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NeoCart Phase 3 Clinical Trial Results Call

September 5, 2018

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NeoCart is limited by Federal Law to investigational use only and not available for sale.

Agenda

1. Executive Summary
2. History – Regulatory Guidance and Clinical Trial Design, Comparators & Current Standards
3. Phase 3 Clinical Trial Design & Demographics
4. Overview of Dual Threshold Responder Analysis
5. Dual Threshold Data Review
6. Current FDA Guidelines for Clinical Trials
7. Current Guidelines Data Review
8. Conclusion & Next Steps

Summary of NeoCart Phase 3 Clinical Trial Results

1. NeoCart demonstrated clinically meaningful improvement at 1 year vs. microfracture on highest hurdle, dual-threshold endpoint. The trial narrowly missed statistical significance and did not meet the primary endpoint by 2 microfracture responders in the mITT population (one sided test: *p=0.025).
   - 62% of NeoCart patients were responders at 6 months vs 46% of microfracture (*p=0.0188).
   - 74% of NeoCart patients were responders at 1 year vs 62% of microfracture (p=0.0714).
   - Based on current MCID on IKDC for example, NeoCart demonstrated statistically significantly superiority.
2. NeoCart demonstrated statistically significant results compared to microfracture at 1 year on KOOS and IKDC endpoints, as established in FDA Guidance & used in ongoing clinical trials conducted by third parties. It also demonstrated superiority at 2 years based on only ~120 patients (visits pending for rest).
3. NeoCart performed better than expected, demonstrating early and sustained clinically meaningful improvements at 1 year and 2 years.
   - However, microfracture did better than expected in what we believe is the most robust study conducted to date under current FDA guidance in a population intended to maximize its performance (low BMI, most appropriate lesion size and strict rehabilitation program).
4. Risk / benefit believed to be established, safety between arms was comparable.
5. **Based on totality of data and published FDA guidelines, we believe NeoCart should be acceptable for review and potential approval. We intend to confirm this with the FDA via a Type A Meeting.**

History of Cartilage Repair Trials & Microfracture

Perspective – Regulatory History & Approved / Cleared Products:

- 1997 Carticel (Genzyme) approved – initially "361 Product" regulated, changed to BLA
- 1997 to 2011 – physicians, industry & FDA (CBER/CDRH) work to define endpoints, comparators, I/E criteria
- December 2011 guidance issued by FDA (superiority, pain/function endpoints, microfracture control)
- 2016 MACI (Vericel) approved – 2 year endpoints, 144 patient study done in EU

Microfracture History - Variable and Challenging Standard of Care:

- The procedure was developed in the early 1990s by Dr. Steadman of the Steadman-Hawkins Clinic/Vail
- Initial excitement, now less so due to variability of results & poor durability
- Microfracture results are highly dependent on lesion size, BMI, age, and rehabilitation protocol
- Surgeons have lobbied to eliminate microfracture as surgical control, but few other options available

NeoCart Phase 3 Background - Robust Dual Threshold Analysis Prior to Issuance of Current FDA Guidance:

- Phase 2 (2006 to 2008) informed Phase 3 design, SPA secured in 2009 due to lack of clarity on trials endpoints, other than microfracture control and superiority design using pain/function
- 2009 to 2010 – Initiated the largest prospectively enrolled trial to date, using highest hurdle endpoints

Other Third-Party Cartilage Therapies - Current Trial Designs:

- Since 2014, four products entered into knee cartilage trials in the U.S. (BLA & PMA's)
- KOOS Pain, Function and / or IKDC Scales used to show superiority (no dual threshold)
- One historical microfracture control arm allowed

NeoCart Phase 3 Clinical Trial Design & Demographics

Screening

Key Inclusion Criteria

- Age: 18-59
- Severe and symptomatic cartilage lesions (0.5-6cm^2)

Key Exclusion Criteria

- Prior lesion treatment
- High BMI
- Significant arthritis
- Concomitant surgeries

n = 249

Randomization

- Arm 1: NeoCart (n = 170)
- Arm 2: Microfracture (n = 79)

Endpoints at 1 Year

Primary

- Knee pain/function improvement:
  - ≥12 pts KOOS pain
  - ≥20 pts IKDC Subjective

Secondary

- Time to full weight-bearing
- Failure: Reop or deterioration
- Collagen layering via MRI

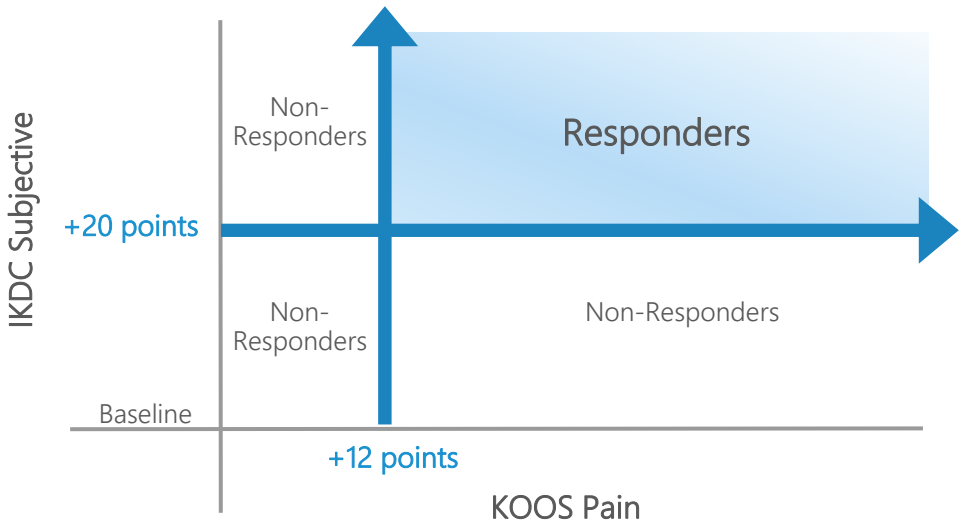
Key Demographics	NeoCart	Microfracture
Sex (Female/Male)	35% F / 65% M	39% F/ 61% M
Age	38.7	38.8
BMI	27.3	26.7
# of Lesions (1/2)	83%	89%
Lesion Size (Min/Max cm^2)	0.5 / 6	0.5 / 5.3
Lesion Size (Mean cm^2)	2.1	1.8
Mean KOOS Pain Score:	54.0	52.4
Mean IKDC Function Score:	40.3	40.0

Dual Threshold : Reasons for Its Use, Design & Impact

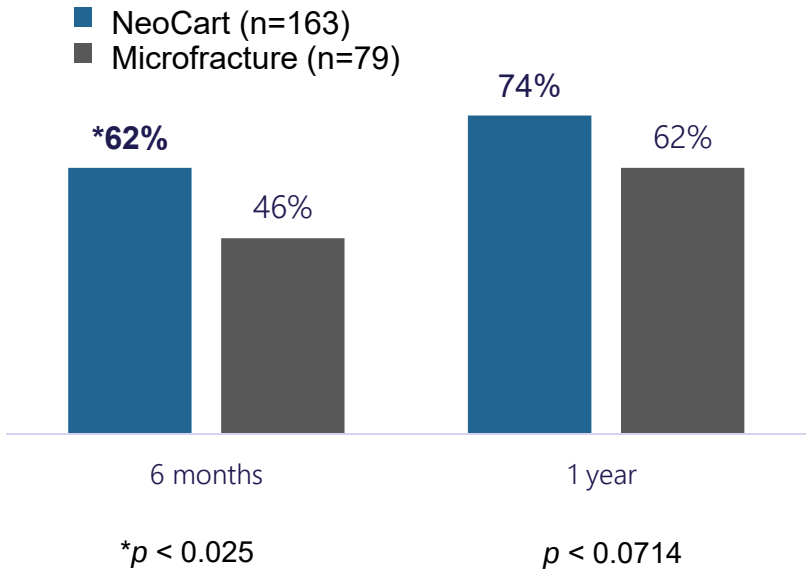
- Dual Threshold Responders typically used in Oncology or Cardiology to further demonstrate magnitudes of clinically relevant effects.
- When our trial was designed in 2009 (prior to FDA guidance released in 2011), it had been rarely used in Orthopedics, particularly with patient reported outcome endpoints.
- Initial thesis: true leveler design to modulate the tendency for patients to accommodate pain or loss of function. Goal is to show that each patient gets better on both scores vs. mean differences on individual scores.
- Minimum clinically important/meaningful differences or cut-off's have greater impact than in other designs – balance of specificity and sensitivity.

NeoCart Phase 3 Clinical Trial Preliminary Data (mITT Population)

Responder Analysis: Responses required on both Pain & Function (~15% delta needed)



Responder Analysis Results: 6 month data significant (early improvement) with 1 year data narrowly missing significance



- 1-year endpoint would have been statistically significant if two microfracture patients had not been responders
- Microfracture patients performed significantly better than expected, and better than in most previous published studies (62% response vs. 50% projected in statistical plan) and real world experience
- Clinicians in this trial requested current MCID analysis, which demonstrated superiority at 1 year

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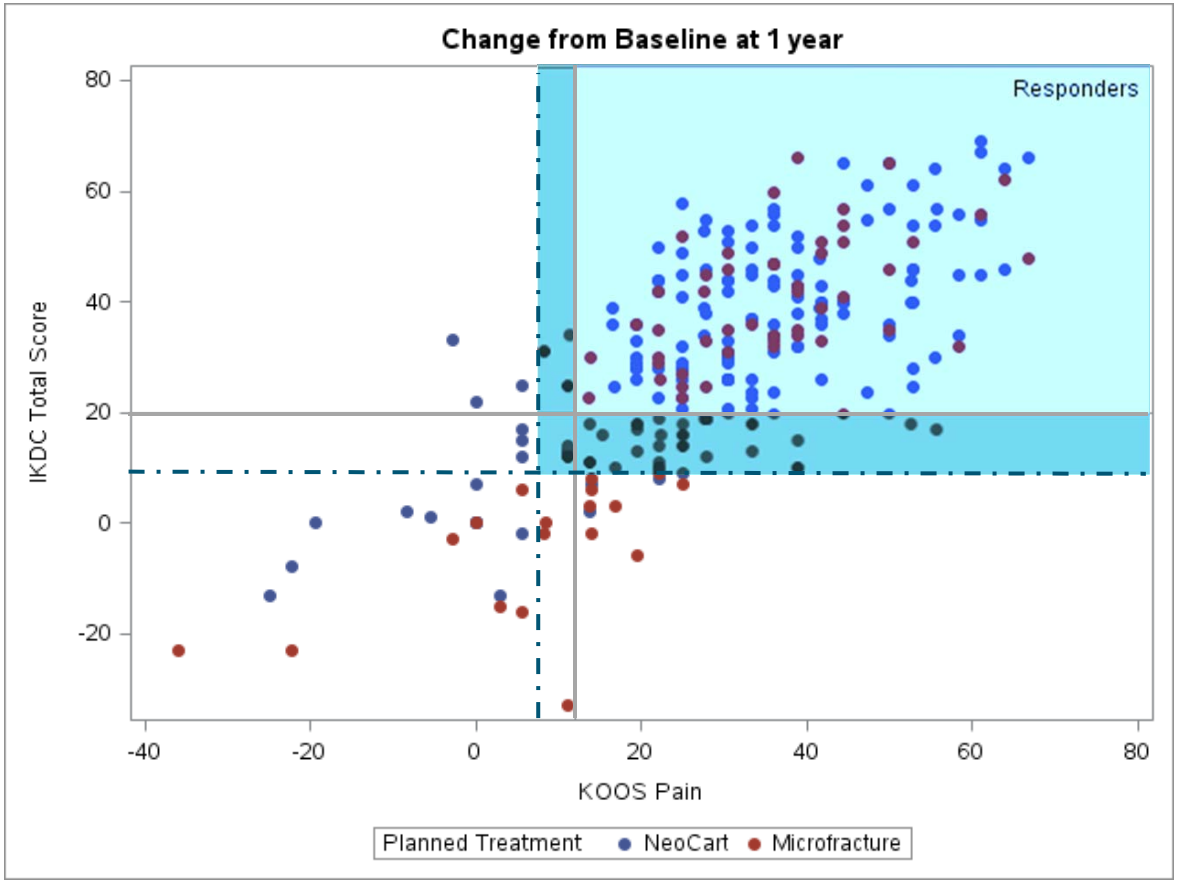
Phase 3 Clinical Trial Results Would Be Statistically Significant at 1 Year Using Current Clinical Guidelines for MCID

IKDC Subjective	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
KOOS Pain	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20

Minimum Clinically Important Difference

Responder Analysis Thresholds



Existing Responder Analysis p=0.0714

MCID Sensitivity Analysis
p=0.0082 to 0.0200

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1-Year Dual Threshold Endpoint: Patient Populations & Observations

Patient Populations (all analyses on mITT):

	NeoCart (N=170)		Microfracture (N=79)		Change	
	Positive Responders	Responder Rate	Positive Responders	Responder Rate	Difference	p value:
Intent to Treat (ITT)	121/170	71.2%	49/79	62.0%	9.2	p=0.1877
Modified ITT (mITT)	121/163	74.2%	49/79	62.0%	12.2	P=0.0714
As Treated (AT)	120/162	74.1%	50/80	62.5%	11.6	p=0.0735
Per Protocol (PP)	118/155	76.1%	43/65	66.2%	10.0	p=0.1362

Other Important Responder Observations:

- In BMI >28: NeoCart 78% response rate vs 48% for microfracture (*p= 0.0168)
- In > 2.2 cm lesions: NeoCart 76% response rate vs 52% for microfracture (*p= 0.0145)
- In two lesions: NeoCart 85% response rate vs 43% for microfracture (p=0.0418)

Failure Observations (% of patients at 1 year with scores below baseline)

- IKDC: 2.5% for NeoCart; 12.7% for microfracture
- KOOS: 3.7% for NeoCart; 3.7% for microfracture
- BOTH: 1.2% for NeoCart; 3.8% for microfracture

Current Study Designs: What Endpoints are FDA Requiring Today?

- If we were designing a knee cartilage trial today?
  - KOOS Pain and/or IKDC function scales vs baseline, superiority vs microfracture
  - Statistically significant mean improvements required on one or both scales (individually)
  - Dual threshold responder not required
  - 2 year endpoints employed, 3 year follow up (1 year being unique and difficult to achieve)
  - Same inclusion / exclusion criteria – more balanced evaluation of microfracture in a more limited population

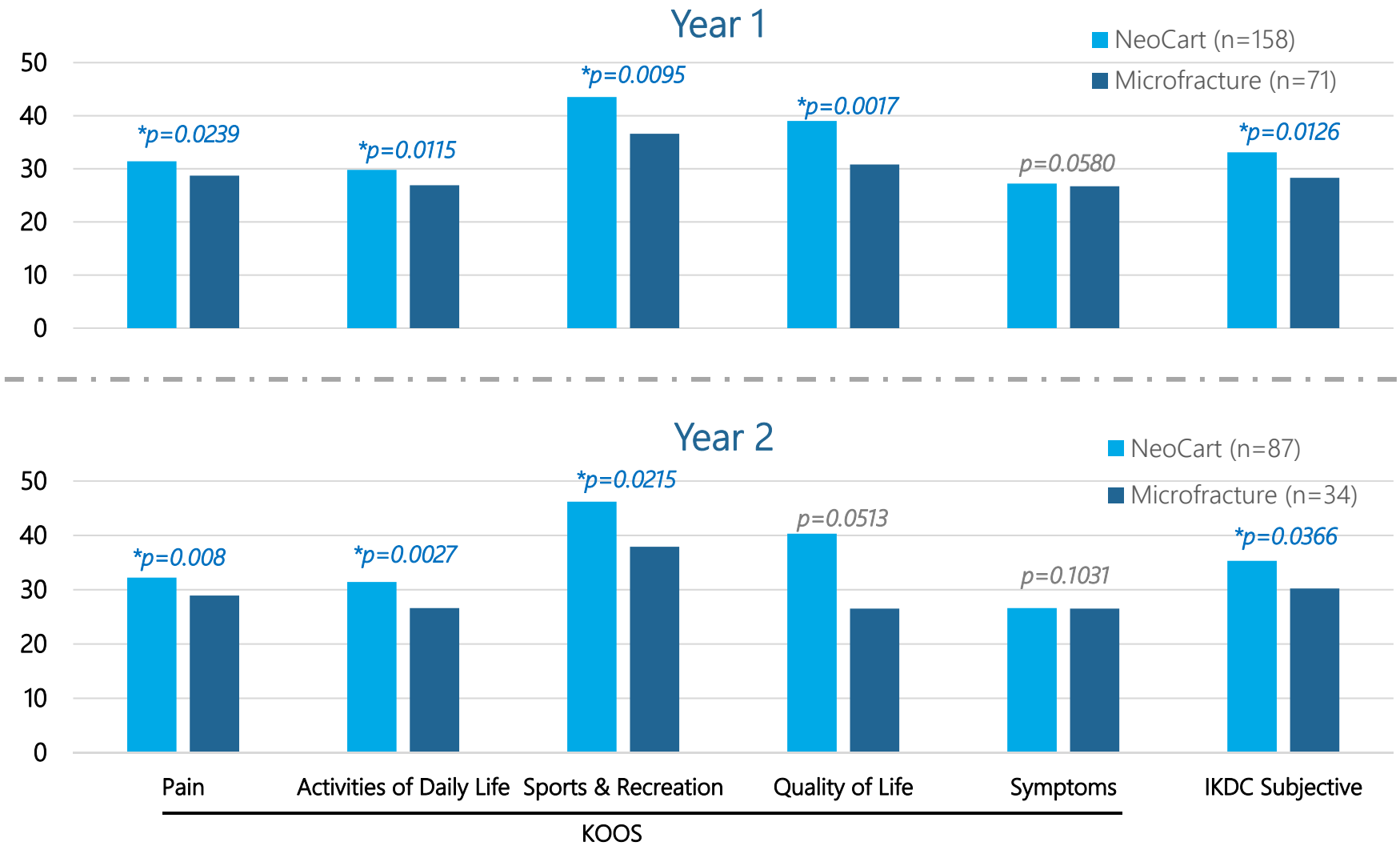
- Using current criteria, how would Phase 3 NeoCart trial have done?

- NeoCart would have demonstrated statistically significant results vs microfracture on relevant IKDC & KOOS scales/endpoints at 1 year & 2 years
  - KOOS Pain – 1 year & 2 years (p=.024 and .008)
  - IKDC Subjective (Pain/Function) – 1 year & 2 years (p=.013 and .037)
  - Note 2 year data only includes ~120 patients (remainder of visits outstanding)

Note: The discussion in this presentation of how NeoCart hypothetically would have performed against endpoints other than those included in its Phase 3 clinical trial are for illustrative purposes only and do not impact or change the outcome of the Phase 3 clinical trial and NeoCart's performance against its endpoints

Clinically Relevant and Statistically Significant Improvement on Most Subscales at 1 and 2 Years

Pain & Function Patient Reported Outcomes (KOOS & IKDC) – Change from Baseline



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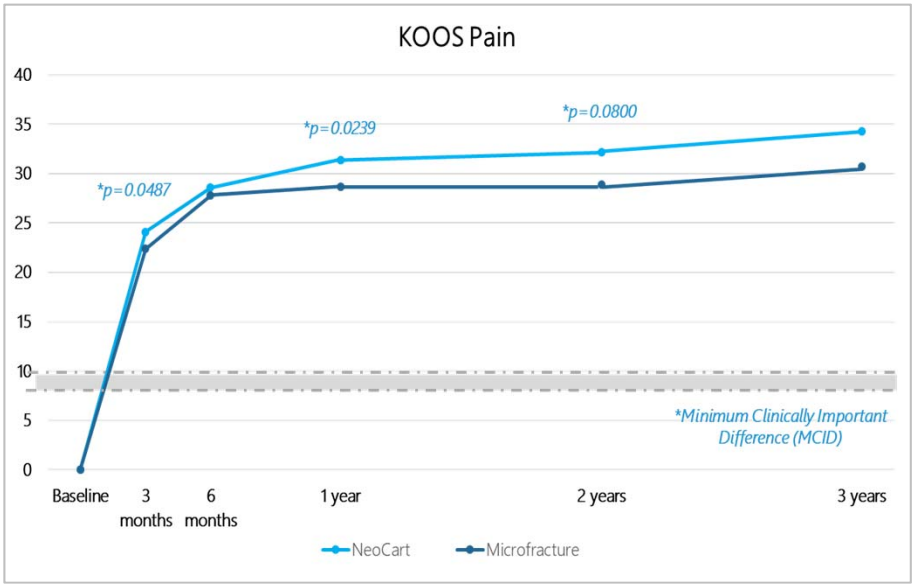
Current FDA Endpoints: KOOS Pain

KOOS pain score (mITT Population)
Change from Baseline
(NeoCart Baseline = 54.0; Microfracture Baseline = 52.4)

	NeoCart		Microfracture		
Visit	N	Mean Improvement	N	Mean Improvement	P-Value
3-months	160	24.1	75	22.4	0.0487
6-months	157	28.6	75	27.0	0.0819
1-year	158	31.4	72	28.7	0.0239
2-years	87	32.2	34	28.9	0.0080
3-years	39	34.3	16	30.7	0.1071



- KOOS Pain is one of several measures used to demonstrate superiority vs baseline, and control arm in ongoing clinical trials for cartilage knee repair

- NeoCart would have demonstrated clinically meaningful improvements in KOOS pain as early as 3 months and sustained through two years with statistical significance

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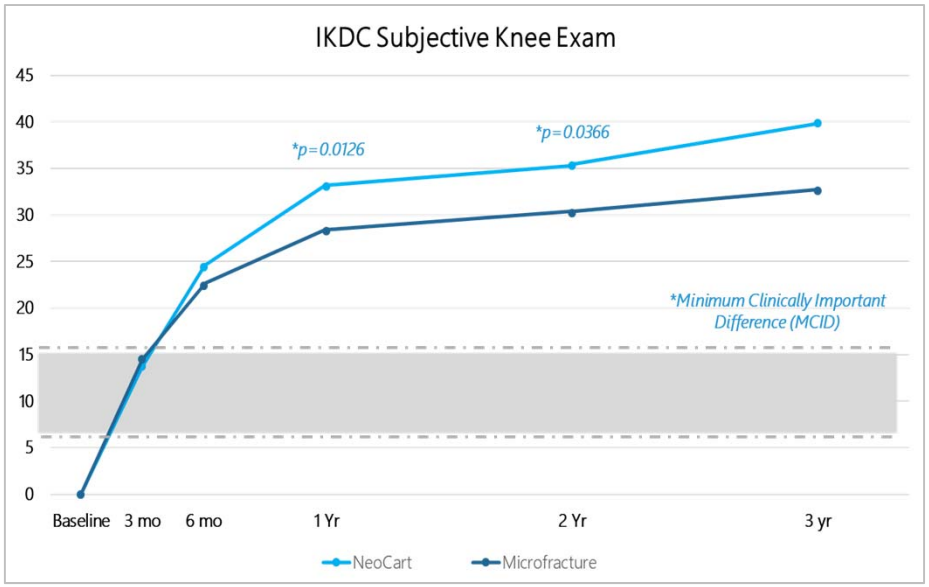
Current FDA Endpoints: IKDC Function/Pain

IKDC subjective knee exam score (mITT Population)

Change from Baseline

(NeoCart Baseline = 40.3; Microfracture Baseline = 40.0)

	NeoCart		Microfracture		
Visit	N	Mean Improvement	N	Mean Improvement	P-Value
3-months	159	13.7	76	14.5	0.9686
6-months	156	24.4	74	22.4	0.1572
1-year	158	33.1	71	28.3	0.0126
2-years	87	35.3	34	30.2	0.0366
3-years	38	39.9	16	32.6	0.2691



- IKDC Pain / Function is used to demonstrate superiority vs baseline, and control arm in ongoing clinical trials for cartilage knee repair
- NeoCart would have demonstrated clinically meaningful improvement in IKDC Subjective Pain / Function as early as 6 months and sustained through two years (statistically significant at one and two years)

Note: The discussion in this presentation of how NeoCart hypothetically would have performed against endpoints other than those included in its Phase 3 clinical trial are for illustrative purposes only and do not impact or change the outcome of the Phase 3 clinical trial and NeoCart's performance against its endpoints

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Key Conclusions & Next Steps

- Based on the totality of the data at 6 months, 1 year, and 2 years, we believe NeoCart has demonstrated superior clinically meaningful results.
- Risk / Benefits: Safety profile of NeoCart was comparable, with data that were superior to standard of care.
- Clinicians who have used NeoCart believe this product could be a market leading therapy, if approved.
- We are requesting meeting with FDA to discuss our BLA filing strategy, and if granted, would expect feedback in October 2018.
- Based on expert feedback, we believe the data supports FDA review & potential FDA approval, without considerable impact to timelines.
- Assuming BLA filed & accepted, targeting early 2020 NeoCart launch, if approved.

References & Supporting Information

Select Publications

1. D Crawford MD, PhD, RJ Williams III, MD, TM DeBerardino MD – *NeoCart, an Autologous Cartilage Tissue Implant, Compared to Microfracture for Treatment of Distal Femoral Cartilage Lesions. An FDA Phase 2 Prospective, Randomized Clinical Trial after two Years.* J Bone Joint Surg Am. 012;94:979-89.

2. D Crawford MD, PhD, DE Anderson, PhD, RJ. Williams III, MD, TM DeBerardino, MD, DC Taylor, MD, CB Ma, MD, and M Kane, MS - *Magnetic Resonance Imaging Characterization and Clinical Outcomes After NeoCart Surgical Therapy as a Primary Reparative Treatment for Knee Cartilage Injuries*, American Journal of Sports Medicine AJSM Vol. 45, No. 4, p 875-883

3. DC Crawford MD, PhD, CM Heveran, WD Cannon Jr, MD, LF Foo, MD, and HG P, MD – *An Autologous Cartilage Tissue Implant NeoCart for* Treatment *of Grade III Chondral Injury to the Distal Femur Prospective Clinical Safety Trial at 2 Years*

4. *Maturation of Human Tissue Engineered Constructs Improves GAG Content and Fibrous Matrix Stability* - JM Middendorf, S Shortkroff, C Dugopolski, S Kennedy, J Siemiatkoski, L Bartell, I Cohen, LJ Bonassar.

5. *Mechanical Characterization of Autologous Chondrocyte Seeded Matrix Grafts After In Vitro Growth* – JM Middendorf, D Griffin, S Kennedy, S Shortkroff, C Dugopolski, J Siemiatkoski, L Bartell, I Cohen, LJ Bonassar

Current U.S. Clinical Trials (www.clinicaltrials.gov)

NOVOCART® 3D for Treatment of Articular Cartilage of the Knee (N3D) https://clinicaltrials.gov/ct2/show/NCT01957722
HyaloFAST Trial for Repair of Articular Cartilage in the Knee (FastTRACK) https://clinicaltrials.gov/ct2/show/NCT02659215
Pivotal Study to Evaluate the Safety & Efficacy of GelrinC for Treatment of Cartilage Defects (SAGE) https://clinicaltrials.gov/ct2/show/NCT03262909
Agili-C™ Implant Performance Evaluation https://clinicaltrials.gov/ct2/show/NCT02423629

Definitions: *Knee injury and osteoarthritis outcome score (KOOS): International Knee Documentation Committee (IKDC), Minimum Clinically Important Difference (MCID); Body Mass Index (BMI); Premarket Approval (PMA); Biologics License Application (BLA); U.S. Food & Drug Administration (FDA)*

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