Application #	CLIN1-12946 #2
Title (as written by the applicant)	Skin regeneration and wound healing with a topical BRAF inhibitor
Therapeutic Candidate (as written by the applicant)	A small molecule inhibitor of BRAF
Indication (as written by the applicant)	Venus leg non-healing ulcerous wounds
Unmet Medical Need (as written by the applicant)	There are no previously approved FDA drugs for this condition that affects to 1 out of 100 Californians.
Major Proposed Activities (as written by the applicant)	• Manufacture study drug, Active Pharmaceutical Ingredient and the Formulated Drug Product to supply the proposed studies • Evaluate study drug stability, efficacy and tolerability in different preclinical models • IND submission and phase 1 clinical trial start-up submission
Funds Requested	$5,005,126
GWG Recommendation	Tier 1: warrants funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 1

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below.

Highest	1
Lowest	2
Count	14
Votes for Tier 1	12
Votes for Tier 2	2
Votes for Tier 3	0

- A score of "1" means that the application has exceptional merit and warrants funding;
- A score of "2" means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement;
- A score of "3" means that the application is sufficiently flawed that it does not warrant funding, and the same project should not be resubmitted for review for at least six months after the date of the GWG's recommendation.

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 12	• The proposed topical gel therapy provides a potential easy to deliver treatment strategy for venous leg ulcers (VLU), a chronic and debilitating condition with currently no effective therapy. • Addressing venous ulceration is important, and there are no effective specific drugs for this. • The applicant provided additional rationale for clinical unmet need, including inclusiveness of population they will serve and reason for their focus on VLU as a target wound. • Selection of the VLU indication was responsive to the reviewer comments from the previous review. There is now a stronger case for an unmet medical need. • Applicant response to concerns stated in first review demonstrate that the original concerns were addressed. • The applicant has provided an adequate response to their selection of venous leg ulcers as the initial indication.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 12	• The rationale supports translation to the clinic. The rationale is based on a clinical observation of skin proliferation and epithelial thickening in melanoma cancer patients administered oral BRAF inhibitors. • The observation was confirmed in animal models of skin wounds including a chronic wound model where topical application of BRAF inhibitors resulted in accelerated wound closure. • There have been good responses to the previous feedback, specifically the addition of some pre-clinical work. • The applicants have addressed the rationale questions in their responses. • No way of knowing if this gel helps, but it is a worthwhile effort to do the research and test the hypothesis. • The science presented around a typical BRAF inhibitor stimulating epithelial stem cells are sound. However, there is a potential for the induction of tumorigenesis with local administration of a BRAF inhibitor. Additional studies demonstrating the lack of potential for the drug for causing carcinogenesis will be required. The potential for this BRAF inhibitor to induce tumorigenesis with local administration should be immediately evaluated as a go/no go experiment.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 11	• Applicants have been very responsive to the initial CIRM review and have added additional nonclinical studies, including a carcinogen study. • The applicant has provided details of four proof of concept studies of wound-healing – two in mice and one each in rats and mini-pigs with the study drug. • An additional toxicity study has been proposed using the two-stage skin carcinogenesis model to support IND submission. • During the funding period the applicant will present a plan on conducting additional carcinogenicity assessment for review by FDA. • Appreciated the addition of the ischemic mouse model, a more sophisticated, relevant model. • They seem to have had constructive dialogue with the FDA to inform their revised development plan. • The manufacturing section has not been changed in this second submission. The drug product will be provided by a CMO based outside CA who will also perform release testing in collaboration with the CMO in CA.

	• The manufacturing procedure is provided but difficult to read. Once enlarged, the figures provide all the required information. It is stated that there are minimal risks since a related agent has previously been prepared and released. • I remain unconvinced that the hind limb ischemia model will readily recapitulate the biology of chronic venous ulceration. Tissue remodeling and venous hypertension that occur in chronic venous ulceration is not necessarily represented by acute arterial ischemia. There are models of venous insufficiency that may be more appropriate for pre-clinical testing.
No: 1	• The preclinical plan for the drug is inappropriate and requires significant rework. Furthermore, additional studies will be required to reach the point to design the definitive IND enabling studies. • The FDA provided a basic roadmap to design an appropriate preclinical program for the drug. This roadmap can be found in the regulatory correspondence. Although several experiments can be done to further refine the FDA's suggested approach, the general roadmap presented is a sound starting point for characterization of the drug. • The investigators were previously unsuccessful at obtaining IND approval with a similar therapy. In fact, the Agency gave similar advice to the investigator, but the IND was withdrawn after being placed on clinical hold. The proposal was rewritten to add in a few studies previously proposed by the reviews, but the strategy behind the development package remains unclear. It is likely that this current proposal will result in the same outcome as the prior drug based on the current plan.
GWG Votes	Is the proposal feasible?
Yes: 12	• Very likely to achieve the recruitment of veteran patients from underserved populations as this is a disproportionately affected community. • Yes, they have included some of the nonclinical studies requested by CIRM. The sequence of the nonclinical studies is a bit unclear. • The timeline is aggressive, but the CRO and other vendor partners appear qualified to help the applicant achieve the timeline. • The applicant provided appropriate responses for the multiple FDA submissions. • The addition of a partner for the manufacturing process increases likelihood of meeting the very ambitious time lines. • The applicant provided clarification for manufacture of the study drug. • As currently designed, the preclinical studies lack a strategic scientific approach and are not deemed feasible. The investigator would be wise to work with nonclinical experts to design initial pharmacokinetic and safety experiments and to design appropriate IND enabling studies. The current approach is to conduct general pharmacokinetic and safety studies, as described by FDA, without putting the properties of the drug into proper context. Although several of my recommendation were added to the plan, no real changes to the strategy behind the development of the drug were made to the proposal.
No: 0	*none*
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 11	• Agree with the focus on the Veterans, an important group to target for therapies for chronic wounds, specifically VLU. • Demonstrates an understanding of the potential barriers to participation by VA patients in the clinical trial. • The applicant emphasized recruitment of veterans and a research institution-affiliated community hospital. CA is a mainly Latinx population.
No: 1	• The focus on the VA to address the underserved community is a bit narrow. A broader approach would have been preferred.

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

DEI Score: 7.0

Up to 7 patient advocate members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate Votes	Has the applicant sufficiently addressed how they have or will incorporate perspectives from individuals with diverse experience and from underserved groups in the implementation of the proposed project?
9-10: Outstanding response	0	*none*
6-8: Responsive	4	• Demonstrates an understanding of the potential barriers to participation in the clinical trial. • Plans do look for ways to reach underserved populations, with some attention to barriers. • Plans outline catchment area, veteran focus including Center for Minority Veterans, and community outreach including telemedicine solutions. • The focus on the veterans is only a narrow segment of the impacted population. • Did not see a clear track record of promoting and valuing DEI.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*