

Vericel BLA 125603 Mid-Cycle Meeting Agenda 6-23-2016

Attendees

Meghna Alimchandani, Pete Amin, Kim Benton, Karen Campbell, Jean Gildner, Nevitt Morris, Tony Hawkins, Patricia Holobaugh, James Kenney, Hyesuk Kong, Shiohjen Lee, Stan Lin, Malcolm Moos, Loan Nguyen, Steven Oh, Raj Puri, Patrick Riggins, Becky Robinson, Bruce Schneider, Stephanie Simek, Terrig Thomas, Allen Wensky, Celia Witten, Michael Yao, Carolyn Yong

Product: Autologous Cultured Chondrocytes Seeded on a Porcine Collagen Membrane (MACI)

Clinical Indication: Repair of symptomatic, full-thickness cartilage defects of the knee (b) (4) in adults.

Reviewer Reports: Status of reviews/inspections and outstanding issues

CMC

- DCGT: Draft reviews of cellular and membrane components are complete

- Cellular Component

- (b) (4)

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- No acceptance criterion for (b) (4)

- Sponsor will provide a specification for (b) (4) based on existing manufacturing data

- Membrane Component

- Outstanding issues described at 6-2-2016 briefing meeting:
 - Genotoxicity and (b) (4) testing
 - (b) (4) Lot Release Testing
 - (b) (4) specification
 - (b) (4) testing acceptance criteria
 - (b) (4) validation (FDA form 483 observation)
 - 21 CFR 820 compliance regarding Design Controls/Design History and corrective and preventative actions (FDA form 483 observation)

- 6-20-2016 - IR regarding ACI-Maix (Matricel) manufacturing
 - Compliance of Matricel with USDA inspections
 - Pre-release quarantine procedures for tissues
 - Certification that facility has not processed tissues from non BSE-free countries
 - (b) (4) analysis results for collagen (b) (4)
 - (b) (4) acceptance criteria for ACI-Maix
 - Conformance to FDA standards regarding package integrity evaluation
 - Justification of (b) (4) specification
- DBSQC: Review to be completed by Late Cycle meeting (9-20-2016)
 - (b) (4) sterility testing method validation
 - 5-26-2016 - IR sent on regarding concerns with the current validation (LOD, organisms used, one temperature)
 - 6-3-2016 - Sponsor responded, providing details of the (b) (4). Acceptable?

Discussion: *There was uncertainty regarding Vericel's sterility testing. In the proposed labeling, it is stated that the compendial test is performed on all samples. Based on observation at the PLI, only (b) (4) is used, unless there is a sterility failure, in which case a compendial test is performed as a check. Clarification is needed as to whether the compendial sterility testing described in the proposed labeling is for MACI (b) (4), prior to FDA approval of the (b) (4). DBSQC will check on this, as it could impact our response to the IR.*

- Lot Release Testing Plan – Exempt due to short shelf-life, autologous product

Karen Campbell will send the updated template and suggested language.

- DMPQ: Inspection conducted May 3rd –May 9th
 - FDA form 483 issued
 - Response to four observations expected to be received, reviewed and resolved prior to the Late Cycle meeting (9-20-2016)

Pete Amin said that a complete response to the form 483 observations was submitted today

- Draft EIR to be completed by 7-30-2016

Pre-Clinical

- All preclinical related information has been completely reviewed and no issues have been identified.

Clinical

- Draft review is largely complete and there are no outstanding IRs

- One outstanding issue is how outcomes of the SUMMIT extension study will be presented in labeling and promotion.
 - No formal hypothesis or statistical testing for the extension study; objectives were inconsistently stated as studying durability of response between the two treatment groups.
 - Sponsor considered participants had non-randomized self-selection bias; based on review, this does not appear to be the case.

Discussion: Michael and Bruce did not consider the withdrawal of 8 out of 16 subjects to be biased, as they withdrew due to their associated clinical site opting not to take part in the extension study. They opined that nearly as 88% of subjects remained for the duration of the extension study, this was very good. In addition, as the MACI treatment effect of superiority over microfracture was maintained it was questioned as to how or whether this data may be included in the labeling and promotional materials.

- Should results of the composite 2° endpoint, which were statistically significant and favored MACI, be presented in labeling in a descriptive manner?
 - Failure in the first two 2° endpoints (histology and MRI) precluded formal testing of the third.

Statistics

- Draft review of SUMMIT trial is complete - No outstanding IRs.
 - Earlier IR on KOOS Pain and Function by site tabulation has been resolved.
 - Parts of the SUMMIT Extension study covering subject observations beyond week 104 (the primary SUMMIT study period) will be added to the review.

Pharmacovigilance

- The available data do not suggest a safety concern that would require REMS, PMR or PMC.
- Vericel's proposed PVP (communication plan, controlled distribution and healthcare provider (HCP) training) is adequate.
- IR - 5-26-2016
 - When/how will Vericel determine if HCP training was completed?
- Response – 6-2-2016
 - Prior to the first case conducted at a hospital/surgery center Vericel's Cell Therapy Specialist will train the surgical support staff (in-service) on how to receive, store, unpack, and handle the implant prior the implantation. In-service will be repeated as needed (e.g new staff or > 1 year since the previous implant).
 - When a biopsy is received, Vericel Customer Care will check to ensure that the HCP has fulfilled the training requirements and that a

knowledge check has been completed. The HCP will not be able to order final product for implantation until they have fulfilled their training requirements.

Discussion: *In the BLA the sponsor states that all training materials will be made available after approval. As there is no need for a REMS this is considered to be OK. However, given that the clinical procedure for MACI is different from that of Carticel it was suggested that we ask the sponsor to provide these materials for review at the mid-cycle telecon*

BiMo

- Inspection of 3 foreign clinical sites (Montpellier, France; Utrecht, Netherlands; Piekary Śląskie, Poland) covering SUMMIT study completed:
- No FDA form 483 issues
- Netherlands inspection: CBER final report: classified as No Action Indicated (NAI)

Mid-Cycle Meeting Summary

- Enter into RMS-BLA and upload into CBER's EDR

Mid-Cycle Communication with Vericel

- Telecon within two weeks following the Mid-cycle meeting to provide Vericel with an update on the status of the BLA review – **Date?**
 - Need to include:
 - Significant issues identified by review committee to date
 - Information requests sent and not received
 - New information requests to be communicated?
 - Preliminary thinking regarding risk management
 - Proposed date for the Late-cycle meeting – 9-20-2016
- Telecon summary to be sent to Vericel via fax or secure email

Labeling

Target date for communication with Vericel of FDA feedback on proposed labeling, PMR, PMC and REMS – November 21st, 2016

- Proprietary name: MACI
- Non-proprietary name: autologous cultured chondrocytes on porcine collagen membrane
- Pharmacologic class - *autologous cellularized scaffold product?*
- Dosage form – *Cellular sheet?*
- *Internal meetings to start?*

Discussion: *As there do not appear to be any major review issues that could lead to a serious delay Drs. Simek and Witten suggested that labelling discussions with the sponsor be brought forward. They also suggested that, if possible, all primary reviews be completed and signed off sooner than required.*