



NIH Recombinant DNA Advisory Committee

Protocol #0912-1016 Status Update

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Presentation Outline

1

Background and Nonclinical Data Update

2

Protocol #0912-1016 Design

3

Protocol #0912-1016 Status Update

4

Study Adjustments

5

Questions and Answers

Osteoarthritis Overview

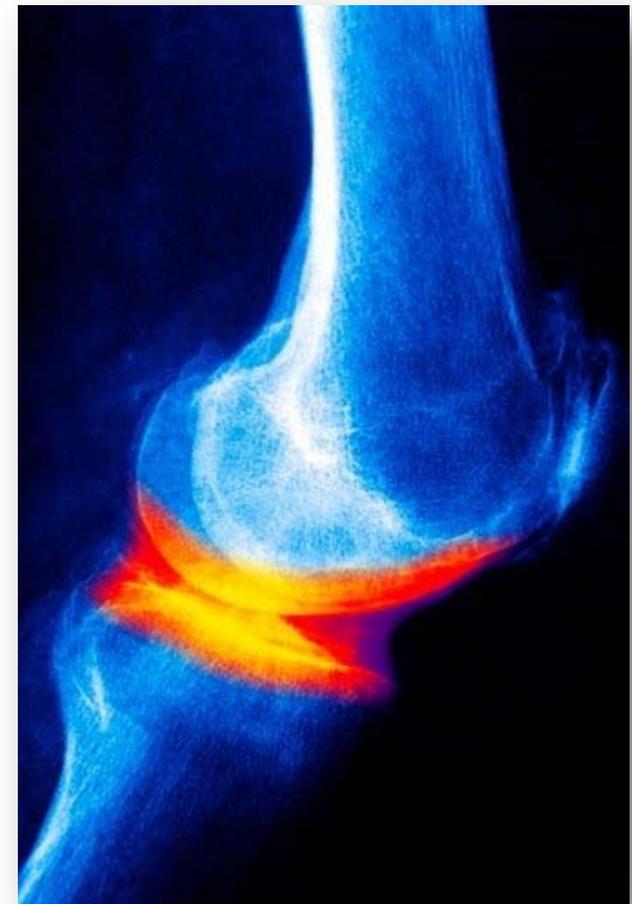
Osteoarthritis is a chronic disease characterized by the breakdown of cartilage that affects over 150 million people worldwide.

O s t e o a r t h r i t i s

- **Causes:** Progressive degeneration of articular cartilage
- **Symptoms:** Joint pain, stiffness and functional impairment
- **Risk Factors:** Age, weight, gender, genetics, and injury

P r e v a l e n c e

- Currently, osteoarthritis is estimated to affect over 27 million adults in the US¹ and over 150 million people worldwide²
- The lifetime risk of developing knee osteoarthritis is estimated at 45% with risk rising to 60% in obese adults³

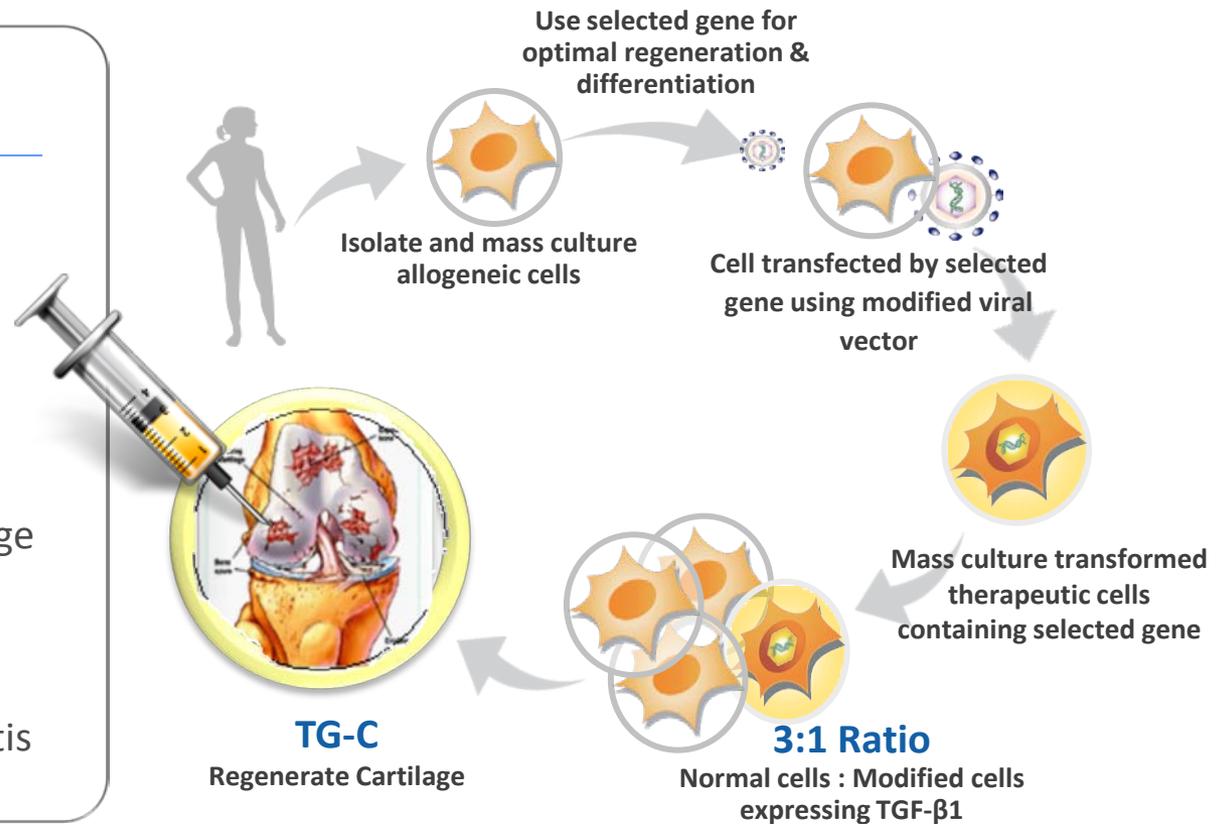


Product: TG-C

Protocol #0912-1016 is designed to assess the effects of a single intraarticular injection of TG-C in treating patients suffering from knee osteoarthritis.

TissueGene-C (TG-C)

- **Technology:** Cell Therapy
- **Therapeutic Protein:** TGF- β 1
- **Delivery:** Single Injection
- **Function:** Regenerate Cartilage
- **Development Stage:** Phase II
- **Indication:** Knee Osteoarthritis



TG-C involves human donor chondrocytes developed to produce the therapeutic protein TGF- β 1 to stimulate cartilage regeneration.

 Protocol #0912-1016 – Background

History

- Protocol #0912-1016 underwent full RAC review at the meeting on March 11, 2010.
- Based on NIH RAC comments, preliminary immune response testing was performed, additional animal testing initiated and the protocol was revised.
- These were submitted to and discussed with the FDA in an End-of-Phase I meeting on September 8, 2010.
- Protocol was revised further based on FDA comments.
- Complete responses to the NIH RAC comments were submitted, and enrollment was initiated on May 17, 2011.



Protocol #0912-1016 - Nonclinical Update

Nonclinical Studies Completed Since March 2010

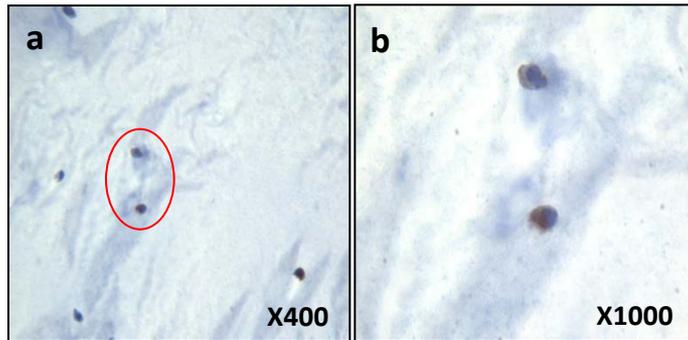
- *Ex Vivo* Cell Adhesion Study of TG-C in Rabbit Knees
 - *>98% of loaded cells adhered to the surface after 30 minutes.*
- *Ex Vivo* Cell Adhesion Study of TG-C in Human Knees
 - *40-60% of loaded cells adhered to the surface after 60 - 120 minutes. Further, exposed bony surfaces (i.e. with no remaining cartilage tissue on the surface) showed lower adhesion rates than surfaces with existing cartilage.*
- *In vivo* efficacy of TG-C in CS-10 (new vehicle) in New Zealand White Rabbits.
 - *Efficacy equivalent to TG-C in previous vehicle (DMEM)*
- *In vivo* acute (14-day) toxicity of CS-10, DMEM, and TG-C in either CS-10 or DMEM.
- *In vivo* tumorigenicity study of irradiated transduced cells (hChonJb#7).
 - *Irradiated hChonJb#7 cells were found to be not tumorigenic*

Protocol #0912-1016 – Nonclinical Update

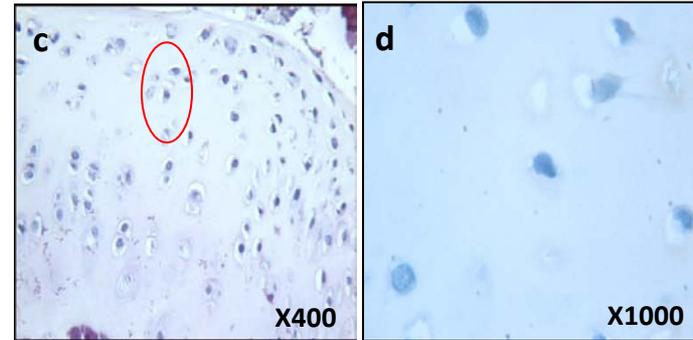
Cell Fate in Rabbit Surgical Defect Model

- An *in vivo* study of the fate of TG-C cells in a rabbit model was conducted.
- Human cells detected in regenerated cartilage 8 and 12 weeks after transplantation of TG-C (arrows)

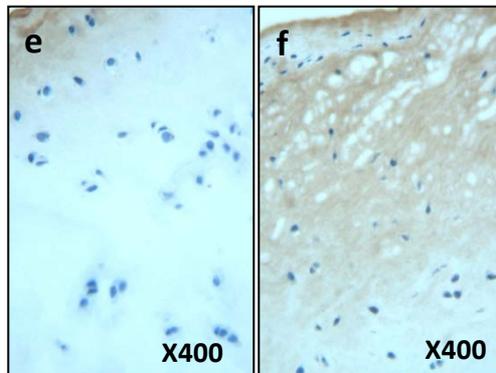
Normal Human Cartilage



Normal Rabbit Cartilage



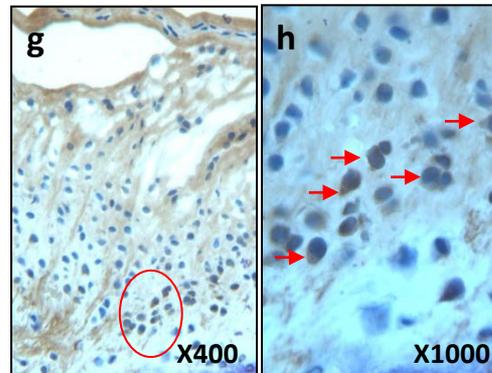
Control Rabbit Cartilage



Normal Site

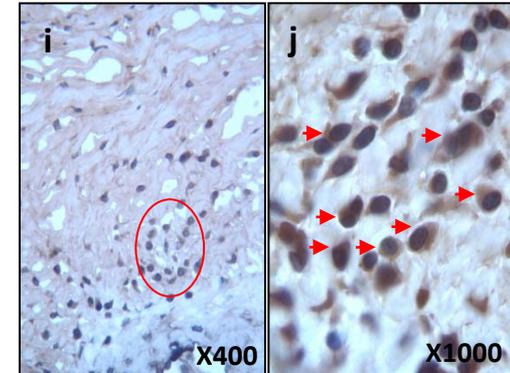
Defect Site

8 wks after transplantation of TG-C



Defect Site

12 wks after transplantation of TG-C



Defect Site



Protocol #0912-1016 – Nonclinical Update

Acute Toxicity of CS-10 (Vehicle) and TG-C in Rabbits

- Designed to evaluate the potential adverse effects of CS-10 cryopreservative for clinical dose administration.
- 14-day acute toxicity of CS-10 (vehicle), DMEM (vehicle from previous formulation), TG-C in CS-10, and TG-C in DMEM at doses of TG-C up to 1.1×10^7 cells per knee.
- No mortality was observed. Nor were there any toxicologically significant changes in responses between CS-10 and DMEM.
- Edema for up to 8 days was observed at the injection site occurred in animals dosed with TG-C in DMEM, but not in any of the other dose groups.
- Of note, histopathological examination revealed signs of inflammation including synovial cell hyperplasia, synovitis, vascularization in the synovium and pannus formation. This is consistent with the known effects of TGF- β 1 (Fava et al, 1991, Allen et al., 1990). These effects were reversible and recoverable.



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Synopsis of Protocol #0912-1016

U.S.	A Phase II Study to Determine the Safety and Efficacy of TG-C in Patients with Grade 3 Chronic Degenerative Joint Disease (DJD) of the Knee
Study Design	Multi-center, placebo-controlled, randomized, double-blind
Study Population	Patients aged 18-70 with Grade 3 (Kellgren and Lawrence) chronic knee DJD
Sample Size	100 patients: A sample size of 100 patients (67 TG-C and 33 control) is needed to see at least a 25% difference from the control group with alpha=0.05, 80% power
Administration	Single intra-articular injection to the damaged joint area
Dose Levels	Dose level: 3×10^7 cells/joint (N=67) Control: Single saline injection (N=33)
Evaluation Schedule	During screening, prior to dosing, 24 hr post-dosing Months 1, 3, 6, 12, 18, and 24 post-dosing



Protocol #0912-1016 Safety Endpoints

Safety Endpoints

- Adverse events (incidence and severity)
- Observation of injection site
- Changes in physical exams
- Clinical chemistry analysis
- Hematology and urinalysis tests

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- TGF- β 1 levels detected by ELISA
- Vector DNA and RCR detected by PCR

Immune Response

- T-cell response, Ab response, WBC count, C-reactive protein (CRP), erythrocyte sed. rate (ESR)
- Multiplex cytokine analysis (IL-1 α , IL-2, IL-4, IL-5, IL-6, IL-10, GM-CSF, IFN γ and TNF α)

Stopping Criteria

- Temporary suspension of dosing and review by IDMC and regulatory authorities will occur for:
- Any serious adverse event attributed to TG-C administration
- A Grade 3 or two persistent Grade 2 events due to TG-C (NCI CTCAE Classification)



Protocol #0912-1016 Efficacy Endpoints

EFFICACY CRITERIA

EVALUATION METHODS

Primary Endpoint

- Knee symptoms, pain and functionality

- IKDC Subjective Knee Evaluation
- 100 mm Visual Analog Scale (VAS)

Secondary Endpoints

- Knee symptoms, pain, and functionality
- Articular knee cartilage damage
- Cartilage regeneration
- Pain reduction
- Inflammation
- Knee functionality
- Need for total knee arthroplasty

- Knee Injury and Osteoarthritis Outcome Score (KOOS)
- Lysholm Knee Score
- 3T MRI (baseline to months 3, 6, and 12)
- Questionnaires, analgesia (incidence and dose)
- Anti-inflammatory medications (incidence and dose)
- Lower Extremity Functional Scale (LEFS)
- Election to undergo total knee arthroplasty (TKA)



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Protocol #0912-1016 Study Status

Enrollment

- Seventy-seven (77) patients have been enrolled (dosed) under Protocol TGC09201 as of June 18, 2012.
- Enrollment was suspended on March 5, 2012 at the request of the IDMC subsequent to their review of the safety data and pending FDA review.
- Enrollment was cleared to resume by the FDA on May 7, 2012. Changes were subject to IRB review. IRBs at all 5 sites have reviewed and approved the changes and enrollment has resumed.

Data Collection and Review

- **No serious adverse events related to TG-C administration have been reported.**
- Data collection for AEs, immune response, laboratory parameters and efficacy is ongoing.
- Scoring for MRIs is currently ongoing; first results expected by the end of June.
- Protocol scheduled interim analysis is for 6 months post-injection for all 100 patients.
- Ad hoc analysis is ongoing and data are summarized as follows.



Protocol #0912-1016 Safety – Adverse Events

Overall

- 138 AEs total from 55 patients out of a total of 77 patients.
- 67 (48.5%) of AEs are considered possibly or definitely related to treatment (active or placebo).

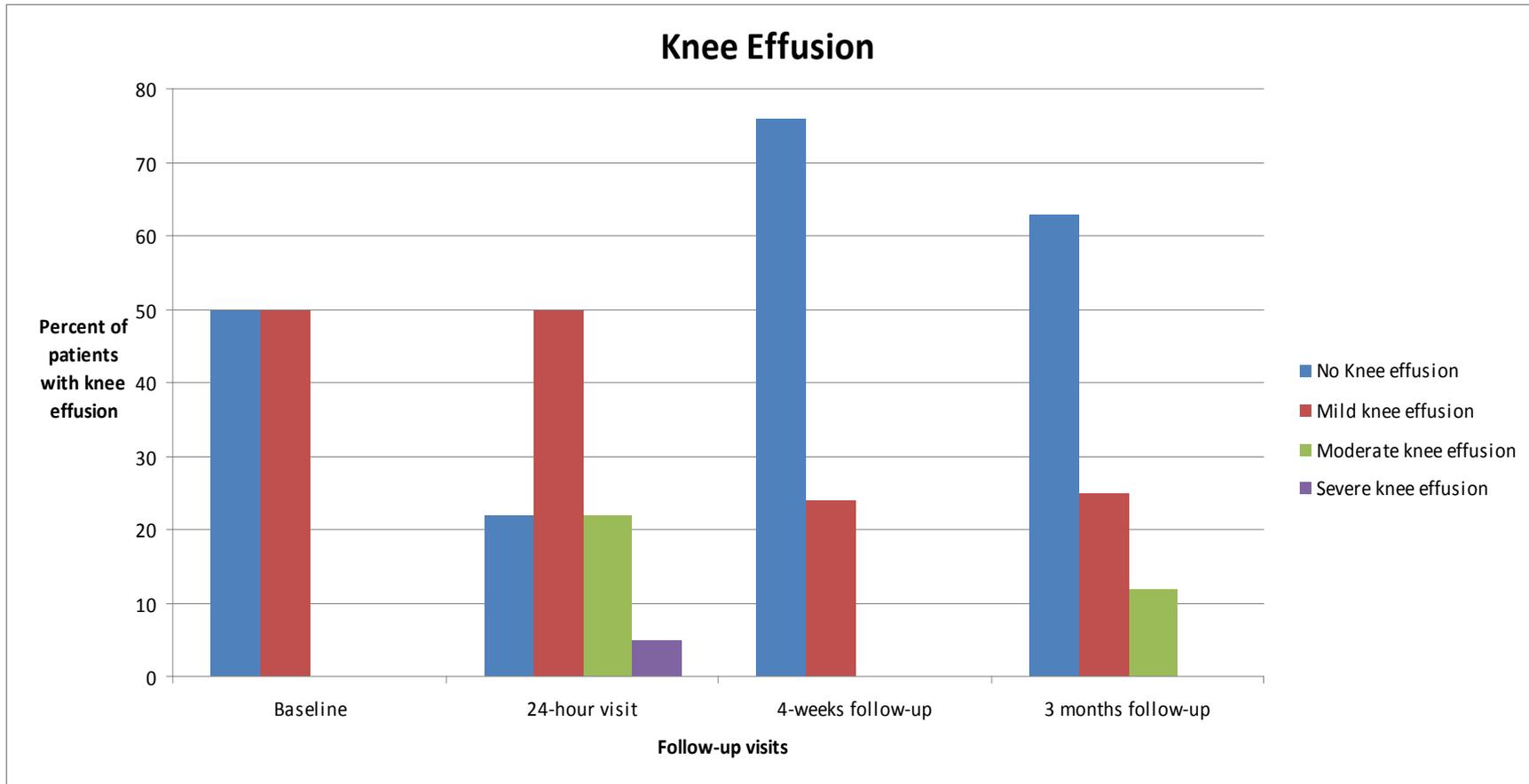
Analysis

- Of the 77 patients, 51 received active, 26 received placebo.
- The most common AEs seen were some form of knee pain, swelling, effusion or other sign of inflammation in the treated knee.
- 31 patients had an AE of this nature. 28 of these 31 patients were active patients.
- Therefore approximately 55% of (28 of 51) patients treated with TG-C exhibit inflammation in the treated knee.
- There were no corresponding changes in immune parameters for these patients.
- TGF- β 1 from the transduced cells may induce an inflammatory reaction.
- Additionally, an intraarticular injection itself may cause an inflammatory reaction.
- Accordingly, AEs of this nature are not unexpected.



Protocol #0912-1016 – AEs at Sinai Hospital

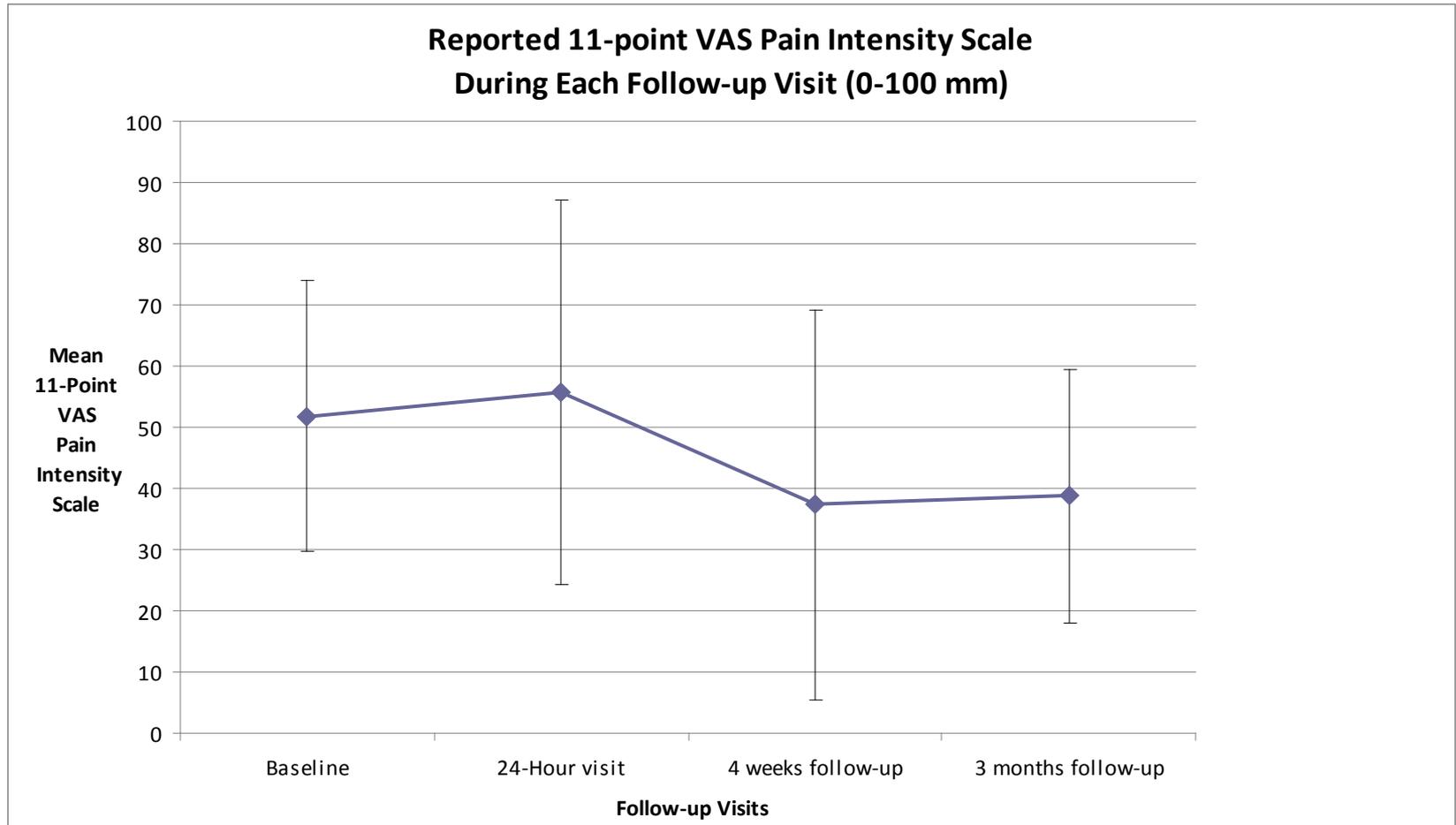
Percentage of Patients with Knee Effusion at Follow-up





Protocol #0912-1016 – VAS Subset at Sinai

Visual Analog Scale Pain Scoring at Follow-up



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Protocol #0912-1016 – Adjustments

Informed Consent Change

- Revised the risk statement in the ICF as follows:

TissueGene-C has been administered to 100 patients throughout several clinical trials. In previous clinical trials some subjects experienced minor side effects at the site of injection including itching, a warming sensation and/or swelling. Approximately 50% of patients in this trial that received TG-C have experienced side effects including pain and swelling of the knee joint. The effects seen were temporary and treatable. Your physician is aware of these effects and can provide treatment should you have these effects and they persist or you find them difficult to tolerate.

Protocol Revision

- The stopping criteria in the protocol have been clarified to define that Injection Site reaction is a localized cutaneous immune response and to add Grade 3 Arthritis (as defined by the NCI CTCAE) with corresponding increases in at least 2 immune parameters.



Protocol #0912-1016 – Adjustments

Guidance for Patients

- A handout will be provided to each patient which provides the following post-injection instructions:
 - Apply a gentle compressive dressing with a cotton roll and elastic bandage for the first 48 hours.
 - Ice the injected knee periodically for the first 24 hours to help prevent swelling.
 - You should avoid strenuous physical activities, especially sports-related activities such as running, biking, etc. You should restrict your physical activities to walking for around 2-3 weeks.
 - In the event you feel some pain, swelling, and/or discomfort please take over-the-counter Advil or Aleve for 3-5 days.
 - If pain, swelling, and/or discomfort occur and are not relieved by the Advil or Aleve, contact the appropriate study staff (see below) to arrange further evaluation and treatment.



Protocol #0912-1016 – Adjustments

Guidance for Investigators

- The Investigator's Brochure has been revised to include the adverse events seen in this study to date.
- The procedure describe in the protocol for guided injections has been reviewed with the investigators.
- A standardized regimen for addressing pain/inflammation has been provided to the investigators so that patients experiencing these types of AEs in the future receive uniform treatment:
 - Treat with Aleve or Advil for 3-5 days (recording the amount taken)
 - If this is not effective the patient should contact the investigator and they can then prescribe either Lodine or Meloxicam.
 - If after 5-7 days, Lodine or Meloxicam is not effective, then a Medrol dose pack can be given (12 to 14 days after injection).
 - Only prescribe narcotics or a corticosteroid injection as a last resort if other treatments are ineffective.



Concluding Remarks

1 Technology and Manufacturing

2 Nonclinical Review

3 Phase I Review

4 Phase II Protocol

5 Questions and Answers