Application #	CLIN2-15901 #2
Title (as written by the applicant)	Autologous BCMA CAR-T Cells for the Treatment of Relapsed Refractory Light Chain Amyloidosis
Therapeutic Candidate (as written by the applicant)	Autologous BCMA CAR-T Cells
Indication (as written by the applicant)	Amyloid light-chain amyloidosis
Unmet Medical Need (as written by the applicant)	Amyloid light-chain (AL) amyloidosis is a devastating, rare plasma cell disorder that results in organ deposition. In the US, there are ~3,972 diagnoses every year. Currently, there is no cure for AL amyloidosis.
Major Proposed Activities (as written by the applicant)	• manufacture product to supply the proposed trial • enrollment of the patients • assess clinical safety of the product
Statement of Benefit to California (as written by the applicant)	Patients with AL amyloidosis face a significant reduction in their quality of life due to the debilitating symptoms and the need for frequent medical interventions. The burden of living with a rare also places emotional and financial strains on patients and their families. According to the Journal of Comparative Effectiveness Research, from 2007 to 2015, the average cost of care AL Amyloidosis patients was over 100,000 dollars annually (Quock, 2018).
Funds Requested	$7,999,467
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 majority score of all of the individual member scores. If there is no majority score, the final score is 2. Additional parameters related to the score are shown below.

Highest	1
Lowest	1
Count	14
Votes for Tier 1	14
Votes for Tier 2	0
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.

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 project hold the necessary significance and potential for impact?
Yes: 13 **No:** 0	• AL amyloidosis is an unmet clinical need without FDA-approved therapies. • The proposal is designed to test a product for treatment of relapsed or refractory light chain amyloidosis, a condition with unmet medical need. • Current approved therapies for AL amyloidosis have not led to sustained remissions. • This would be an innovative treatment for patients with AL and the preliminary data is encouraging. • Pilot data show short-term efficacy and safety for the BCMA CAR-T. • 70% complete response in amyloidosis in preliminary studies is positive. Applicants propose to treat several dozen additional patients in a dose escalation study. • Peak CAR-T levels in the blood are higher, and soluble BCMA antigen levels in the plasma are lower among responding than non-responding AL amyloid patients, consistent with the CAR-T's in vivo efficacy. • Yes, CAR-T cells have curative potential, and amyloidosis is in need of transformative treatments such as this. It is unclear whether the therapy will be less expensive than current treatment given the high target antigen and tumor burden with likely cytokine release syndrome (CRS), but the product has curative potential.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• The nonclinical and clinical data presented in the proposal support the rationale. • Among the AL patients treated to date, the product had an overall response rate of 100%, 90% complete response/very good partial response, and a 70% complete response rate. • The toxicity profile of the product is acceptable, with 17.5% of multiple myeloma subjects treated in cohort 3 developing Grade 3 CRS. Per discussions with the FDA, the maximum dose of the planned AL study will be at a lower dose of cells. • While the clinical activity of the drug in myeloma patients is high, progression free survival does not appear to have a stable plateau, similar to what has been seen with the commercial BCMA product. • The eligibility criteria for the AL amyloid study are appropriate. • The lymphodepletion regimen proposed for this phase 1 trial has been used with the CD19 CAR-T product for adult diffuse large B cell lymphoma patients and is generally well tolerated. • The target antigen makes sense, so does the CAR design and preclinical data. Fresh infusion does not have my support simply because of the huge logistical challenges. • The rationale is sound, though there are minor concerns about the stability of the fresh product. • There was also question about the statement that the manufacturing site has manufactured hundreds of products but not had any product failure or sterility "issues". This reads as if they've never had a failure or positive sterility which is highly unlikely.
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	• The manufacturing facilities at the proposed location are excellent. A new manufacturing facility is being built by the sponsor. • The proposed manufacturing process for the phase 1 AL study utilizes an open manufacturing system that is feasible for a clinical trial with a planned enrollment of several dozen subjects. The company has produced sterile products with these standard operating procedures. A closed-manufacturing system is in development. • The product will be manufactured and shipped to the site at 4 degrees Celsius. • The CAR-T product demonstrated cytotoxicity against plasma cells from AL patients in vitro.

	• Using the current costimulatory domain in the CAR-T led to better persistence and less exhaustion versus a different co-stimulatory domain during pre-clinical development; the current CAR structure is appropriate for the AL study. • Yes, well planned with dose escalation, toxicity management, etc... • A minor concern remains regarding the infusion of a fresh product and how to handle patients for whom manufacturing fails after patients have received lymphodepleting chemotherapy. • It appears that the applicant is still considering a high dose arm, although the clinical protocol has been revised in line with the FDA guidance to remove the highest cell dose level. What is the plan to obtain more safety data at the high dose level to convince the FDA?
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• The expertise and experience of the team is excellent. • Accrual rates are feasible with the engagement of multiple California sites. • CAR-T cells will be sampled 48 hours prior to harvest for a potency release assay. Sampling at this time point represents the drug substance at harvest in terms of phenotype and transduction efficiency. • The logistics of shipping a fresh product to California sites is feasible. A plan to test the stability of a fresh product during shipment to the clinical sites is missing from the proposal. • The manufacturing process looks sound, product release also; fresh product release is less feasible. Cryopreserved products are recommended. That should be their back-up plan. Possibly work on a process to maximize cell viability and potency post-thaw. • The applicant has confirmed that point-of-care manufacturing will not occur, greatly reducing the complexity of the cell product controls.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• Yes, it does. They have done their due diligence on populations eligible for this therapy following US census data and epidemiology. • The applicant proposes a reasonable plan to serve various California populations. • Diversity and community engagement plan is adequate. • Satisfactory but somewhat perfunctory and nonspecific.

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate and nurse 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 and nurse 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 & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	6	• The applicant demonstrates understanding about the race, ethnicity, sex, gender, and age-based health disparities of amyloidosis by choosing to center the planned clinical study in rural Central Valley communities extending to the state borders. Their goals for these communities are appropriate to achieve an inclusive distribution of subjects. • Their planned advertising campaigns will raise awareness of the benefits of their cell therapy. Further, language of marketing, education, and trial materials will be tailored to the diverse communities.

		• They address a key barrier to participation by offering one-time treatment vs. weekly treatments and streamlined visit schedules. • Cultural sensitivity activities will include implementation of published guidance, training for their team, and convening a panel for guidance and oversight. • Good catchment area to draw from. • Adequate DEI plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*