, a copy of which is attached hereto as Exhibit 99.1 and incorporated herein by reference. Quantum Leap Healthcare Collaborative ("Quantum Leap") is the sponsor of I-SPY COVID-19 TRIAL. We have agreed to participate in the study by providing our product candidate razuprotafib for evaluation in the study. The study is a Phase 2 randomized, controlled, multicenter study with an adaptive design, and is intended to assess the therapeutic potential of study agents, including razuprotafib, for the treatment of acute respiratory distress syndrome ("ARDS") in adult patients with moderate to severe COVID-19. We will supply quantities of razuprotafib for use in the study, as well as provide financial support totaling approximately $1.5 million.

Item 9.01 Financial Statements and Exhibits

(d) Exhibits

Exhibit No.	Description
99.1	Press release issued by Aerpio Pharmaceuticals, Inc., on May 27, 2020.
99.2	Aerpio Pharmaceuticals, Inc., corporate presentation.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

AERPIO PHARMACEUTICALS, INC.

Date: May 28, 2020

By: /s/ Joseph Gardner, Ph.D.
Joseph Gardner
President and Founder

Aerpio Pharmaceuticals, Inc. and Quantum Leap Healthcare Collaborative Announce the Selection of Razuprotafib for Evaluation in the I-SPY COVID Trial for the Treatment of Acute Respiratory Distress Syndrome in COVID-19 Patients

SAN FRANCISCO, CINCINNATI, DATE (May 27, 2020) – Aerpio Pharmaceuticals, Inc. ("Aerpio") (Nasdaq: ARPO) and Quantum Leap Healthcare Collaborative™ (Quantum Leap) announced today an agreement has been reached to evaluate razuprotafib in a new randomized, investigational treatment arm in the I-SPY COVID Trial for the treatment of acute respiratory distress syndrome (ARDS) in adult patients with moderate to severe COVID-19.

Approximately 10-15% of those infected with the highly contagious SARS-CoV2 virus, the cause of COVID-19, develop ARDS with a death rate in the 2-10% range. Nearly 70% of COVID-19 patients admitted to the ICU require ventilation for a mean of 14 days, and over 50% will not survive. The unprecedented rate of SARS-CoV-2 (COVID-19) infection, over 5.6 million world-wide, has already led to more than 350,000 deaths.

The goal of this the I-SPY COVID Trial is to rapidly screen multiple promising agents, in the setting of an adaptive platform trial, for the treatment of critically ill COVID-19 patients to identify agents that will have a high impact on reducing mortality, and the need for as well as duration of, mechanical ventilation.

Preclinical models, large human observational studies, and human genetic studies from leading groups worldwide have independently arrived at the concept that a vascular endothelial receptor, Tie2, may play a pivotal role in the defense against microvascular breach in acute respiratory distress syndrome (ARDS) [1-4]. We hypothesize that razuprotafib, being developed as a first-in-class Tie2 activating compound, will exhibit an acceptable safety profile and show efficacy for the treatment of COVID-19 associated ARDS as a potentially life-saving therapeutic for patients suffering from the devastating respiratory effects of COVID-19.

This study arm will evaluate razuprotafib's potential to sufficiently stabilize the pulmonary vasculature, in order to slow or prevent the progression of COVID-19 associated pulmonary pathology, decrease the need for ventilator support, and reduce mortality.

"The I-SPY COVID Trial is designed to rapidly identify and test agents with the potential to provide substantial benefit to patients suffering with acute respiratory distress syndrome (ARDS) from COVID-19, a condition where effective agents are lacking. We are delighted that Aerpio has agreed to

participate in this trial with their agent razuprotafib, as we look forward to evaluating its potential to improve care for this group of patients," said James Palazzolo, CEO of Quantum Leap Healthcare Collaborative.

Joseph Gardner, PhD, Aerpio's President and Founder, commented "We are very pleased to have razuprotafib selected for inclusion in the I-SPY clinical trial. It will allow us to evaluate the drug in severely ill COVID-19 patients and quickly assess both preliminary safety and efficacy and guide future development plans. If successfully developed, approved and commercialized, razuprotafib has the potential to help save lives and render the disease less life threatening in the patients most at risk."

As part of the collaboration, Aerpio will supply the investigational drug and provide financial and regulatory support. The Quantum Leap/ I-SPY team, as sponsor, will provide the clinical sites and clinical expertise. Aerpio has already produced subcutaneous razuprotafib to support the rapid start-up of this arm of the trial.

Quantum Leap, sponsor of the I-SPY 2 TRIALs which is well-known for its adaptive platform trial in breast cancer, announced plans on April 28 to employ a similar methodology and launch a new trial to study acute respiratory distress syndrome (ARDS) in COVID-19 patients. The I-SPY COVID Trial, sponsored by Quantum Leap, will include ARDS experts from the University of California at San Francisco and from more than 20 I-SPY 2 U.S. sites along with the COVID R&D Consortium, a consortium organized by the R&D heads of major US and European pharmaceutical and biotechnology companies. It is a Phase 2 randomized, controlled, multicenter study with an innovative adaptive design aimed to identify and rapidly test promising new treatments for their potential use against COVID-19 related ARDS.

About the I-SPY COVID Trial

The I-SPY COVID Trial (Investigation of Serial studies to Predict Your Therapeutic Response with Imaging And molecular analysis) was designed to rapidly screen promising experimental treatments and identify those most effective in specific patient subgroups based on molecular characteristics (biomarker signatures). The trial is a unique collaborative effort by a consortium that includes the U.S. Food and Drug Administration (FDA), industry, patient advocates, philanthropic donors, and clinicians from multiple major U.S. research centers. Under the terms of the collaboration agreement, Quantum Leap Healthcare Collaborative is the trial sponsor and manages all study operations. For more information, visit www.ispytrials.org.

About Quantum Leap Healthcare Collaborative

Quantum Leap Healthcare Collaborative (Quantum Leap) is a 501c(3) charitable organization established in 2005 as a collaboration between medical researchers at University of California, San Francisco and Silicon Valley entrepreneurs. Our mission is to integrate high-impact research with clinical

processes and systems technology, resulting in improved data management and information systems, greater access to clinical trial matching and sponsorship, and greater benefit to providers, patients, and researchers. Quantum Leap provides operational, financial, and regulatory oversight to I-SPY. For more information, visit www.quantumleaphealth.org.

About Razuprotafib (previously AKB-9778)

Razuprotafib binds to and inhibits vascular endothelial protein tyrosine phosphatase (VE-PTP), an important negative regulator of Tie2. Decreased Tie2 activity contributes to vascular instability in many diseases including diabetes. Razuprotafib activates the Tie2 receptor irrespective of extracellular levels of its binding ligands, angiopoietin-1 (agonist) or angiopoietin-2 (antagonist) and may be the most efficient pharmacologic approach to maintain normal Tie2 activation. As seen preclinically, activation of Tie2 by razuprotafib stabilizes vasculature which may have beneficial effects in a variety of disease states, including ARDS associated with COVID-19 infections.

About Aerpio Pharmaceuticals

Aerpio Pharmaceuticals, Inc. is a biopharmaceutical company focused on developing compounds that activate Tie2 to treat ocular diseases and diabetic complications. Recently published mouse and human genetic data implicate the Angpt/Tie2 pathway in maintenance of Schlemm's canal, a critical component of the conventional outflow tract. The Company's lead compound, razuprotafib (formerly AKB-9778), a first-in-class small molecule inhibitor of vascular endothelial protein tyrosine phosphatase ("VE-PTP"), is being developed as a potential treatment for open angle glaucoma, and the Company intends to investigate the therapeutic potential of razuprotafib in other indications. The Company is also evaluating development options for ARP-1536, a humanized monoclonal antibody, for its therapeutic potential in the treatment of diabetic vascular complications including nephropathy and diabetic macular edema ("DME"). The Company's third asset is a bispecific antibody that binds both VEGF and VE-PTP which is designed to inhibit VEGF activation and activate Tie2. This bispecific antibody has the potential to be an improved treatment for wet age-related macular degeneration and DME via intravitreal injection. Finally, the Company has exclusively out-licensed AKB-4924 (now called GB004), a first-in-class small molecule inhibitor of hypoxia-inducible factor-1 (HIF). GB004 is being developed by AKB-4924's exclusive licensor, Gossamer Bio, Inc. (Nasdaq: GOSS). For more information, please visit www.aerpio.com.

Forward Looking Statements

This press release contains forward-looking statements. Statements in this press release that are not purely historical are forward-looking statements. Such forward-looking statements include, among other things, the Company's product candidates, including razuprotafib, ARP-1536 and the bispecific antibody asset, the clinical development plan therefor and the therapeutic potential thereof, the Company's plans and expectations with respect to razuprotafib and the development therefor and therapeutic potential thereof in addressing COVID-19 and the intended benefits from the Company's collaboration with Gossamer Bio for GB004, including the continued development of GB004 and the milestone and royalty payments related to

the collaboration. Actual results could differ from those projected in any forward-looking statements due to several risk factors. Such factors include, among others, the continued development of GB004 and maintaining and deriving the intended benefits of the Company's collaboration with Gossamer Bio; ability to continue to develop razuprotafib or other product candidates, including in indications related to COVID-19; the inherent uncertainties associated with the drug development process, including uncertainties in regulatory interactions, the design of planned or future clinical trials, commencing clinical trials and enrollment of patients in clinical trials; obtaining any necessary regulatory clearances in order to commence and conduct planned or future clinical trials; the impact of the ongoing COVID-19 pandemic on the Company's business operations, including research and development efforts and the ability of the Company to commence, conduct and complete its planned clinical activities; and competition in the industry in which the Company operates and overall market conditions; and the additional factors set forth in our Annual Report on Form 10-K for the year ended December 31, 2019, as updated by our subsequent Quarterly Reports on Form 10-Q and our other subsequent filings with the SEC.

These forward-looking statements are made as of the date of this press release, and the Company assumes no obligation to update the forward-looking statements, or to update the reasons why actual results could differ from those projected in the forward-looking statements, except as required by law. Investors should consult all the information set forth herein and should also refer to the risk factor disclosure set forth in the reports and other documents the Company files with the SEC available at www.sec.gov.

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Or

Investors:
Irina Koffler
LifeSci Advisors
ikoffler@lifesciadvisors.com

References:

1 Saharinen, P., Eklund, L. & Alitalo, K. Therapeutic targeting of the angiopoietin-TIE pathway. *Nat Rev Drug Discov* **16**, 635-661, doi:10.1038/nrd.2016.278 (2017).
2 Parikh, S. M. The Angiopoietin-Tie2 Signaling Axis in Systemic Inflammation. *J Am Soc Nephrol* **28**, 1973-1982, doi:10.1681/ASN.2017010069 (2017).
3 Higgins, S. J. *et al.* Tie2 protects the vasculature against thrombus formation in systemic inflammation. *J Clin Invest* **128**, 1471-1484, doi:10.1172/JCI97488 (2018).
4 Leligdowicz, A., Richard-Greenblatt, M., Wright, J., Crowley, V. M. & Kain, K. C. Endothelial Activation: The Ang/Tie Axis in Sepsis. *Front Immunol* **9**, 838, doi:10.3389/fimmu.2018.00838 (2018).

Exhibit 99.2

aerpio pharmaceuticals

Covid-19 Program

May 28, 2020

Forward looking statements

- *This presentation has been prepared by Aerpio Pharmaceuticals ("we", "us" or the "Company") and includes forward-looking statements. Statements in this presentation that are not purely historical are forward-looking statements. Such forward-looking statements include, among other things, our product candidates, including razuprotafib, the clinical development plan therefor and the therapeutic potential thereof, our plans and expectations with respect to razuprotafib and the development therefor and therapeutic potential thereof in addressing COVID-19. Forward-looking statements speak only as of the date hereof unless it is stated otherwise.*

- *Although we believe that the expectations reflected in these forward-looking statements are reasonable, actual results could differ from those projected due to several risk factors. Such factors include, among others, the continued development of GB004 and maintaining and deriving the intended benefits of the Company's collaboration with Gossamer Bio; ability to continue to develop razuprotafib or other product candidates, including in indications related to COVID-19; the inherent uncertainties associated with the drug development process, including uncertainties in regulatory interactions, the design of planned or future clinical trials, commencing clinical trials and enrollment of patients in clinical trials; obtaining any necessary regulatory clearances in order to commence and conduct planned or future clinical trials; the impact of the ongoing COVID-19 pandemic on the Company's business operations, including research and development efforts and the ability of the Company to commence, conduct and complete its planned clinical activities; and competition in the industry in which the Company operates and overall market conditions; and the additional factors set forth in our most recent Annual Report on Form 10-K, as updated by our subsequent Quarterly Reports on Form 10-Q and our other subsequent filings with the Securities and Exchange Commission.*

- *This presentation also contains estimates and other statistical data made by independent parties and by us. Management bases all estimates and projections as to events that may occur in the future (including projections of revenue, development plans and timing of clinical trial results) upon their best judgments as of the date of this presentation. Whether or not such estimates or projections may be achieved will depend upon the Company achieving its overall business objectives and the availability of funds. The Company does not guarantee that any of these projections will be attained. Actual results will vary from the projections, and such variations may be material. New risks emerge from time to time, and except as required by law, neither we nor any other person makes any representation as to the accuracy or completeness of such data or undertakes any obligation to update such data after the date of this presentation. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this presentation.*

- *This presentation may contain trade names, trademarks or service marks of other companies. The Company does not intend the use or display of other parties' trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of, these other parties. Solely for convenience, the trade names, trademarks or service marks in this presentation are referred to without the symbols ® and ™, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.*

Covid-19 Program: Aerpio Invited into I-SPY Network

Aerpio has been selected to participate in the I-SPY clinical platform to treat respiratory distress (ARDS) in Covid-19 patients with razuprotafib (AKB-9778)

I-SPY (Quantum Leap Health Collaborative, QLHC) – invited Aerpio into their platform trial to treat severe Covid-19 patients; I-SPY network supports clinical sites and acts as the clinical CRO for their sites with the target to treat 120 severe Covid-19 patients. Aerpio supplies drug and provides regulatory support for the trial. Drug supply already produced to support a fast start up of the trial.

Aerpio (razuprotafib = AKB-9778) was one of four drugs selected to be included in the I-SPY platform trial and is the highest priority drug on their platform (dozens of programs were evaluated)

Covid Grant: Background I-SPY (QLHC) Organization

I-SPY – Quantum Leap Healthcare Collaborative (QLHC)

Originally formed as collaborative network to run rapid trials using adaptive design in oncology to optimize drug combinations and new entities for cancer; Leadership from UCSF Medical School, Carolyn Calfee, MD, Professor of Medicine and Critical Care UCSF; and Laura Esserman, MD, Co-Principal Investigator of I-SPY2, Member, QLHC Board of Directors

Initiated I-SPY2 trial in their collaborative network to run a platform trial in Covid-19 patient March 17th 2020

I-SPY **Has selected 4 drugs to include in Covid Network Trial with Aerpio's drug as top priority**

> "Aerpio's drug is the one that most excites the investigators." Dr. Michael Matthay Professor of Pulmonary and Critical Care Medicine, UCSF and ISPY investigator

Aerpio COVID-19 Steering Committee

Strong Support from Highly Regarded Steering Team; received significant input on trial design and introductions to I-SPY team

Member	Affiliation
Dr. Gordon Bernard	Professor of Medicine, Melinda Owen Bass Chair in Medicine, Associate Vice Chancellor for Research, Vanderbilt University Medical Center
Dr. Chris Kontos	Professor of Medicine, Professor of Pharmacology and Cancer Biology, Duke University
Dr. Michael Lotze	Professor of Surgery, Immunology and Bioengineering, Vice Chair of Research, Department of Surgery, University of Pittsburgh
Dr. John Marshall	Professor of Surgery, St. Michael's Hospital, University of Toronto
Dr. Samir Parikh	Associate Professor of Medicine, Director, Center for Vascular Biology Research Associate Vice Chair for Research, Department of Medicine Beth Israel Deaconess Medical Center, Harvard Medical School
Dr. Marc Pritzker	Professor of Medicine, Surgery and Biomedical Innovation, Cardiovascular Division, University of Minnesota
Dr. Wesley Self	Associate Professor of Emergency Medicine, Vanderbilt University Medical Center

Covid-19 Program: Summary of Science Supporting Hypothesis (detailed slides in next section)

Preclinical:
Multiple animal models performed by collaborators show that Tie2 activation rescues animals from “cytokine storm” associated with ARDS and sepsis

Both Tie2 and VE-PTP highly expressed in lung

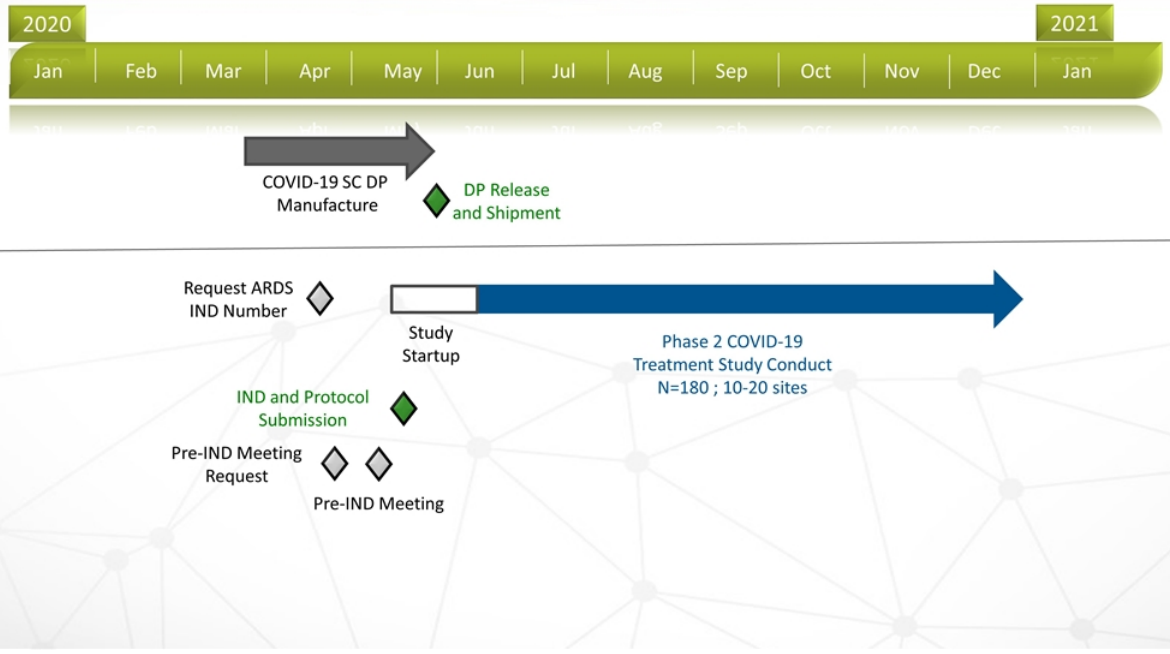
Tie2 activation inhibits NF kappa B which is a known pro-inflammatory mediator in vascular endothelial cells (data published by collaborators)

Clinical:
Aerpio clinical data demonstrates eNOS activation (via acute blood pressure reduction) which supports vascular stabilizing anti-inflammatory effect

Aerpio clinical data demonstrates lowering of C-reactive protein (CRP) a marker of vascular inflammation. Covid-19 patients have dramatically high levels of CRP

Several recent articles demonstrate that Covid-19 infection produces a “vasculitis” that results in profound leak of fluid and inflammatory cells into the lung

Aerpio COVID-19 Timeline: Phase 2 Safety and Efficacy Milestone Q1 2021



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Covid-19 Program: Scientific Rationale

May 28, 2020

COVID-19 Associated Respiratory Failure: A Deadly Pandemic without a Treatment

Special Article

Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)

Waleed Alhazzani[1,2], Morten Hylander Møller[3,4], Yaseen M. Arabi[5], Mark Loeb[1,2], Michelle Ng Gong[6], Eddy Fan[7], Simon Oczkowski[1,2], Mitchell M. Levy[8,9], Lennie Derde[10,11], Amy Dzierba[12], Bin Du[13], Michael Aboodi[6], Hannah Wunsch[14,15], Maurizio Cecconi[16,17], Younsuck Koh[18], Daniel S. Chertow[19], Kathryn Maitland[20], Fayez Alshamsi[21], Emilie Belley-Cote[1,22], Massimiliano Greco[16,17], Matthew Laundy[23], Jill S. Morgan[24], Jozef Kesecioglu[10], Allison McGeer[25], Leonard Mermel[8], Manoj J. Mammen[26], Paul E. Alexander[2,27], Amy Arrington[28], John E. Centofanti[29], Giuseppe Citerio[30,31], Bandar Baw[1,32], Ziad A. Memish[33], Naomi Hammond[34,35], Frederick G. Hayden[36], Laura Evans[37], Andrew Rhodes[38]

Critical Care Medicine
DOI: 10.1097/CCM.0000000000004363

- Most recommendations "Weak" or "uncertain"
- Older antivirals have failed, the scientific rationale for chloroquine is tenuous
- Remdesivir shows activity and gets EUA, but is "not a magic bullet"
- ➢ No therapies addressing the host response other than immune modulators

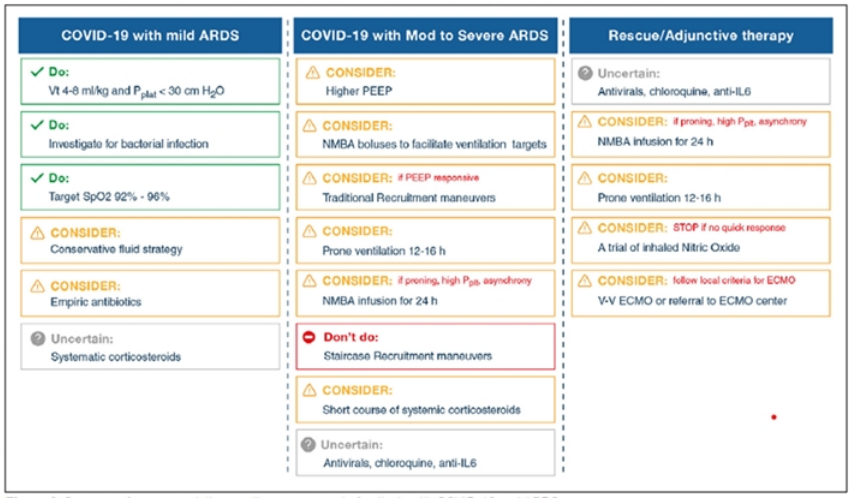
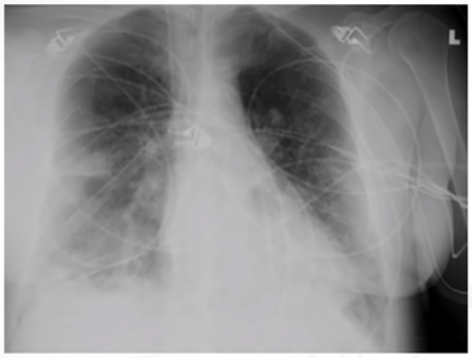
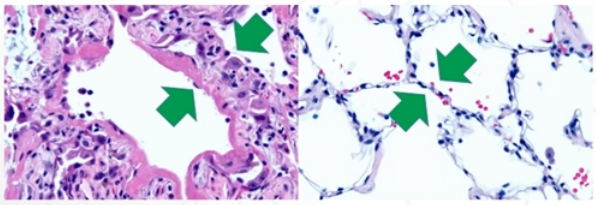


Figure 3. Summary of recommendations on the management of patients with COVID-19 and ARDS.

COVID-19 is a Rapidly Progressive Viral Infection that Quickly Leads to Respiratory Failure





~30% progress to ARDS within 2 days of admission

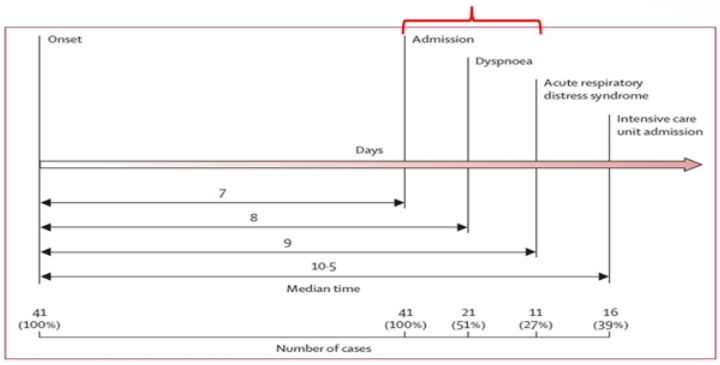
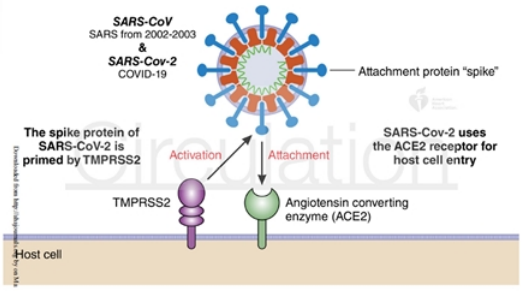
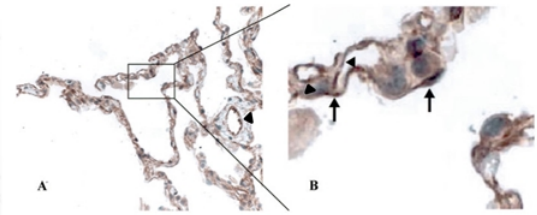


Figure 2: **Timeline of 2019-nCoV cases after onset of illness**

- Rapid progression to respiratory failure leads to mortality and overwhelms the healthcare system (ICU and ventilator capacity)
- ➢ What is needed is an effective host targeted intervention to ameliorate progression of the pulmonary pathology

The SARS-CoV-2 Receptor, ACE2, is Expressed on Pulmonary Epithelium **and Endothelium** Indicating both are Disease Targets





ACE2 expression in normal lung tissue: overview (A) and higher magnification (B). Positive staining for ACE2 is clearly present on alveolar epithelial cells (arrow) and microvessel/capillary endothelium (arrow-head).

Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality
Robert O. Bonow, MD, MS; Gregg C. Fonarow, MD; Patrick T. O'Gara, MD; Clyde W. Yancy, MD, MSc
JAMA Cardiology Published online March 27, 2020

"It is noteworthy that the articles from China by Shi et al,[10] Guo et al,[11] and Yang and Zin[12] address the unique marked affinity of SARS-CoV-2 for the host angiotensin-converting enzyme 2 receptor, which has been shown previously for other coronaviruses,[13] raising the possibility of direct viral infection **of vascular endothelium** and myocardium."

Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis
I Hamming, W Timens, MLC Bulthuis, AT Lely, GJ Navis and H van Goor
J Pathol 2004; 203: 631–637

"ACE2 was present in **arterial and venous endothelial cells** and arterial smooth muscle cells in all organs studied."

The pulmonary endothelium in acute respiratory distress syndrome: insights and therapeutic opportunities
Fraser R Millar, Charlotte Summers, Mark J Griffiths, Mark R Toshner and Alastair G Proudfoot
Thorax 2016;71:462–473. doi:10.1136/thoraxjnl-2015-207461

"The pulmonary endothelium is increasingly seen as pivotal in both the progression and the resolution of ARDS and is therefore primed as a therapeutic target."

COVID-19 can Infect and Replicate in Human Capillary Organoids

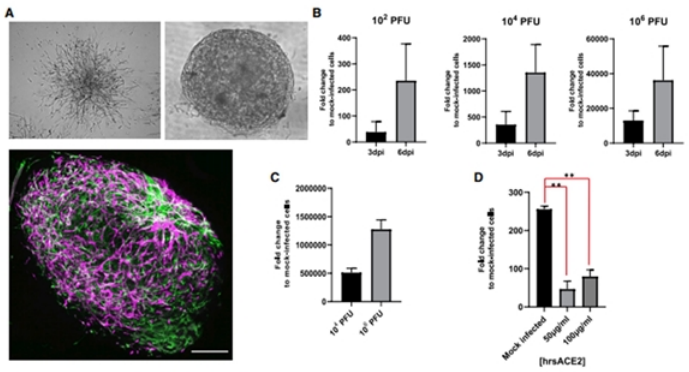


Figure 3. SARS-CoV-2 Infections of Blood Vessels Organoids

(A) Representative images of vascular capillary organoids using light microscopy (magnifications ×10) (upper panels) and immunostaining of blood vessel or- ganoids using anti-CD31 to detect endothelial cells and anti-PDGFRβ to detect pericytes. DAPI (blue) was used to visualize nuclei. Scale bars, 500 μm and 50 μm (inset).

(B) Recovery of viral RNA from blood vessel organoids at day 3 and 6 post-infection (dpi) with SARS-CoV-2, demonstrating that the virus can infect the vascula organoids. Data are represented as mean ± SD.

(C) Determination of progeny virus. Supernatants of SARS-CoV-2 infected blood vessel organoids were collected 6 dpi and then used to infect Vero E6 cells. Afte 48 h, Vero E6 cells were washed and viral RNA assessed by qRT-PCR. The data show that infected blood vessel organoids can produce progeny SARS-CoV-2 viruses, depending on the initial level of infection. Data are represented as mean ± SD.

(D) Effect of hrsACE2 on SARS-CoV-2 infections of blood vessel organoids. Organoids were infected with a mix of 10^6 infectious viral particles and hrsACE2 for 1 h. 3 dpi, levels of viral RNA were assessed by qRT-PCR. hrsACE2 significantly decreased the level of SARS-CoV-2 infections in the vascular organoids. Data are represented as mean ± SD (Student's t test: $^{**}p < 0.01$).

Monteil et al. Cell Correspondence https://doi.org/10.1016/j.cell.2020.04.004

Endothelial Cell Infection and “Endotheliitis” in COVID-19

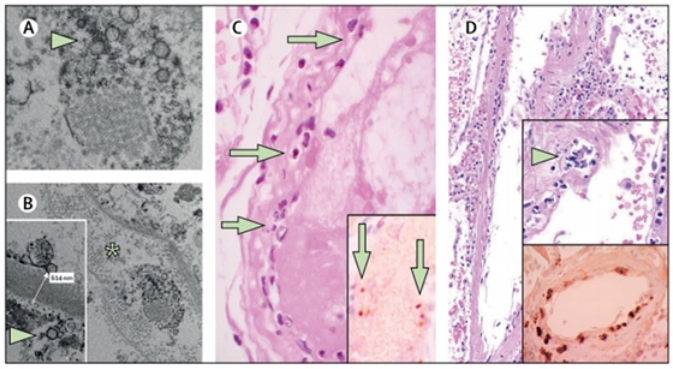


***Figure*: Pathology of endothelial cell dysfunction in COVID-19**
(A, B) Electron microscopy of kidney tissue shows viral inclusion bodies in a peritubular space and viral particles in endothelial cells of the glomerular capillary loops. Aggregates of viral particles (arrow) appear with dense circular surface and lucid centre. The asterisk in panel B marks peritubular space consistent with capillary containing viral particles. The inset in panel B shows the glomerular basement membrane with endothelial cell and a viral particle (arrow; about 150 nm in diameter). (C) Small bowel resection specimen of patient 3, stained with haematoxylin and eosin. Arrows point to dominant mononuclear cell infiltrates within the intima along the lumen of many vessels. The inset of panel C shows an immunohistochemical staining of caspase 3 in small bowel specimens from serial section of tissue described in panel D. Staining patterns were consistent with apoptosis of endothelial cells and mononuclear cells observed in the haematoxylin-eosin-stained sections, indicating that apoptosis is induced in a substantial proportion of these cells. (D) Post-mortem lung specimen stained with haematoxylin and eosin showed thickened lung septa, including a large arterial vessel with mononuclear and neutrophilic infiltration (arrow in upper inset). The lower inset shows an immunohistochemical staining of caspase 3 on the same lung specimen; these staining patterns were consistent with apoptosis of endothelial cells and mononuclear cells observed in the haematoxylin-eosin-stained sections. COVID-19=coronavirus disease 2019.

“Our findings show the presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death. These findings suggest that SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement (as noted with presence of viral bodies) and of the host inflammatory response. In addition, induction of apoptosis and pyroptosis might have an important role in endothelial cell injury in patients with COVID-19. COVID-19- endotheliitis could explain the systemic impaired microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19. This hypothesis provides a rationale for therapies to stabilise the endothelium while tackling viral replication, particularly with anti-inflammatory anti-cytokine drugs, ACE inhibitors, and statins.7–11 This strategy could be particularly relevant for vulnerable patients with pre-existing endothelial dysfunction, which is associated with male sex, smoking, hypertension, diabetes, obesity, and established cardiovascular disease, all of which are associated with adverse outcomes in COVID-19.”

Varga et al. The Lancet April 17, 2020 https://doi.org/10.1016/ S0140-6736(20)30937-5

Patient Characteristics Associated with Endothelial Dysfunction and Vascular Injury are Risk Factors for ARDS and Mortality

Table 4. Bivariate Cox Regression of Factors Associated With ARDS Development or Progression From ARDS to Death

	ARDS		Death	
Patient characteristics and findings	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Clinical characteristics				
Age (≥65 vs <65), y	3.26 (2.08-5.11)	<.001	6.17 (3.26-11.67)	<.001
Gender (male vs female)	1.47 (0.92-2.36)	.11	0.56 (0.30-1.05)	.07
Highest patient temperature (≥39 °C vs <39 °C)	1.77 (1.11-2.84)	.02	0.41 (0.21-0.82)	.01
Comorbidities				
Hypertension (yes vs no)	1.82 (1.13-2.95)	.01	1.70 (0.92-3.14)	.09
Diabetes (yes vs no)	2.34 (1.35-4.05)	.002	1.58 (0.80-3.13)	.19
Laboratory findings				
Infection-related indices				
hs-CRP, mg/L (>5 vs ≤5)	4.81 (1.52-15.27)	.008	NA	NA
IL-6, pg/L	1.02 (1.00-1.05)	.09	1.03 (1.01-1.05)	.01
ESR, mm/h	1.01 (1.00-1.02)	.19	1.01 (0.99-1.02)	.32
Serum ferritin, ng/mL (>300 vs ≤300)	3.53 (1.52-8.16)	.003	5.28 (0.72-38.48)	.10
Coagulation function				
PT, s	1.56 (1.32-1.83)	<.001	1.08 (0.84-1.38)	.54
APTT, s	0.97 (0.94-1.01)	.13	0.96 (0.91-1.00)	.06
D-dimer, μg/mL	1.03 (1.01-1.04)	<.001	1.02 (1.01-1.04)	.002

Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China
Chaomin Wu, MD; Xiaoyan Chen, MD; Yanping Cai, MD; et al
JAMA Intern Med. Published online March 13, 2020.
doi:10.1001/jamainternmed.2020.0994

"Of 201 patients, the median age was 51 years (interquartile range, 43-60 years), and 128 (63.7%) patients were men. Eighty-four patients (41.8%) developed ARDS, and of those 84 patients, 44 (52.4%) died."

Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic
Elissa Driggin, et al.
JACC https://doi.org/10.1016/j.jacc.2020.03.031 JAC 27204

"Increased case-fatality rates in the previously referenced analysis of 44,672 confirmed COVID-19 cases from Wuhan, China were noted in patients with CVD (10.5%), diabetes (7.3%), hypertension (6.0%), all notably higher than the overall case-fatality rate of 2.3%."

Active Tie2 is Essential for Maintaining Endothelial Function and Vascular Stability

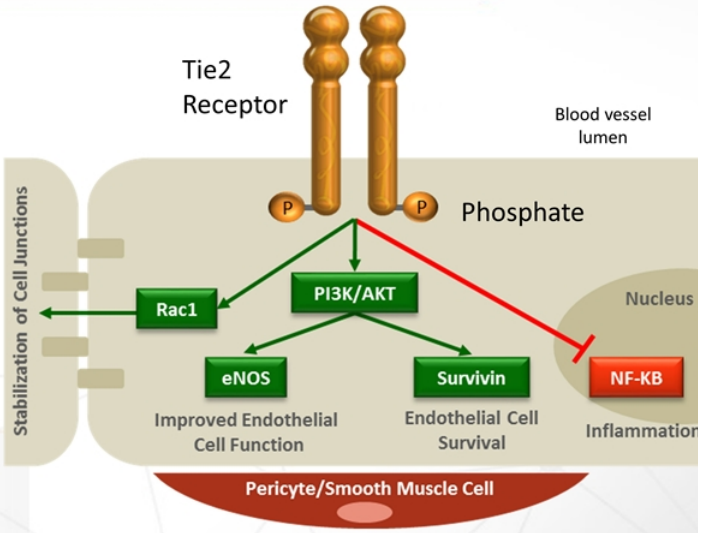
Tie2 is a transmembrane receptor found on endothelial cells, the foundation for vascular stability

Tie2 activity…

- Maintains integrity of endothelial cell junctions
- Enhances endothelial cell function and viability
- Inhibits vascular inflammation

Inactive Tie2 = Vascular Destabilization

- Promotes endothelial dysfunction and pathologic vascular inflammation and leakage
- Enables pathologic neovascularization



Hypothesis: Restoring Tie2 Activation Enhances Endothelial Function and Vascular Stability to Improve Outcomes in COVID-19

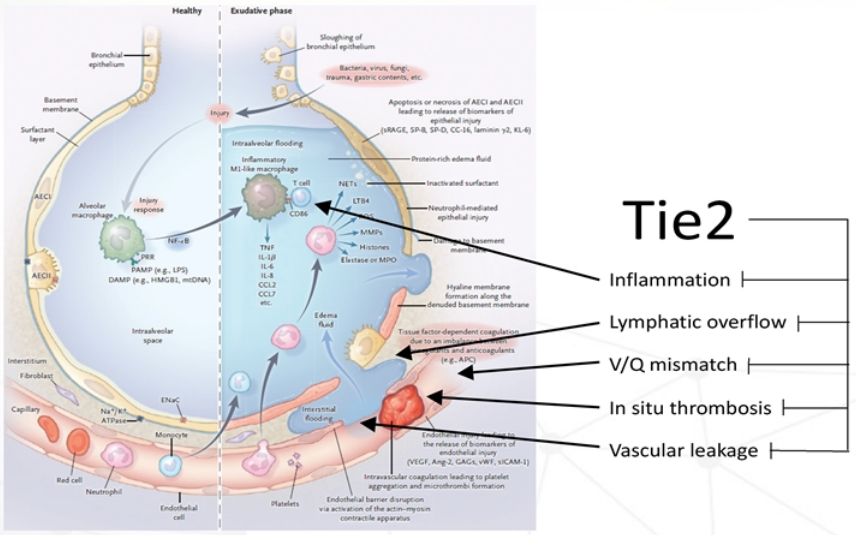
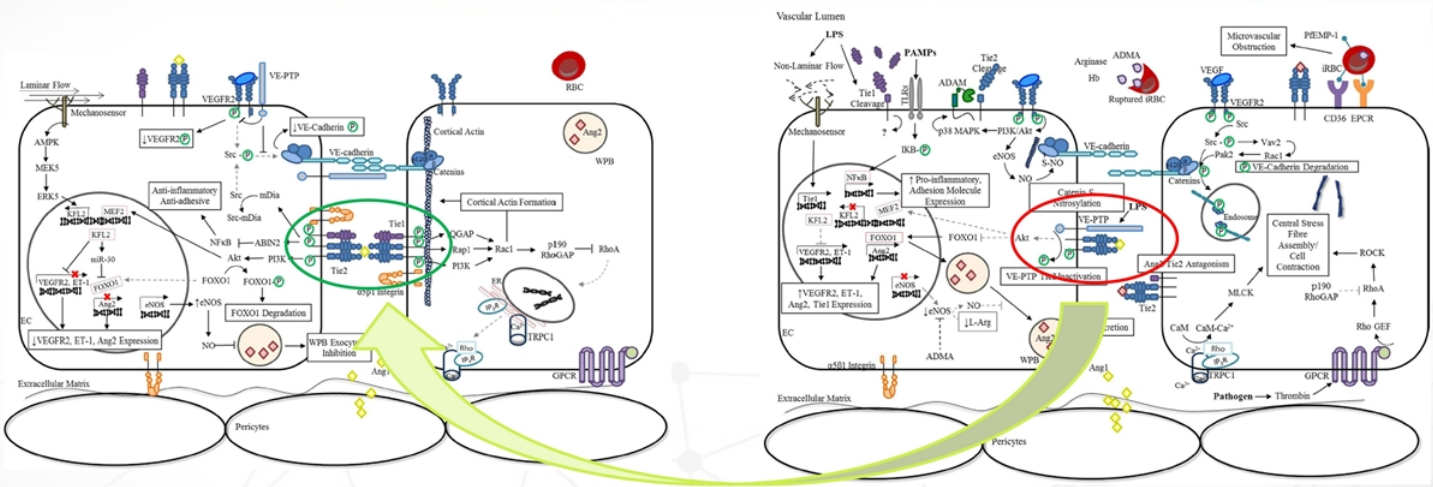


Figure 1: ARDS pathophysiology and Tie2. Left schema from collaborator B. Taylor Thompson, et al. NEJM 2017. Tie2 activation exerts multiple salutary effects.

Table 1: Disparate Models of Lung Injury Improve with Tie2 Activation*
Biological/Chemical Warfare
Phosgene Systemic anthrax lethal toxin
Common Infections/Inflammation
Intratracheal LPS Parenteral LPS Abdominal sepsis from CLP IL-6
Others
Hyperoxic lung injury Serotonin pulmonary hypertension Monocrotaline

* References available on request

Tie2 Signaling in Health (left) and in COVID-19/ARDS (right)

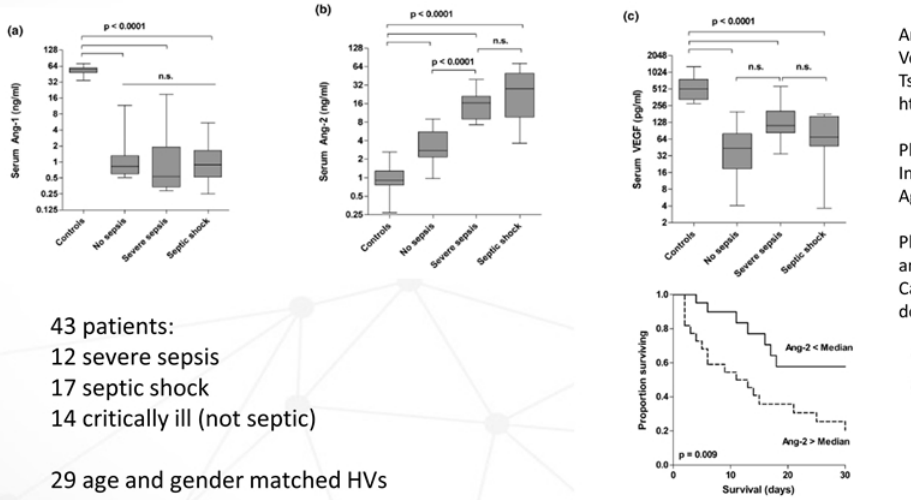


Razuprotafib (AKB-9778)

- VE-PTP, the molecular target of Razuprotafib, is the most downstream negative regulator of Tie2
- Razuprotafib inhibits VE-PTP restoringTie2 activation and vascular stability to improve outcomes in COVID-19/ARDS

Leligdowicz et al. Frontiers in Immunol, 2018 doi: 10.3389/fimmu.2018.00838

Circulating Angpt2 Correlates with Disease Severity and Predicts Mortality in Septic and ARDS Patients



43 patients:
12 severe sepsis
17 septic shock
14 critically ill (not septic)

29 age and gender matched HVs

Kumpers et al. Critical Care 12:R147, 2008

Kaplan-Meier curves of survival stratified to Angiopoietin (Ang) 2.
(less versus greater than median; Log rank test p = 0.009).

Angiopoietin-2 Levels as Predictors of Outcome in Mechanically Ventilated Patients with Acute Respiratory Distress Syndrome. Tsangaris et al. *Disease Markers*, Vol 2017 https://doi.org/10.1155/2017/6758721

Plasma Angiopoietin-2 Predicts the Onset of Acute Lung Injury in Critically Ill Patients. Agrawal et al. *Am J Respir Crit Care Med,* Vol 187: 736–742, 2013

Plasma angiopoietin-2 in clinical acute lung injury: Prognostic and pathogenetic significance. Calfee et al. *Crit Care Med,* 40(6): 1731–1737, 2012 doi:10.1097/CCM.0b013e3182451c87

Lilly Advances Anti-Angpt2 Antibody (LY3127804)

BioSpace

Eli Lilly to Begin Testing RA Drug Olumiant and an Anti-Ang2 Drug in COVID-19 Patients

Eli Lilly is also advancing LY3127804, an investigational selective monoclonal antibody against Angiopoietin 2 (Ang2), to Phase II testing in pneumonia patients hospitalized with COVID-19 who are at a higher risk of progressing to acute respiratory distress syndrome (ARDS). Ang2 is known to be elevated in ARDS patients and Lilly will test whether inhibiting the effects of Ang2 with a monoclonal antibody can reduce the progression to ARDS or the need for mechanical ventilation in COVID-19 patients, Eli Lilly said. The study with LY3127804 is expected to begin later this month at multiple sites in the United States (NCT04342897).

https://clinicaltrials.gov/ct2/show/NCT04342897?term=LY3127804&cond=COVID&draw=2&rank=1

While this seems like a reasonable approach neutralizing Angpt2:

- Requires presence of Angpt1 to restore Tie2 activation (Regula et al. *EMBO Mol Med* 8:1265-1288, 2016)
- Does not deal with Angpt1 resistance due to increased expression of VE-PTP (Shen et al. *JCI* 124:4564-4576, 2014; Souma et al. *PNAS* 115:1298-1303, 2018; Carota et al. *J Exp Med* 216:936-949, 2019)
- Could be counter productive as Angpt2 may maintain low level of Tie2/Akt activation required for viability of stressed endothelium (Daly et al. *PNAS* 103:15491-15496, 2006)

Razuprotafib (AKB-9778) Preclinical Summary

- Razuprotafib is a highly optimized, small molecule VE-PTP inhibitor that activates Tie2, to enhance endothelial function and stabilize blood vessels, including pulmonary, renal and cerebral vasculature.
- VE-PTP is upregulated in “stressed” endothelium in conditions relevant to COVID-19 including diabetes, hypertension and hypoxia.
- Razuprotafib reduces LPS (lipopolysaccharide/endotoxin) mediated vascular leakage and leukocyte transmigration (neutrophil and lymphocyte) in the lung, two key components of COVID-19 pulmonary pathology that contribute to respiratory failure.
- Razuprotafib reduces lung toxicity and improved survival in a mouse model of IL2-induced cytokine storm possibly relevant to cytokine storm that is associated with poor outcomes in COVID-19.
- Razuprotafib improved outcomes in LPS-induced acute renal injury and cerebral ischemia indicating potential benefits of restoring Tie2 activation in crucial vascular beds outside the lung.
- Chronic (6-9 months) GLP toxicity studies in three species (monkey, dog and rat) at many fold over clinical exposures have been well tolerated with no dose-limiting adverse effects identified.

Razuprotafib (AKB-9778) Clinical Summary

- Razuprotafib administered by subcutaneous injection is highly bioavailable with a predictable, dose related pharmacokinetic profile.
- Razuprotafib has been dosed safely at single subcutaneous doses of up to 80 mg in healthy volunteers and 30 mg in patients with diabetes (BID for 28 days)
- Razuprotafib 15 mg QD or BID has been dosed safely for 12-48 weeks in over 250 patients with diabetic eye disease
- In diabetic patients dose with 15 mg QD or BID, there has been clear evidence of target engagement and efficacy (lower blood pressure, reduced macular edema in combination with anti-VEGF therapy, and decrease in UACR and hsCRP)
- Razuprotafib drug substance has been scaled up to 10 kg batches, an amount sufficient for treating 10-12,000 patients for 14 days
- When prepared as a solution for injection in single dose, sterile syringes, Razuprotafib is stable at room temperature for at least 2 years, making storage and dosing convenient in the non-ICU or ICU setting

➢ In summary, razuprotafib is a Phase 2/3-ready drug that restores Tie2 activation to stabilize the pulmonary vasculature providing breakthrough potential for reducing the severity of COVID-19 associated pulmonary pathology.