Application #	CLIN2-13267
Title (as written by the applicant)	Phase 1 Treatment of Urethral Strictures in Humans
Therapeutic Candidate (as written by the applicant)	An engineered urethral segment comprising autologous urothelial, smooth muscle, and progenitor cells within a tubular scaffold.
Indication (as written by the applicant)	Autologous engineered urethral constructs for the replacement of urethral strictures that are too long for treatment with conventional methods.
Unmet Medical Need (as written by the applicant)	Current treatment options for short urethral strictures often fail in the long-term when applied to long segment strictures. Autologous engineered urethras provide a long-term cure for long segment strictures and completely restores normal urinary function.
Major Proposed Activities (as written by the applicant)	• Submit CIRM application to achieve funding for phase 1 clinical trial and submit an IND amendment to add a trial site in California • Manufacture engineered urethral constructs using autologous urothelial, smooth muscle, and progenitor cells • Complete phase 1 clinical trial and analyze patient outcomes
Funds Requested	$3,841,593
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	1
Count	15
Votes for Tier 1	15
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, 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: 15	• This project aims to use a autologous tissue engineered tubular construct to treat long segment urethral strictures. The project, if successful, will address an unmet medical need and bring an improvement in standard of care for this patient population. • The applicant responded well to GWG critiques in their revision document, but missed the opportunity to clearly present the unmet need and potential for impact in the proposal itself. • Urethroplasty procedures are quite rare, around 1000/year total in the US, because most cases are treated with excision primary anastomosis. This limits the potential for impact and the ability to commercialize a product. However, urethroplasty is viewed as a superior treatment option and more procedures might be done if there was a better option than onlay grafts using skin or buccal mucosa. • There is also value in this project to demonstrate the feasibility of a cell-seeded scaffold to repair vessels that must withstand physiological pressures. • There is a lack of clarity in the Target Product Profile for what level of success is targeted. This is not unexpected at this early stage of development, although not ideal. A drug coated balloon for the treatment of anterior urethral stricture provides some guidance (significant improvement in Maximum Urinary Flow Rate and Freedom From Repeat Intervention). The applicant does collect this type of information in the study.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 15	• The rationale is sound and based on a body of pre-clinical and some pediatric clinical data. The data do support continuation of the project. • The main challenge is in the very complicated manufacturing process which requires the isolation and seeding of autologous urethral cells and smooth muscle cells on a PGA scaffold tube coated in PLGA. The urethral cells are seeded on the lumen of the scaffold and after these cells adhere and expand over a couple of days the smooth muscle cells are seeded on the outside of the scaffold.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 15	• There are ten patients in the clinical trial. I would have liked to see fuller justification for this number - why only ten? I would expect variability in outcomes given the product is autologous and incorporates two separate cell types and a PGA coated device. • The applicants did not respond to the question from the prior GWG review about the rationale for the study sample size. It should be a relatively straightforward question to answer for a phase 1. • The applicant was generally responsive to the prior GWG recommendations. The study design is reasonable for a phase 1 trial. • The Investigator Brochure is weak (9 pages, no data) and not what would be expected for a rigorous scientific and clinical document. I believe this reflects a lack of regulatory and clinical experience in the team. They will need additional help after phase 1 if this product candidate is to be developed. • From a manufacturing perspective I think the project is now well planned. There have been quite a number of interactions with FDA starting in 2015 concerning manufacturing issues. These issues have been resolved to FDA's satisfaction and from a manufacturing perspective they are now in a position to make product for the clinic. • The product is to be manufactured by a facility with great experience in regenerative medicine projects. The manufacturing summary is clear and detailed (within the page limitations). • The investigators also provide a 177 page, very detailed manufacturing plan. This provides both manufacturing data and some pre-clinical information on manufacturing strategies and results. • They also include a very detailed point-by-point response to issues raised by the FDA in correspondence dating from 2016. Most notably, they attribute a cited failure rate during pre-clinical runs to the quality of the cadaveric tissue that was used in these experiments. • Given the facility's experience and the quality of the supporting documentation provided, I believe that the Manufacturing Section fully supports this application.

	• While de-identification of individual participant data is critical, the applicant could 'jitter' key variables (such as date) on the primary outcome measures, so that statistical tests can be checked by independent parties, and reported results can be reproduced. • A data sharing plan should be explicit about exactly which variables will be shared, and the statistical workflow/code also needs to be made available.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 15	• I appreciate the addition of a medical monitor. Going forward they would need more clinical and regulatory input. • After five years of back-and-forth the FDA agrees that the safety profile is acceptable. • For the future, I feel they should engage additional regulatory expertise/experience to take this further if the phase 1 trial is a success. • The applicants have demonstrated that the project is feasible.
No: 0	*none*
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 15	• Yes, although the proposal is not specific regarding the operational components. • There are a number of references to DEI-oriented resources available at the trial site that may increase the project's impact in underserved and unserved communities. • I am not aware of the demographics for this condition. Obviously it only affects males. Both trial sites appear to have well-developed programs, both internally and in terms of reaching underserved populations with urinary tract conditions. • I thought overall their DEI section was acceptable, but I do appreciate that the applicant may be relying too heavily on the reputation of the institutions instead of putting forward their specific plans for engaging institutional resources in support of this trial.
No: 0	*none*

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: 6.5

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	3	• The applicant has a clear focus on DEI, as evidenced by their selection of trial sites. • The applicant has beneficial ties to minority health advocacy and health equity organizations. • This approach would be a significant improvement over the current practice. • The urology department at the California trial site has worked to address known gaps in care including women's bladder and pelvic health, transgender health, and congenital urological health.
3-5: Not fully responsive	1	• The applicant does not address how success of the project would lead to a translational advance that impacts underserved communities.

		• The applicant does not describe or address potential barriers to trial participation, so it is difficult to evaluate whether they can achieve inclusive trial recruitment. • They appear to have adequate DEI-related expertise on the team, and to value diverse perspectives on their team.
0-2: Not responsive	0	*none*