Why didn't Amarin pursue a triglyceride lowering indication for VASCEPA® (icosapent ethyl) prior to seeking a cardiovascular risk reduction indication in Europe, as it did in the United States?

There are multiple reasons why Amarin did not pursue a TG lowering indication for VASCEPA® in Europe, including the following:

1) In 2016, the European Medicines Agency (EMA) provided guidance for drug development sponsors that reflects the general and long-standing unwillingness at EMA to accept biomarker changes beyond LDL-C as a sole basis for drug approval for treatment of lipid disorders.[i] A strong preference for outcomes trials is also present. Other lipid parameters including, triglycerides (TG), are considered secondary in importance to LDL-C. For drugs focused on modification of secondary lipid parameter demonstration of a positive clinical outcome such as reduced morbidity and mortality is required. Note that no drug has received approval for an indication in a broad-based group of patients with very high TG levels in Europe following the issuance of this guidance.

2) In the United States, FDA has recognized TG lowering as a validated surrogate endpoint for drug approval in patients with TGs of at least 500 mg/dL. EMA has not adopted this approach. EMA is considered more averse to reliance on lipid level reductions as a basis for regulatory approvals generally, as reflected in the 2016 guidance. The primary clinical benefit for lowering TGs in this patient population is to reduce the risk of pancreatitis. The secondary benefit is cardiovascular risk reduction (discussed in item 1). An outcomes study for pancreatitis is difficult to conduct. To our knowledge, such a study has never been successfully conducted or even undertaken for any lipid-lowering drug. Such a trial would necessarily be relatively long-term and expensive to conduct due to the need to enroll a sufficiently large number of patients to support statistical powering to enable the possibility to show a difference between drug effect and placebo.

3) The number of patients with very high TG levels in Europe is generally considered to be insufficient to justify the investment and risk of conducting a large, long-term outcomes study, even if such a trial could be reasonably designed. This drug development approach could fit more of an orphan drug model (high drug price). But that approach would be inconsistent with pursuing the larger cardiovascular risk opportunity with the same drug. Note also that in Europe the sponsors of drugs reach agreements on a country-by-country basis for reimbursement. These agreements for reimbursement are specific to the drug and its indication and the patient population. Accordingly, a pathway of entering Europe for a TG lowering indication and witnessing off label use for an alternative indication (e.g., cardiovascular risk reduction) is highly restricted. If Vascepa were to be introduced, following a successful outcomes study for treating pancreatitis, its only use allowed under the reimbursement pathway would be for pancreatitis and in the very specific narrow population where the benefit was demonstrated. In this respect, Europe is different than the United States. Doctors in the United States have considerable flexibility in prescribing drugs off-label

and pharmacies have considerable flexibility in switching to generic, AB-rated drugs. While product reimbursement rules can vary between countries in Europe, particularly in the largest of countries in Europe, we have observed and anticipate such practices to be restricted by the reimbursement authorities. These authorities seek to ensure that each reimbursed product is used in line with its approval label and within the patient population specified in such label.

Dated: September 25, 2020

[i] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-lipid-disorders_en-0.pdf