For what stages of COVID-19 infection is Amarin researching the use of VASCEPA® (icosapent ethyl)?

Amarin is supporting investigator-sponsored pilot studies of VASCEPA® (icosapent ethyl) for potential treatment of individuals at three different stages of COVID-19 infection:

1) in people *at risk* of exposure to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),

2) in patients with *active* COVID-19 infection, and

3) in people with *underlying heart disease who are at increased risk for severe illness* from COVID-19.

The goals of these studies are to generate data on the efficacy, safety, and activity of VASCEPA, if any, in such individuals on endpoints that relate to the prevention, treatment, or recovery of infections with SARS-CoV-2 and clinical sequelae of COVID-19. If these evaluations suggest that further studies are warranted, a decision will be made at that time on additional research.

The three investigator-sponsored studies that Amarin is supporting, as previously publicly described, are:

- Canada (status: completed): The VASCEPA COVID-19 CardioLink-9 clinical trial (NCT04412018) investigated the effects of VASCEPA (icosapent ethyl) on high-sensitivity C-reactive protein (hsCRP), an inflammatory biomarker, changes in other biomarkers and changes in patient symptoms in individuals who tested positive for SARS-CoV-2 and had associated symptoms. The Canadian Medical and Surgical Knowledge Translation Research Group conducted this trial led by Dr. Subodh Verma MD, PhD, FRCSC, FAHA, a cardiac surgeon-scientist at St. Michael's Hospital in Toronto and a professor at the University of Toronto, and by Dr. Deepak L. Bhatt MD, MPH, Executive Director of Interventional Cardiovascular Programs at Brigham and Women's Hospital and Professor of Medicine at Harvard Medical School. The trial primary endpoint was the effect of VASCEPA versus usual care on hsCRP levels from baseline to 14 days in 100 participants who tested positive for SARS-CoV-2 and had associated symptoms such as fever or cough. The clinical study design also included other endpoints that assess rates and severity of coronavirus disease 2019 (COVID-19) in this high-risk group. The results of CardioLink-9 were presented as a late-breaker clinical trial by Dr. Deepak L. Bhatt at the National Lipid Association (NLA) Virtual Scientific Sessions on December 12, 2020. The presentation slides can be downloaded here, and our press release summarizing these results can be found here.

- Argentina (status: ongoing): The PREPARE-IT clinical trial (NCT04460651) is investigating the effects of VASCEPA (icosapent ethyl) on reducing SARS-CoV-2 infections and subsequent clinical events associated with COVID-19 in 2,000 healthcare providers, or relatives of COVID-19 index cases who have been in contact, and at high risk of contracting the novel coronavirus (expanded by the sponsoring investigator from the original study target size of 1,500 subjects while blinded to study results). The study is sponsored by ECLA (Estudios Clínicos Latinoamérica), and headed by cardiologist and ECLA founder, Dr. Rafael Díaz. Dr. Deepak L. Bhatt leads the Executive Committee of the study along with Dr. Díaz and others. The co-primary endpoints are the

percentage of subjects who become SARS-CoV-2 positive and the clinical status of subjects based on the WHO descriptive COVID-19 categorical score which ranges from no infection or limitation of activities to death. For additional information on the trial, please see the clinicaltrials.gov listing.

- United States (status: ongoing): The MITIGATE clinical trial is investigating the effects of VASCEPA (icosapent ethyl) on laboratory-confirmed viral upper respiratory infection (URI) rates, clinical impact and outcomes, especially with SARS-CoV-2 infection which causes COVID-19, in 1,500 adults with established atherosclerotic cardiovascular disease (ASCVD) who are at increased risk for severe illness from COVID-19. A control group consisting of 15,000 adults meeting the same eligibility criteria will be passively followed for outcomes. The trial is being led by Dr. Andrew P. Ambrosy, Associate Program Director for Research (Fellowship), Department of Cardiology, Kaiser Permanente San Francisco Medical Center, and Dr. Alan S. Go, Regional Medical Director, Clinical Trials Program and Associate Director, Cardiovascular and Metabolic Conditions Research, Division of Research, Kaiser Permanente Northern California. The co-primary study endpoints are the rate of moderate-to-severe laboratory-confirmed viral URI, including COVID-19 and influenza, prompting urgent care encounters, emergency department visits, or hospitalization and the worst clinical status due to a laboratory-confirmed viral URI based on an ordinal scale taking hospitalization, death, supplemental oxygen, and other clinical factors into account. For additional information on the trial, please see the clinicaltrials.gov listing, as well as the recent posting of the rationale and design paper for MITIGATE[1]: https://www.sciencedirect.com/science/article/pii/S0002870321000314

Current understanding of the biology of COVID-19 is that patients who have or are at high risk for developing ASCVD are at higher risk of death and severe effects from infection, and that the morbidity and mortality associated with COVID-19 are due both to the direct toxicity of the virus as well as the body's robust inflammatory response leading to so called cytokine storm.[2,3,4,5] Based on data related to the mechanism of action and effects of VASCEPA, it is hypothesized that VASCEPA may play a potential beneficial role in preventing SARS-CoV-2 infection and to potentially reduce clinical severity in patients infected by this or other viruses.[6,7]

The clinical effects of VASCEPA may be multi-factorial. Multiple pleotropic mechanisms of action associated with VASCEPA based on pioneering preclinical studies in a variety of tissue systems support the rationale to test its effects in patients with active infection or at risk for COVID-19 disease.

Some of these postulated mechanisms include the following:

- Potential antiviral/antimicrobial effects[5,8]
- Fibrosis and cardiac damage mitigation in animal models[9,10]
- Anti-inflammatory effects (acute) in pulmonary/lung tissue[11,12]

Dated: March 2, 2021

[1] Ambrosy AP, Malik UI, Thomas RC, et al. Rationale and Design of the Pragmatic Randomized Trial of Icosapent Ethyl for High Cardiovascular Risk Adults (MITIGATE). Am Heart J. 2021 Jan 28:S0002-8703(21)00031-4. doi: 10.1016/j.ahj.2021.01.018. Epub ahead of print. PMID: 33516752.

[2] Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020; (published online May 19.) https://doi.org/10.1016/S0140-6736(20)31189-2

[3] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054-1062.

[4] Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-1034.

[5] Panigrahy D, Gilligan MM, Huang S, et al. Inflammation resolution: a dual-pronged approach to averting cytokine storms in COVID-19? *Cancer Metastasis Rev*. 2020;1-4. doi:10.1007/s10555-020-09889-4.

[6] Morita M, Kuba K, Ichikawa A, et al. The lipid mediator protectin D1 inhibits influenza virus replication and improves severe influenza. Cell. 2013;153:112-25.

[7] Das UN. Can Bioactive Lipids Inactivate Coronavirus (COVID-19)? *Arch Med Res*. 2020;51(3):282-286.

[8] Desbois, A.P. (2013). Antimicrobial Properties of Eicosapentaenoic Acid (C20:5n −3). In Marine Microbiology, S.-K. Kim (Ed.). doi:10.1002/9783527665259.ch20.

[9] Eclov JA, Qian Q, Redetzke R, et al. EPA, not DHA, prevents fibrosis in pressure overload-induced heart failure: potential role of free fatty acid receptor 4. *J Lipid Res*. 2015;56(12):2297-2308.

[10] Ito S, Sano Y, Nagasawa K, et al. Highly purified eicosapentaenoic acid ameliorates cardiac injury and adipose tissue inflammation in a rat model of metabolic syndrome. *Obes Sci Pract*. 2016;2(3):318-329.

[11] Mickleborough TD, Tecklenburg SL, Montgomery GS, Lindley MR. Eicosapentaenoic acid is more effective than docosahexaenoic acid in inhibiting proinflammatory mediator production and transcription from LPS-induced human asthmatic alveolar macrophage cells. Clin Nutrition. 2009;28:71-77.

[12] El Kebir D, Gjorstrup P, Filep JG. Resolvin E1 promotes phagocytosis-induced neutrophil apoptosis and accelerates resolution of pulmonary inflammation. Proc Natl Acad Sci U S A. 2012;109(37):14983-14988.