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California Institute for Regenerative Medicine
1999 Harrison Street, Suite 1650
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Dear Independent Citizens Oversight Committee (ICOC):

Ankasa wishes to express our appreciation for the careful consideration provided by the review team for our grant application, **CIRM CLIN2-12139, Phase 1b/2a clinical trial and manufacturing development of ART352-L, an endogenous stem cell reactivation therapy to enhance bone autograft osteogenic performance**, as well as for the more than 12 million dollars in support CIRM has invested to date to bring this program from concept to clinic. In reading the reviewers' comments, we felt compelled to address some key misunderstandings with regard to unmet need and study design.

Degenerative spondylolisthesis is a widespread unmet medical need.

Prior to initiating development, Ankasa consulted with multiple groups of surgeon key opinion leaders in busy orthopedic practices to identify the most critical unmet needs for bone formation. Five surgeons from a diverse set of practice settings distributed across the United States were initially put through a rigorous interview process using a battery of questions aimed at understanding gaps in treating patients in need of augmented bone healing. From these interviews, it was clear that 50+ year old patients undergoing spinal fusion suffered from unsafe or inadequate treatment with available options.

Subsequently, Ankasa assembled a Clinical Advisory Board of expert spine surgeons, each with more than two decades experience, one of whom was the then-current president of the North American Spine Society (NASS). This group of distinguished surgeons unanimously agreed that the addition of a biologic therapy that could safely replace the only other approved in the last 20 years, BMP2, would be a tremendous asset to their clinical practices and to the medical market. This was further supported by the advice of CIRM's clinical advisor, Dr. Chris Bono, who participated by phone, when we met face-to-face with CIRM in August, 2019. Independently, each of these groups was in full agreement that of the multiple spine disorders afflicting 50+ year old patients, degenerative spondylolisthesis represented the most critical and significant unmet medical need.

To further support the advice received from these clinical groups, Ankasa engaged in both market and literature research on the unmet needs in spinal fusion and other bone disorders. From this, it was clear that as we age, our bone loses its capacity to heal, and strategies to safely increase bone healing are a massive unmet need. Nearly 90% of people over 50 have some degeneration of their spinal discs. This is called degenerative disc disease (DDD) and leads to debilitating and disabling back pain; treatment costs are in excess of $100 billion a year in the US alone. To increase spinal stability and relieve pain, 750,000 of these patients undergo spinal fusion surgery each year, where bone harvested from the patient is laid along the spinal column to fuse adjacent vertebrae.

Sadly, due to the decreased ability to form new bone in patients over 50, 40% of procedures do not result in the intended fusion and up to 25% require costly and painful revision procedures. Because bone heals slowly, particularly in this population, these patients often endure a minimum of 2 years of ongoing disability before having a revision procedure. The only currently approved bone-forming biologic therapy, BMP2, is associated with major safety issues that have resulted in a "black box" warning label from the FDA that limit its use. Considering our overall aging population, ART352-L has the potential to have a broad impact on this major unmet need, providing a solution to enhance spinal fusion outcomes for hundreds of thousands of older patients and thus reduce their pain, disability, and cost of care.

An uncontrolled Phase 1b/2a safety evaluation is a required gateway to a properly sized randomized controlled study.

Ankasa has been in close communication with the FDA regarding development of ART352-L since 2018. The clinical development team at Ankasa has vast experience and a strong track record of developing biologic therapeutics for many different disabling bone and joint disorders. The design of the Phase 1b/2a study therefore was neither a mistake nor a miscalculation, but rather was carefully co-developed with FDA and an appointed Data and Safety Monitoring Board (DSMB) to assess its primary endpoint of safety. To that end, the current funding proposal describes an uncontrolled 12 patient trial with staggered enrollment between individual patients and between groups (cohorts) of patients as dictated by the FDA. Efficacy signals will be noted based on historical data, but the study is fundamentally designed for safety assessment.

To the reviewers' point, true efficacy can only be assessed compared to a control arm; however, assessing efficacy is not the intention of the currently submitted proposal, and 12 patients does not provide the necessary statistical power, with or without a control, to evaluate efficacy. Thus, including a control in the study would waste a significant amount of both resources and time. The Phase 1b/2a study is a necessary prerequisite to a fast follow-on pivotal (Phase 2/3) trial, the funding for which is outside the scope of this grant cycle. This follow-on study, for which the protocol has already been provisionally developed, will seek to demonstrate both safety and efficacy of ART352-L in the 50+ year old population. This subsequent study will be a properly powered (140-180 patients), randomized controlled trial, in complete alignment with what the reviewers indicated was crucial to the study design in the current review. A plan is in place to gain agreement on this protocol and study design from the FDA once the 6-month safety data are collected in the Phase 1b/2a study. Based on conversations with the FDA, this regulatory strategy was the fastest and most efficient path forward, while ensuring safety of participants in this and subsequent trials.

ART352-L has tremendous potential for clinical and market success

The clinical development of ART352-L is supported by a strong experimental data package from a large number of laboratory studies that have definitively shown that ART352-L enhances bone healing, even in aged animals, with a superior safety profile to BMP2 in head to head testing. The therapeutic potential of this agent has been published in numerous high profile, peer-reviewed articles over the last decade, and the data package was sufficiently compelling for the FDA to allowed Ankasa to open an IND and begin clinical development. The treatment procedure has been rigorously standardized to the extent possible in a surgical setting, as FDA considers this the final step of manufacture and has been fully supportive of the specifications around the current level of standardization. Further, any cold chain challenges for manufacturing the product will be eliminated by the development of the freeze-dried (lyophilized) formulation, the plan and costs for which are included in the current grant application.

As mentioned previously, the promise of ART352-L has been recognized and endorsed previously by CIRM, resulting in > $12 million dollars of funding to advance the product to this important phase of development. During each funding period, the Ankasa team has delivered on all CIRM milestones on or ahead of schedule, culminating in the initiation of this exciting first in human trial.

We are happy to address any additional questions that arise and once again wish to thank CIRM, the reviewers, and the ICOC for this opportunity.

Sincerely,

Gloria Matthews, DVM, PhD, DACVS

Chief Medical Officer