



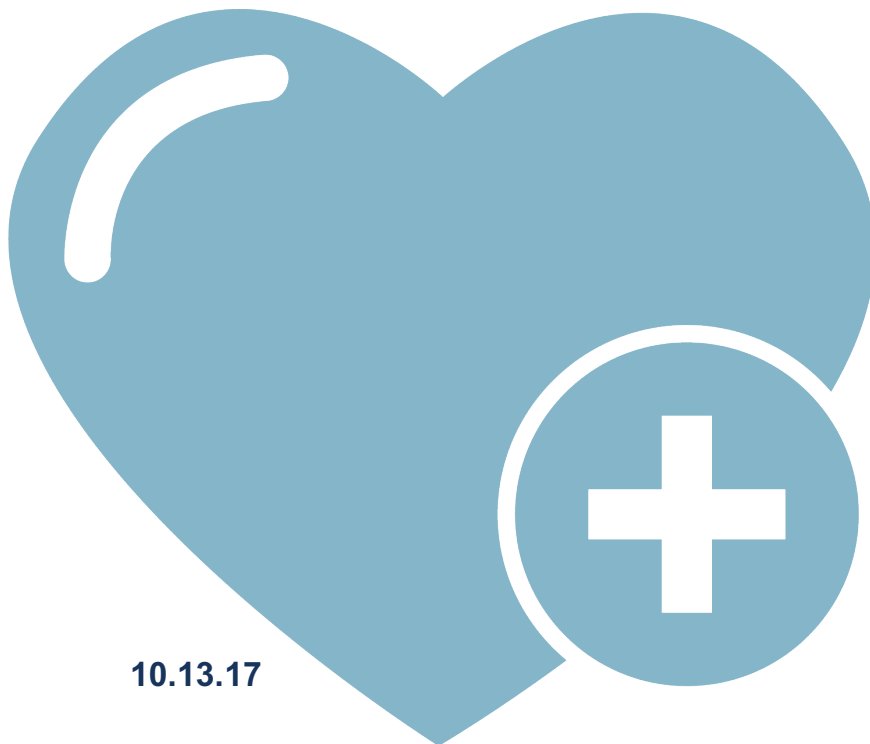
# Grants Working Group Public Review Summary

Evaluation of the Safety and Tolerability of KA34 in a Phase 1,  
Double-Blind, Dose Escalation Trial in Patients with Knee  
Osteoarthritis

Application Number: CLIN2-10388  
(Revised Application)

Review Date: 26 September 2017

Clinical Trial Stage Project Proposal (CLIN2)



10.13.17

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## Evaluation of the Safety and Tolerability of KA34 in a Phase 1, Double-Blind, Dose Escalation Trial in Patients with Knee Osteoarthritis

**APPLICATION NUMBER: CLIN2-10388 (Revised application)**

**REVIEW DATE: 26 September 2017**

**PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects**

### Therapeutic Candidate or Device

KA34 is an intra-articularly delivered small molecule therapeutic candidate which directs the differentiation of endogenous stem and progenitor cells

### Indication

Osteoarthritis

### Therapeutic Mechanism

KA34 promotes the differentiation of cartilage endogenous stem cells through increased chondrogenic gene expression to generate healthy chondrocytes. KA34 will potentially limit the progression of and/or reverse the osteoarthritis disease process. KA34 may generate new cartilage matrix within the pre-existing matrix without fibrotic cartilage formation and aims to improve the clinical joint scores.

### Unmet Medical Need

There are no approved disease-modifying therapies available which stop the joint damage in 30 million osteoarthritis patients in the United States. This grant will support execution of a Phase 1 clinical trial to evaluate the safety of the small molecule, KA34, which stimulates cartilage repair.

### Project Objective

Completion of a Phase I clinical trial for KA34

### Major Proposed Activities

Completion of clinical site selection, start-up activities and execution of the Phase I single and multiple ascending dose clinical study with KA34

Data analysis and reporting on the Phase I single and multiple ascending dose clinical study with KA34 in osteoarthritis patients

Evaluation of potential KA34 treatment-associated biomarkers to support future clinical development of KA34 in osteoarthritis

### Funds Requested

\$8,447,523 (\$0 Co-funding)

### Recommendation

Score: 1

Votes for Score 1 = 11 GWG members

Votes for Score 2 = 3 GWG members

Votes for Score 3 = 0 GWG members

- A score of "1" means that the application has exceptional merit and warrants funding;

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- 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.

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## Review Overview

This is a revised application that previously received a score of "2". Knee osteoarthritis is a major cause of disability and there is a lack of approved disease-modifying therapies. Reviewers thought that the preclinical data supported the scientific rationale, which is that the proposed product stimulates cartilage growth from endogenous progenitor cells.

In the initial review of the application reviewers had several concerns with the phase 1 study design including feasibility of patient enrollment, lack of clarity on efficacy readouts and potential for variation in therapy administration between clinical sites.

The applicant modified the clinical protocol to standardize injection administration and provided clarifications on patient enrollment rate and necessity for preliminary efficacy readouts. A majority of the reviewers found the applicant's responses to be satisfactory and recommended the project for funding.

## Review Summary

**Does the project hold the necessary significance and potential for impact?**

**a) Consider whether the proposed treatment fulfills an unmet medical need.**

- Knee osteoarthritis (OA) is a major cause of disability.

**b) Consider whether the approach is likely to provide an improvement over the standard of care for the intended patient population.**

- The proposed treatment could forestall or prevent surgical intervention for knee OA patients.
- There are no disease-modifying therapies directed at improving quantity and quality of knee cartilage.

**c) Consider whether the proposed treatment offers a sufficient value proposition such that supports its adoption by patients and/or health care providers.**

- The proposed treatment has the potential to decrease disability in knee OA patients and to reduce the need for surgical intervention.

**c) If a Phase 3 Trial is proposed is the therapy for a pediatric or rare indication or, if not, is the project unlikely to receive funding from other sources?**

- N/A

**Is the rationale sound?**

**a) Consider whether the proposed project is based on a sound scientific and/or clinical rationale, and whether the project plan is supported by the body of available data.**

- The preclinical data supports the scientific rationale that the proposed product enhances cartilage production by acting on endogenous progenitor cells.
- In the initial review of the application, reviewers were concerned that the

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preclinical data did not inform on the durability of the treatment effect. Reviewers thought that the applicant's response, which acknowledged that treatment durability was still unknown but that safety and efficacy of frequent dosing will be carefully studied in phase 1 and 2 trials, was adequate at this time.

**b) Consider whether the data supports the continued development of the treatment at this stage.**

- The preclinical data support clinical study of the proposed treatment.

**Is the project well planned and designed?**

**a) Consider whether the project is appropriately planned and designed to meet the objective of the program announcement and to achieve meaningful outcomes to support further development of the therapeutic candidate.**

- In the initial review of the application, reviewers were concerned that the frequency of WOMAC surveys and lack of clarity on MRI scoring criteria would place an undue burden on patients without producing useful information. The applicant's response clarified the necessity for WOMAC testing and indicated that MRI data would inform on preliminary efficacy. Some reviewers continued to express concern that the testing may not benefit patients.
- In the initial review of the application reviewers recommended that therapy administration be standardized across study sites by requiring use of ultrasound guided injections. The applicant agreed with the reviewers' recommendation and revised the study protocol.

**b) Consider whether the proposed experiments are essential and whether they create value that advances CIRM's mission.**

- Reviewers agreed that the clinical trial activities designed to assess product safety were essential and would create value that advances CIRM's mission.
- Reviewers thought that the MRI imaging and WOMAC surveys may help link structural and pain level data in patients.
- Reviewers thought that the biomarker development activity could be helpful in establishing an efficacy profile in later stage clinical studies.
- Some reviewers were concerned that study activities focused on preliminary efficacy readouts were not in the best interest of the patients.

**c) Consider whether the project timeline is appropriate to complete the essential work and whether it demonstrates an urgency that is commensurate with CIRM's mission.**

- The project timeline is appropriate and demonstrates urgency.

**Is the project feasible?**

**a) Consider whether the intended objectives are likely to be achieved within the proposed timeline.**

- In the initial review of the application reviewers questioned whether the trial

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enrollment projections are realistic and feasible. Reviewers were satisfied with the applicant's response, which noted that the enrollment projections are based on feedback from clinical investigators and multiple CROs.

**b) Consider whether the proposed team is appropriately qualified and staffed and whether the team has access to all the necessary resources to conduct the proposed activities.**

- The team is qualified and experienced to conduct the proposed phase 1 study.

**c) Consider whether the team has a viable contingency plan to manage risks and delays.**

- The team has an appropriate contingency plan to manage enrollment delays.

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## CIRM Recommendation to Application Review Subcommittee

The CIRM recommendation to the Application Review Subcommittee is considered after the GWG review and did not affect the GWG outcome or summary. This section will be posted publicly.

**RECOMMENDATION:** Fund (CIRM concurs with the GWG recommendation).