



Synvisc-One



**FDA – Genzyme  
Panel Advisory  
Committee Meeting  
(P940015 – S012)**

December 9th, 2008  
Gaithersburg, MD



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# Agenda

## Introduction

**Michael Halpin, M. Engr., RAC**

Vice President, Regulatory Affairs  
Genzyme Corporation

## Overview of OA Treatment and Clinical Research Methodology

**Richard Polisson, M.D., MHSC**

Senior Vice President, Clinical Research  
Genzyme Corporation

## Clinical Study Results

**Lena Holmdahl, M.D., Ph.D.**

Vice President, Clinical Research  
Genzyme Corporation

## Statistical Considerations

**Clare Elkins, MSc**

Director, Biostatistics  
Genzyme Corporation

## Clinical Meaning in an OA Pain Setting

**Robert Dworkin, Ph.D.**

Professor of Anesthesiology, Neurology, Oncology, and Psychiatry,  
University of Rochester School of Medicine and Dentistry

## Expert Opinion on Synvisc-One

**Lee Simon, M.D.**

Associate Clinical Professor of Medicine, Harvard Medical School,  
Boston, Massachusetts; Associate Clinical Professor of Medicine,  
Beth Israel Deaconess Medical Center, Boston, Massachusetts

## Concluding Remarks

**Michael Halpin**

Vice President, Regulatory Affairs  
Genzyme Corporation

# External Experts Available to Committee

**Robert Dworkin, Ph.D.**

Professor of Anesthesiology, Neurology, Oncology, and Psychiatry  
University of Rochester School of Medicine and Dentistry

**Lee Simon, M.D.**

Associate Clinical Professor of Medicine  
Harvard Medical School, Boston, Massachusetts;  
Beth Israel Deaconess Medical Center, Boston, Massachusetts

**Ralph D'Agostino, Sr., Ph.D.**

Professor of Mathematics, Statistics, and Public Health  
Boston University, Boston, MA

**Pr. Xavier Chevalier, M.D., Ph.D.**

Head of Rheumatology Department  
Henri Mondor Hospital / University Paris XII, Créteil – France

# Introduction

- Viscosupplementation
- Synvisc
- Proposed Modification: Synvisc-One
- FDA advice used in Synvisc-One pivotal trial design

# Viscosupplementation

- Local treatment injected into the intra-articular joint space of the knee
- Hyaluronic Acid (HA) based products
- Provide pain relief for knee OA
- Indicated for use:
  - Patients who fail to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen)
- Require 3 to 5 weekly injections
- 2 - 2.5 mL per syringe

# Five Products Available in U.S.

Brand	Joint	Year Approved	# Injections	Duration
Hyalgan	Knee	1997	5	26 Weeks
<i>Synvisc</i>	<i>Knee</i>	<i>1997</i>	<i>3</i>	<i>26 Weeks</i>
Supartz	Knee	2001	5	26 Weeks
Orthovisc	Knee	2004	4	22 Weeks
Euflexxa	Knee	2004	3	12 Weeks

# Synvisc Commercial History

- Commercially available for 16 years
- Approved by FDA in 1997
- Currently available in over 70 countries
  - Over 4.6 million patients treated
  - Over 13 million injections performed
- Very low reported rate of serious related AEs

# Synvisc-One Description

- Allows a single injection form of Synvisc
- Change to packaging and Instructions only
- Indication for use is the same for both products

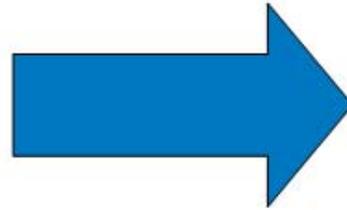
## Synvisc

- Hylan G-F 20
- 2 mL per Syringe
- 3 x (1 Injection/ week)
- 6 mL Total Volume

## Synvisc-One

- Same
- 6 mL per Syringe
- Single Injection
- Same

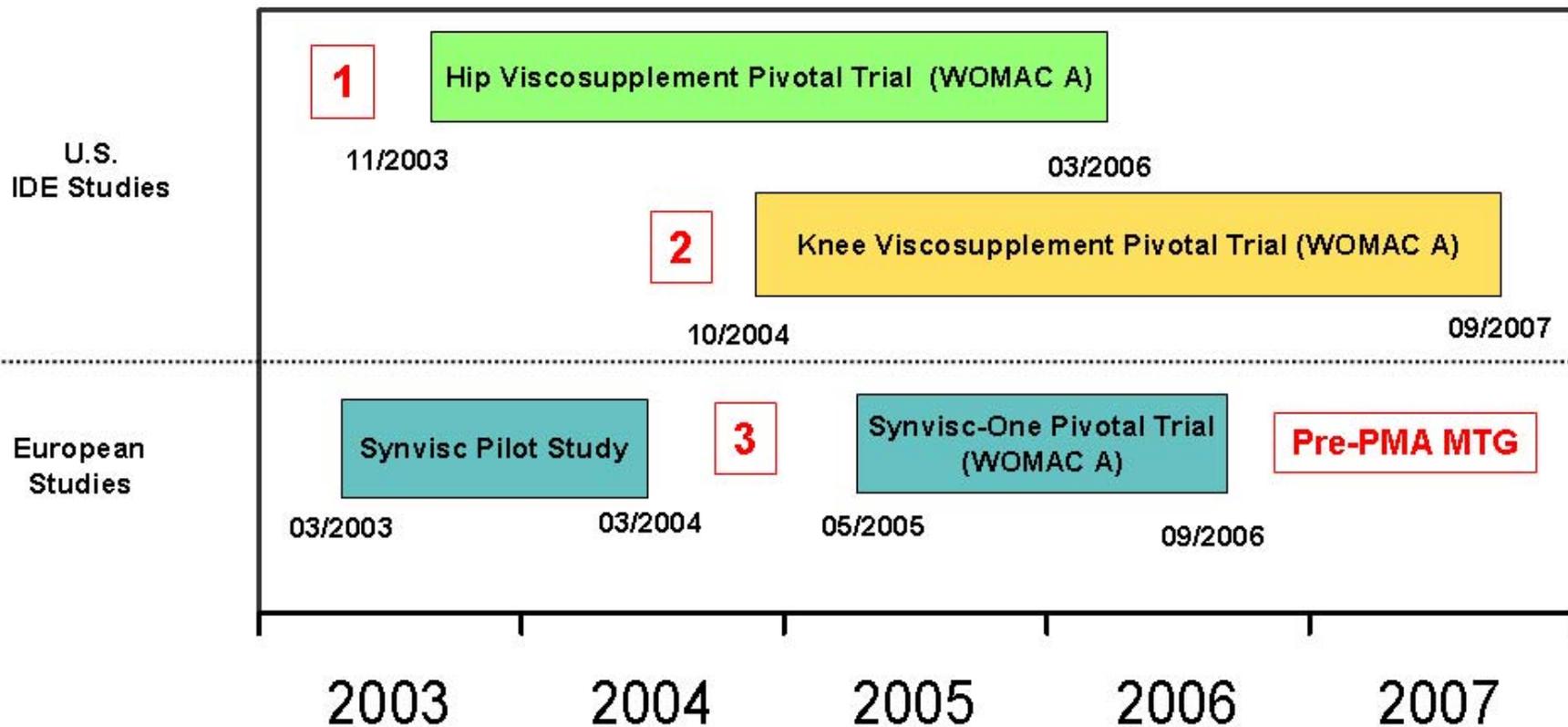
# Proposed Alternative Treatment Regimen



# Proposed Indication for Synvisc-One

- Synvisc-One is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics, e.g., acetaminophen

# Interactions with FDA



# Trial Guidance Incorporated from FDA

- U.S. Based IDE Trial Input 1 2
  - WOMAC A as primary endpoint
  - Repeated measures rather than a Landmark Analysis
- FDA Meeting - Synvisc-One Pilot Study Review 3
  - Additional clinical trial required
  - Double blind design
  - Saline control comparator (not Synvisc)

# Synvisc-One Experience Outside U.S.

- Synvisc-One Approvals
  - EU approval in December 2007
  - Additional Approvals in 2008
    - Argentina, Israel, Malaysia, Philippines, Singapore, Mexico
- ~ 10,000 patients treated to date
- No serious related adverse events reported



Synvisc-One



# Overview of OA Treatment and Clinical Research Methodology

**Richard P. Polisson, M.D., MHSc.**  
Senior Vice President,  
Clinical Research



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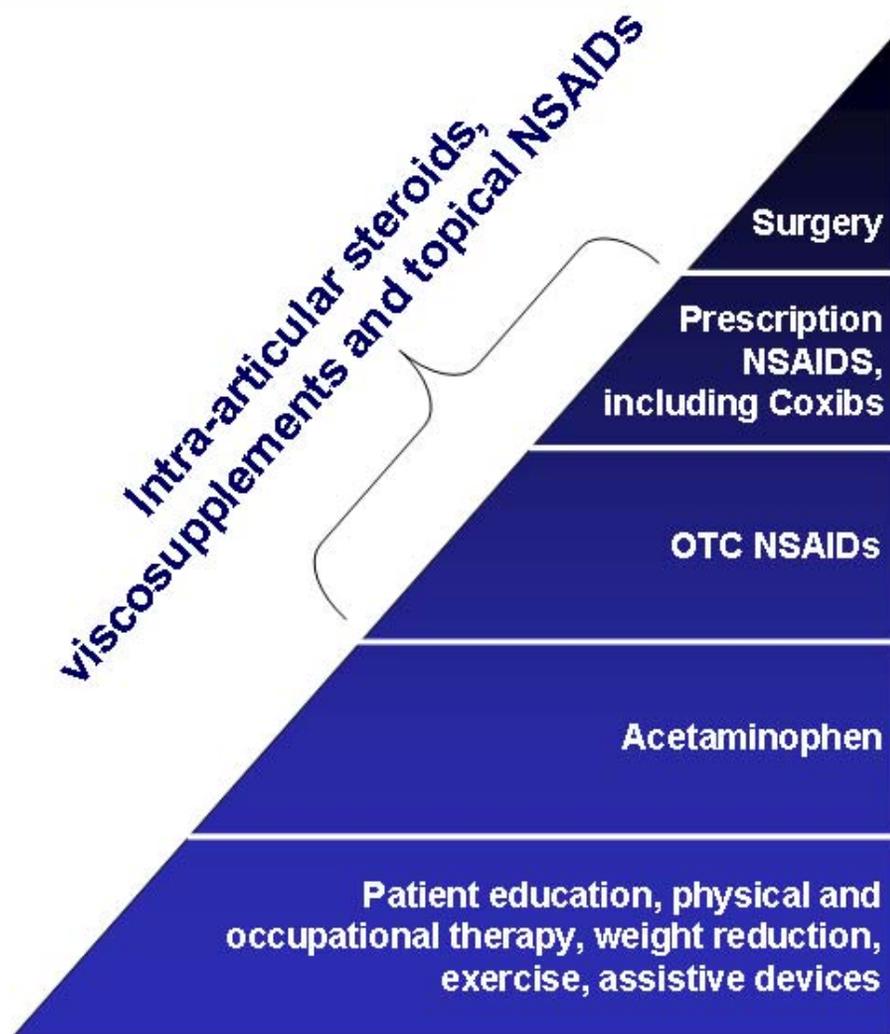
# Outline

- Overview of Osteoarthritis (OA) and Current Therapies
- Use of Viscosupplements in OA
- OA Clinical Trial Methodology and Endpoints

# Osteoarthritis is a Common Disorder Manifested by Pain on Ambulation

- OA is the most common joint disorder in the U.S.
- An estimated 27 million Americans have symptomatic OA in any joint (an increase of 6 million from 1995 – 2005)
  - Knee OA is most prevalent: 16.7% of adults  $\geq 45$  years
- OA is a local disorder without systemic features
- OA is expressed by pain on ambulation

# The Current Treatment Algorithm for OA



## Shortcomings

- Major, costly, invasive procedure
- Primarily indicated for “end-stage” OA patients
- Many symptomatic OA patients are not candidates for TJR
  
- GI bleeding or other complications
- CV risks
- Renal complications
  
- GI bleeding or other complications
- CV risks
- Renal complications
  
- Hepatotoxicity
- CV risks
  
- Poor patient compliance

# Viscosupplementation is an Effective and Accepted Therapy for OA Pain

- Comparable pain relief to oral therapies and superior to placebo
- Local therapy
  - Avoids toxicity and associated costs of systemic therapy
  - Critical option if contraindications to NSAIDs or joint replacement
- Recommended by National Professional Societies
  - American College of Rheumatology, 2000
  - American Pain Society, 2002
  - American Academy of Orthopaedic Surgeons, 2004
  - European League Against Rheumatism, 2007
  - Osteoarthritis Research Society International, 2008

# Clinical Trials in OA Therapy are Complex and Nuanced

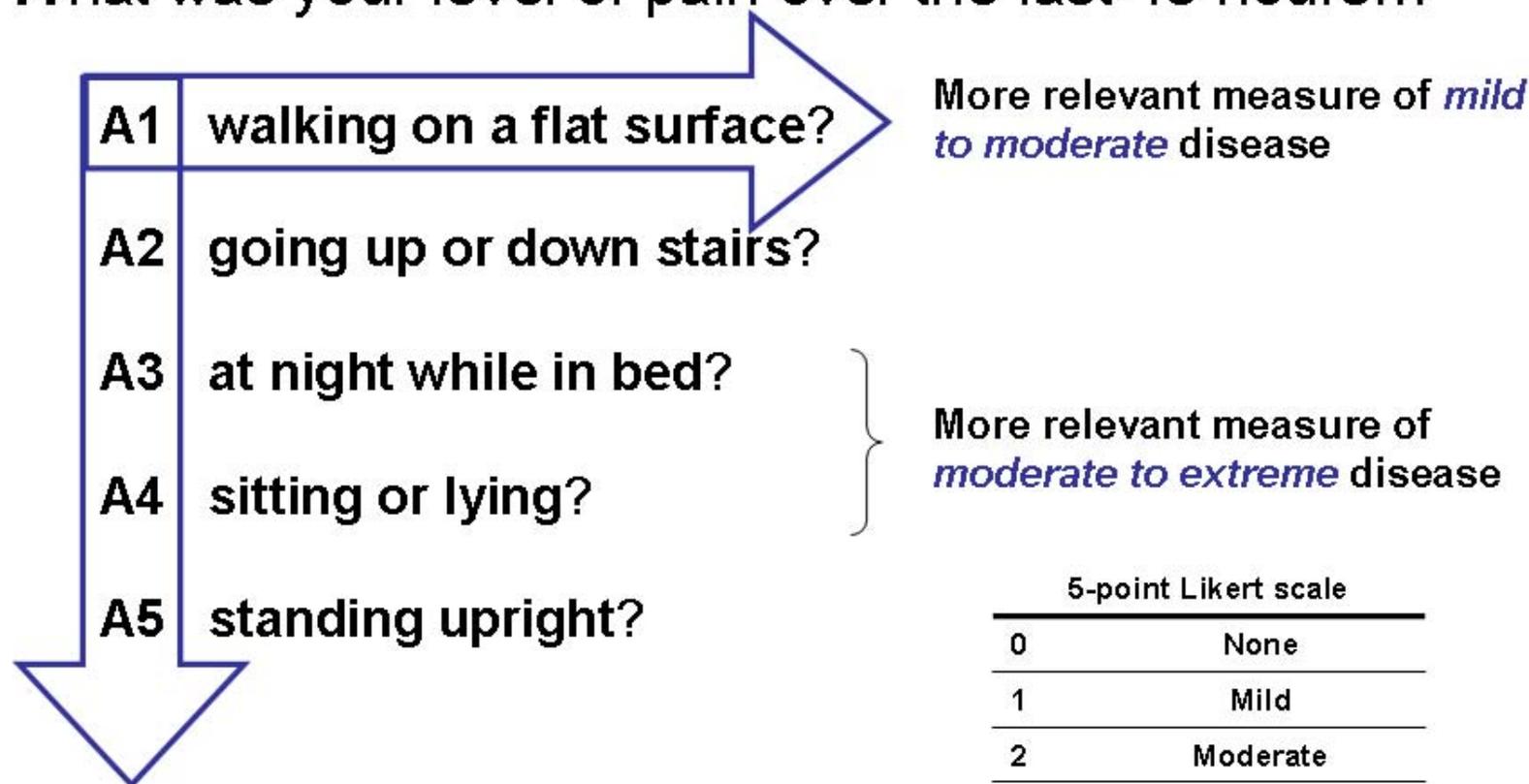
- OA Clinical Features and Population
  - Heterogeneity of OA expression and symptom cycles
  - Co-morbid diseases and concomitant medications
- Trial Design, Analysis, and Interpretation
  - Large response in placebo and control groups
  - Other control group issues
  - Impact of “rescue” medication
  - Effect of local therapy expected ONLY on the target joint
  - Subjective endpoints

# Outcome Measures in OA Trials are Subjective

- Disease Specific Assessment
  - WOMAC Osteoarthritis Index: Validated/widely used
    - “A” Pain: 5 questions
    - “B” Stiffness: 2 questions
    - “C” Function: 17 questions
- Overall Global Assessment
  - Patient (reported) global self-assessment (PTGA)
  - Blinded evaluator global assessment (COGA)
- Responder Analysis
  - A1 Responder
  - OMERACT-OARSI Responder

# WOMAC A and A1 are Commonly Used in OA trials

What was your level of pain over the last 48 hours...



WOMAC A: Endpoint requested by FDA for other IDE clinical trials

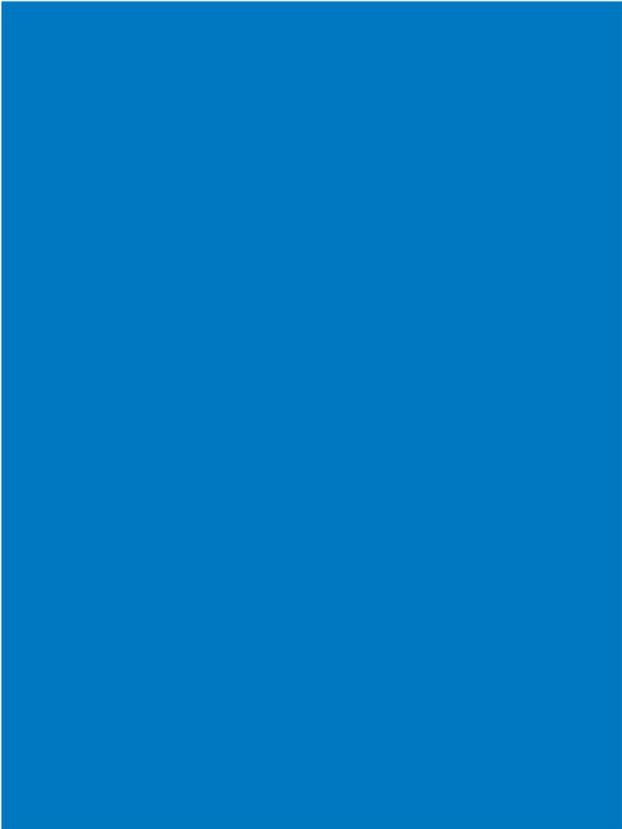
5-point Likert scale	
0	None
1	Mild
2	Moderate
3	Severe
4	Extreme

# Summary

- OA is challenging to treat and study
  - The NSAID-coxib problem complicates OA management
- OA clinical trials utilize Patient Reported Outcomes
  - Improvement in Patient Reported Outcomes (WOMAC A, A1, PTGA) reflect clinical benefit
- Viscosupplements are an effective and safe local treatment for OA
  - Recommended by multiple professional societies



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## Clinical Study Results

**Lena Holmdahl, M.D., Ph.D.**  
Vice President, Clinical Research



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# Overview

- What motivated us: Pilot study
- How we did it: Pivotal study design
- What we found: Efficacy and safety results
- Concluding remarks



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**How We Did It:  
Prior Research and Pivotal  
Study Design**



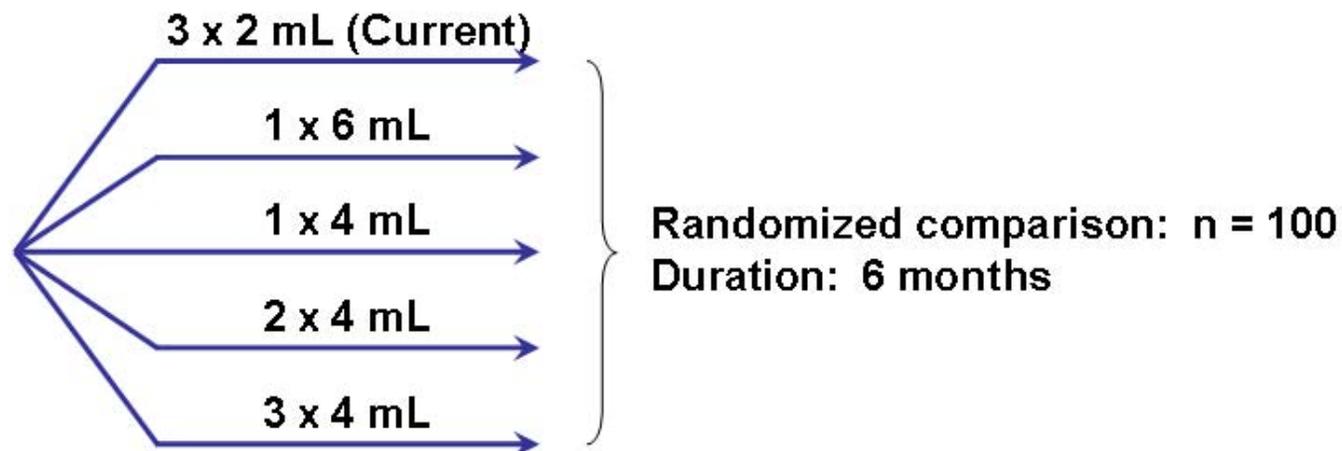
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# Pilot Study: Objective and Design

- Objective: To investigate if it was possible to simplify and/or improve treatment with Synvisc
  - Number of injections
  - Injected volume
- Design



# Pilot Trial: Key Findings

- All treatments were safe
- All treatments were efficacious
- Ranked the performance relative to
  - Efficacy endpoints (WOMAC A1, PTGA, COGA)
  - Safety
- 1 x 6 mL had the best ranking

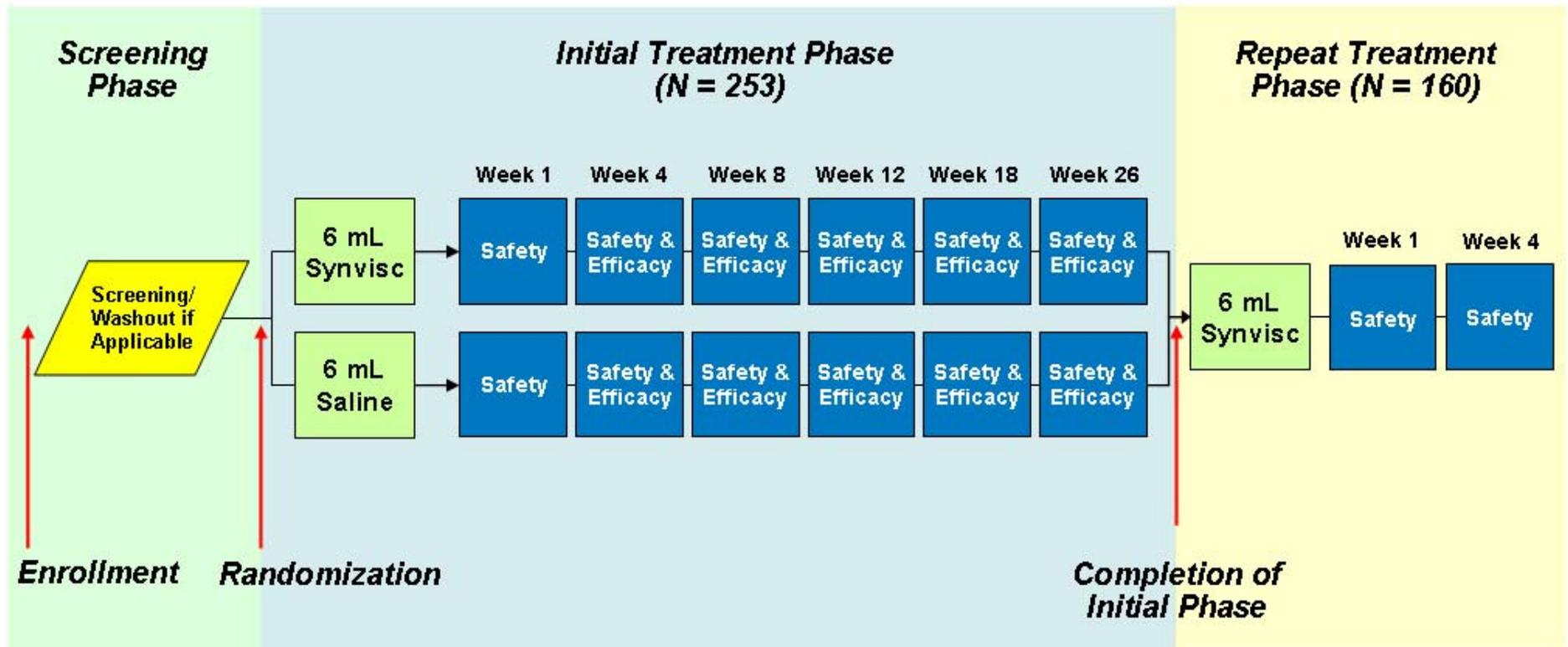
# Pivotal Study Design Considerations

- Patient reported outcomes require blinding of patients and caregivers
- Blinding options
  - Comparison to current 3 x 2 mL
  - 1 x 6 mL Synvisc vs. 1 x 6 mL saline
- Design: Multicenter, randomized, double blinded controlled trial
- Adherence with regulatory criteria for valid scientific evidence

# Patient Population

- Target: Patients with mild to moderate OA likely to benefit from viscosupplementation
- Key inclusion criteria
  - Fulfilled consensus criteria for diagnosis of OA
  - Joint pain
    - Pain on walking: Score of 2-3 on WOMAC A1
    - Score of 1.5 – 3.5 on WOMAC A pain scale
- Key exclusion criteria
  - End-stage disease
  - Non-responsive symptomatic OA in the lower limbs

# Pivotal Study Events Flowchart



# Pre-specified Efficacy Endpoints

## Primary Efficacy Endpoint

- WOMAC A score over 26 weeks

## Secondary Efficacy Endpoints

- WOMAC A1 (walking pain)
- PTGA (patient global assessment)
- COGA (clinical observer global assessment)
- WOMAC A score at week 26
- WOMAC C (function)
- OMERACT-OARSI (responder analysis)

## Tertiary Efficacy Endpoints

- Total WOMAC (A, B, C)
- WOMAC B (stiffness)
- Average daily use of rescue medication

# Statistical Methods: Primary Endpoint

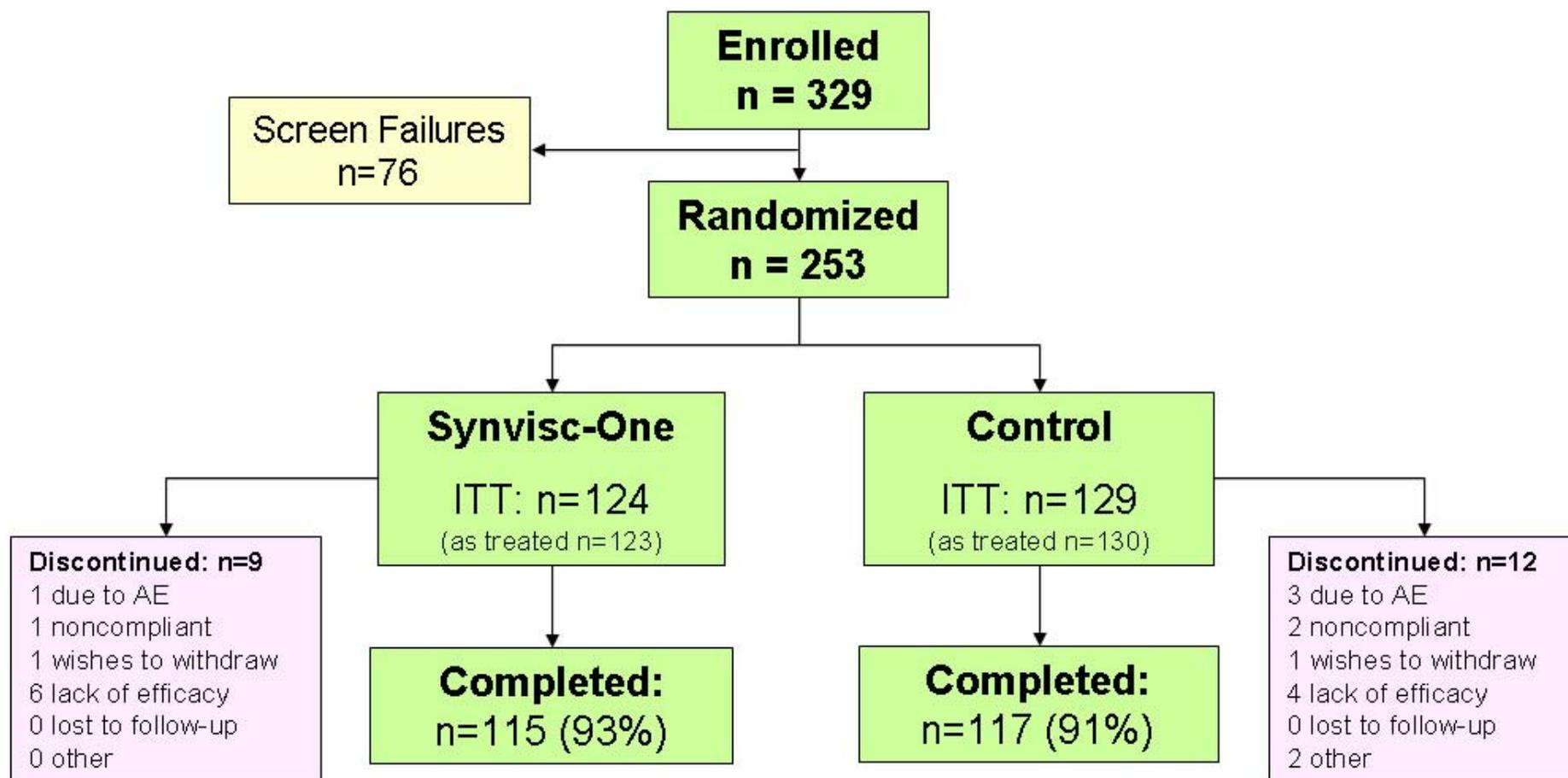
- Primary Endpoint
  - Repeated Measures Analysis of Covariance (ANCOVA)
  - Included terms: Treatment, site, visit, visit-by-treatment interaction, and the Baseline WOMAC Subscale A score as a covariate
- Pre-specified in Protocol
- Pre-specified in Statistical Analysis Plan

# Statistical Methods: Secondary Endpoints

- Ordinal endpoints were WOMAC A1, PTGA, COGA
  - Analyzed using generalized estimating equations (GEE) for a proportional odds logistic regression model
- Continuous endpoints WOMAC A at 26 weeks and WOMAC C
  - Analyzed using the repeated measures ANCOVA
- Binary endpoints collected over time (responder analyses) including OMERACT-OARSI and WOMAC A1
  - Analyzed using generalized estimating equations (GEE) for binary response logistic regression model

***Three methods of analysis because there were  
three different types of data collected***

# Patient Disposition: A High Degree of Completed Subjects

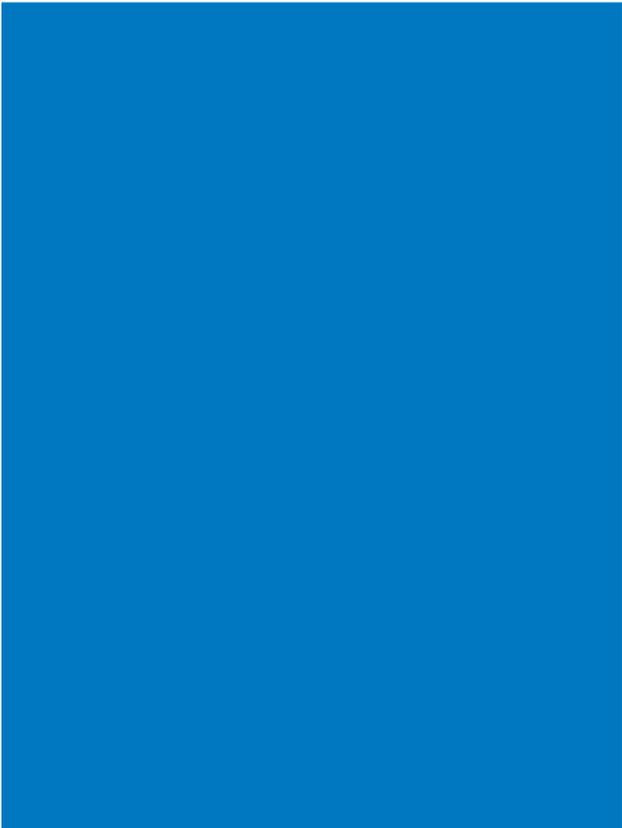


# Study Population was Representative and Randomization Balanced

	Synvisc-One (N=124)	Control (N=129)
WOMAC A, Mean (SD)	2.30 (0.43)	2.25 (0.41)
Age, Mean (SD)	63.6 (9.64)	62.5 (9.17)
BMI, Mean (SD)	29.08 (4.814)	29.77 (5.742)
Sex, (M/F)	32/92	41/88
Race, n (%)		
Caucasian	118 (95.2)	125 (96.9)
Non-Caucasian	6 (5)	4 (3)
Other symptomatic OA, n (%)		
In the contralateral knee	68 (55.3)	76 (58.5)
In either hip	12 (9.8)	18 (13.8)



Synvisc-One



# What We Found: Efficacy Results



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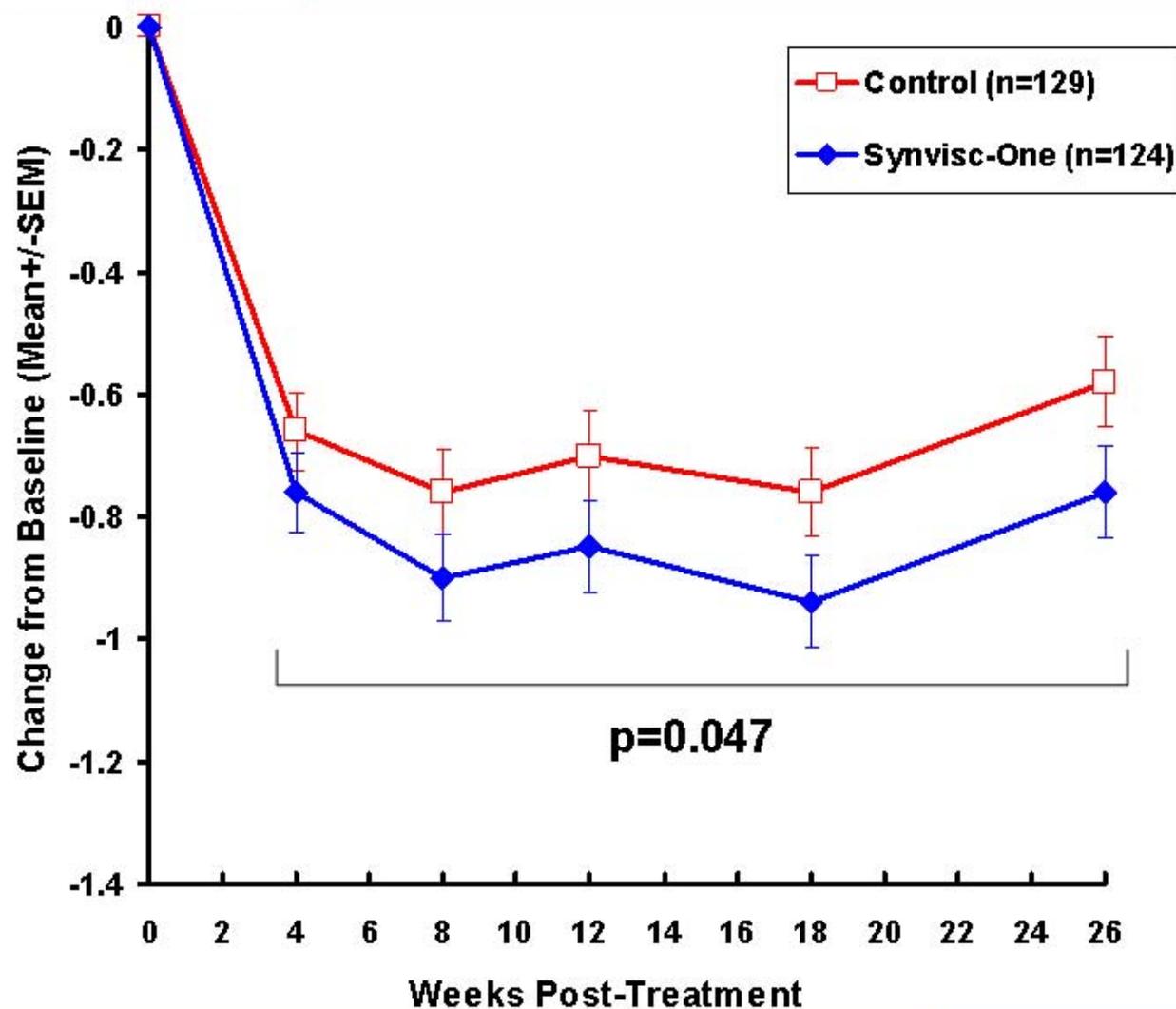
# Primary Efficacy Endpoint was Met

- WOMAC A Pain Score Over 26 weeks

Intent-to-Treat Population					
	Baseline Mean (SE)	Overall Mean (SE)	Change	Difference from Control (95% CI)	p-value
Synvisc (n=124)	2.30 (0.04)	1.43 (0.06)	-0.84 (0.06)	-0.15 (-0.302, -0.002)	0.047
Control (n=129)	2.25 (0.04)	1.59 (0.06)	-0.69 (0.06)		

**Effect Size of Synvisc-One = 0.23**  
(Effect Size = Treatment Difference / Standard Deviation)

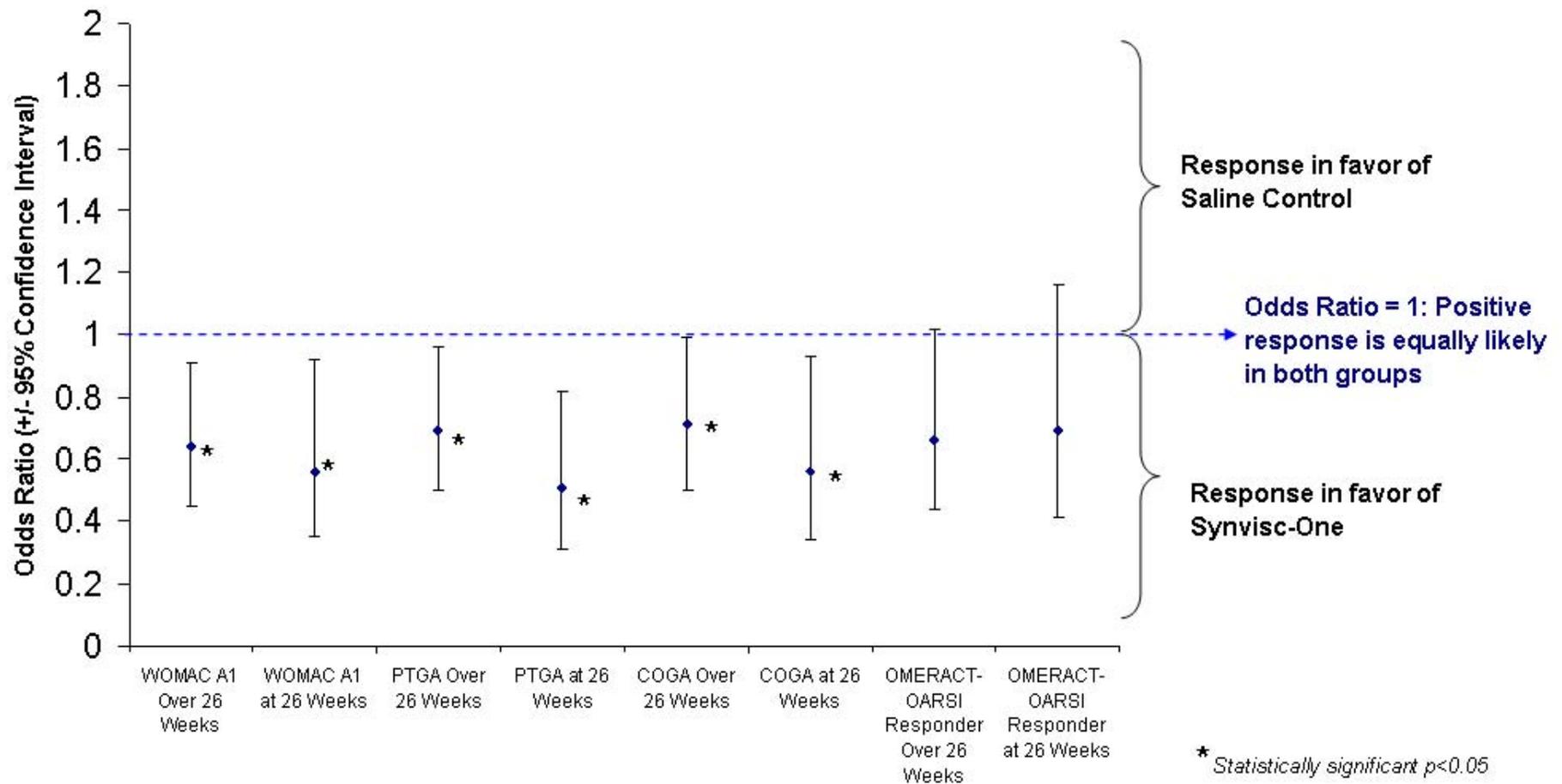
# Primary Efficacy Endpoint WOMAC A Pain Score



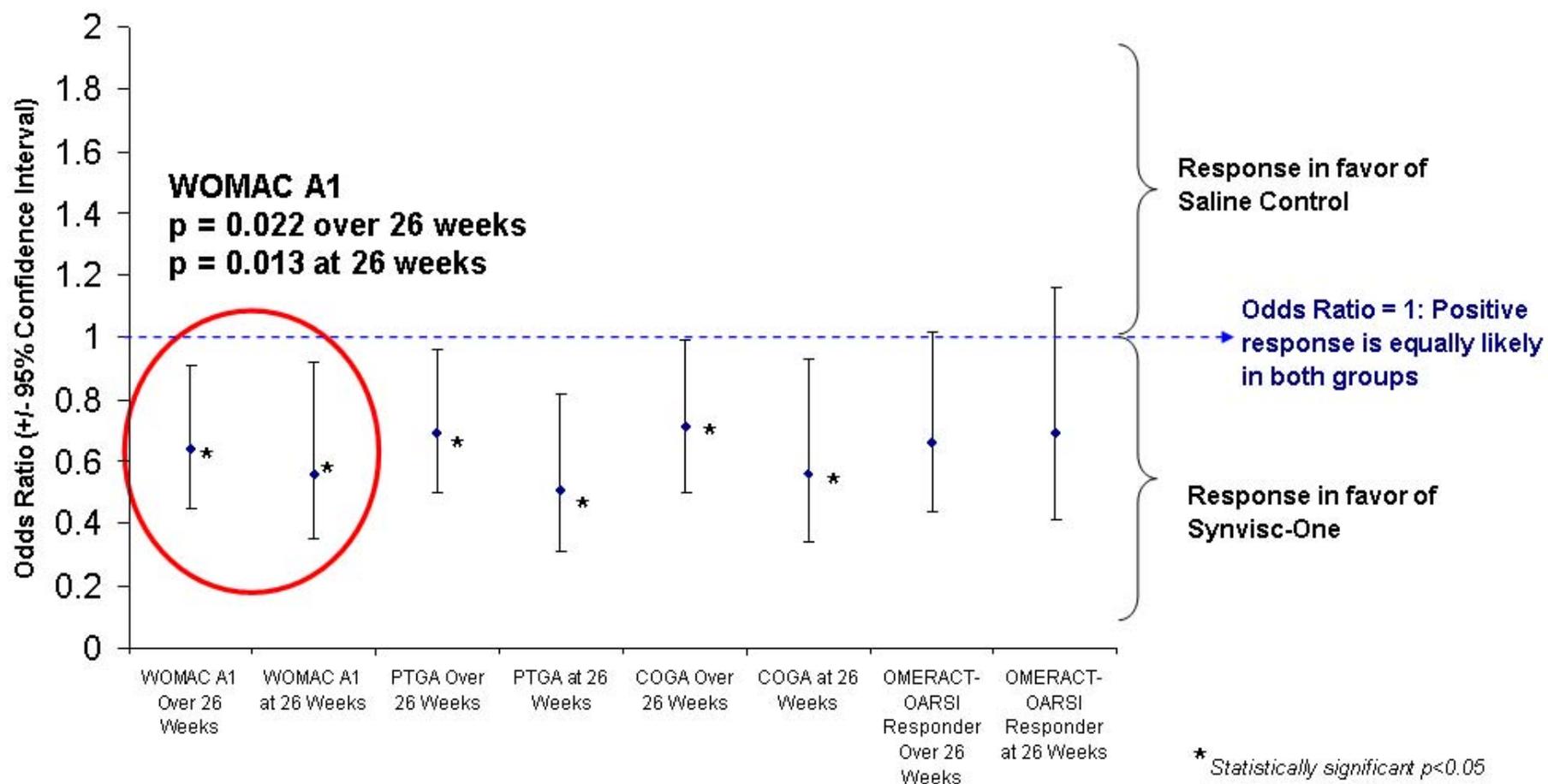
# Overview of Key Results – ITT Population

Primary Endpoint	Estimate of Treatment Difference (95% CI)		Effect Size	p-value
<b>WOMAC A</b>	Over 26 weeks	-0.15 (-0.302, -0.002)	0.23	0.047
<b>Secondary Endpoints</b>	<b>Odds Ratio (95% CI)</b>			
<b>WOMAC A1</b>	Over 26 weeks	0.64 (0.45, 0.91)	0.36	0.013
	At week 26	0.56 (0.35, 0.92)	0.44	0.022
<b>PTGA</b>	Over 26 weeks	0.69 (0.50, 0.96)	0.31	0.029
	At week 26	0.51 (0.31, 0.82)	0.49	0.005
<b>COGA</b>	Over 26 weeks	0.71 (0.50, 0.99)	0.29	0.041
	At week 26	0.56 (0.34, 0.93)	0.44	0.025
<b>OMERACT-OARSI</b>	Over 26 weeks	0.66 (0.44, 1.02)	0.34	0.059
	At week 26	0.69 (0.41, 1.16)	0.31	0.156
<b>WOMAC A</b>	<b>Estimate of Treatment Difference (95% CI)</b>			
	At week 26	-0.18 (-0.372, 0.011)	0.22	0.064
<b>WOMAC C</b>	Over 26 weeks	-0.03 (-0.18, 0.12)	0.04	0.679
	At week 26	-0.11 (-0.31, 0.09)	0.13	0.266

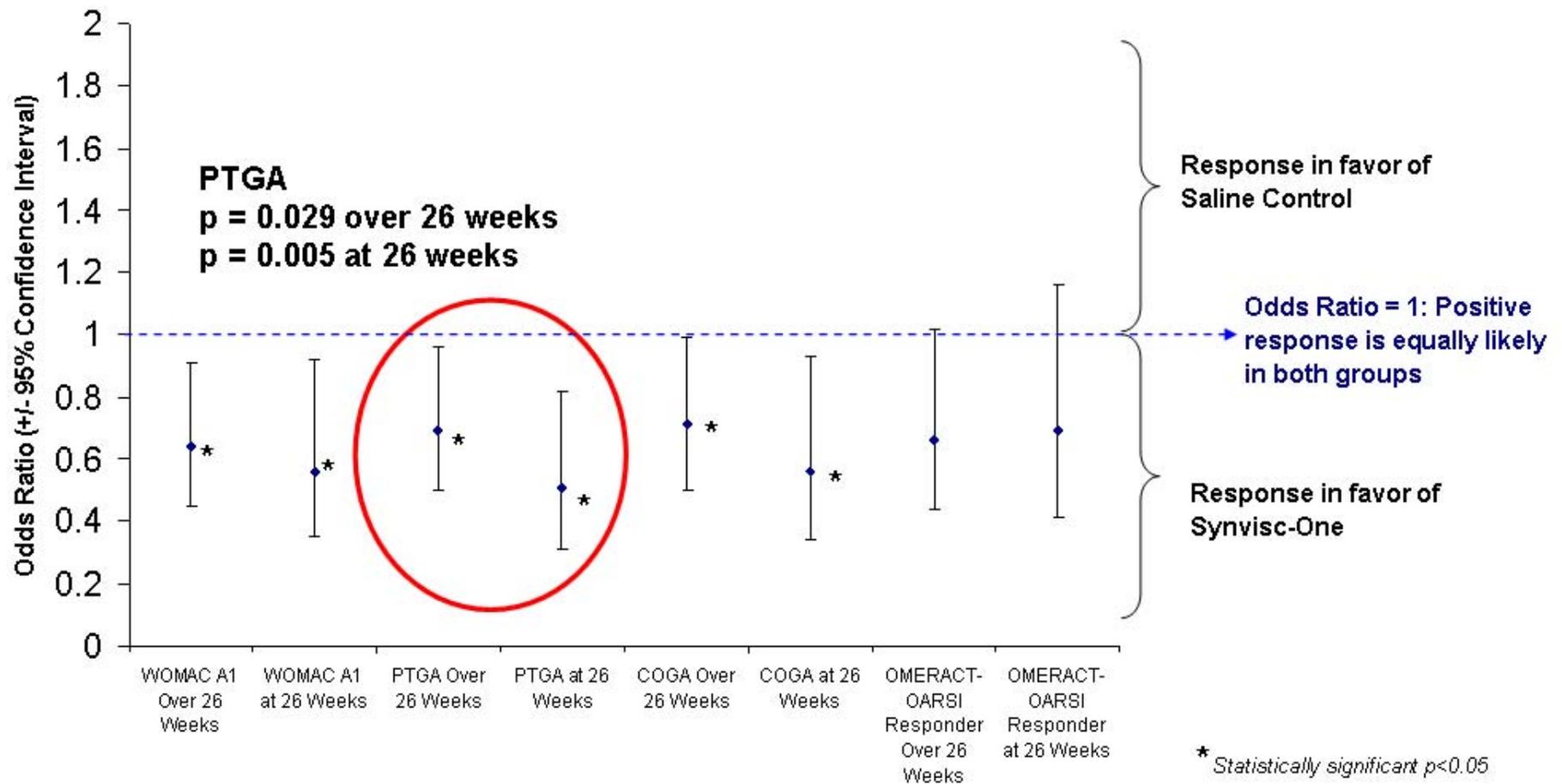
# Secondary Endpoints: Overview



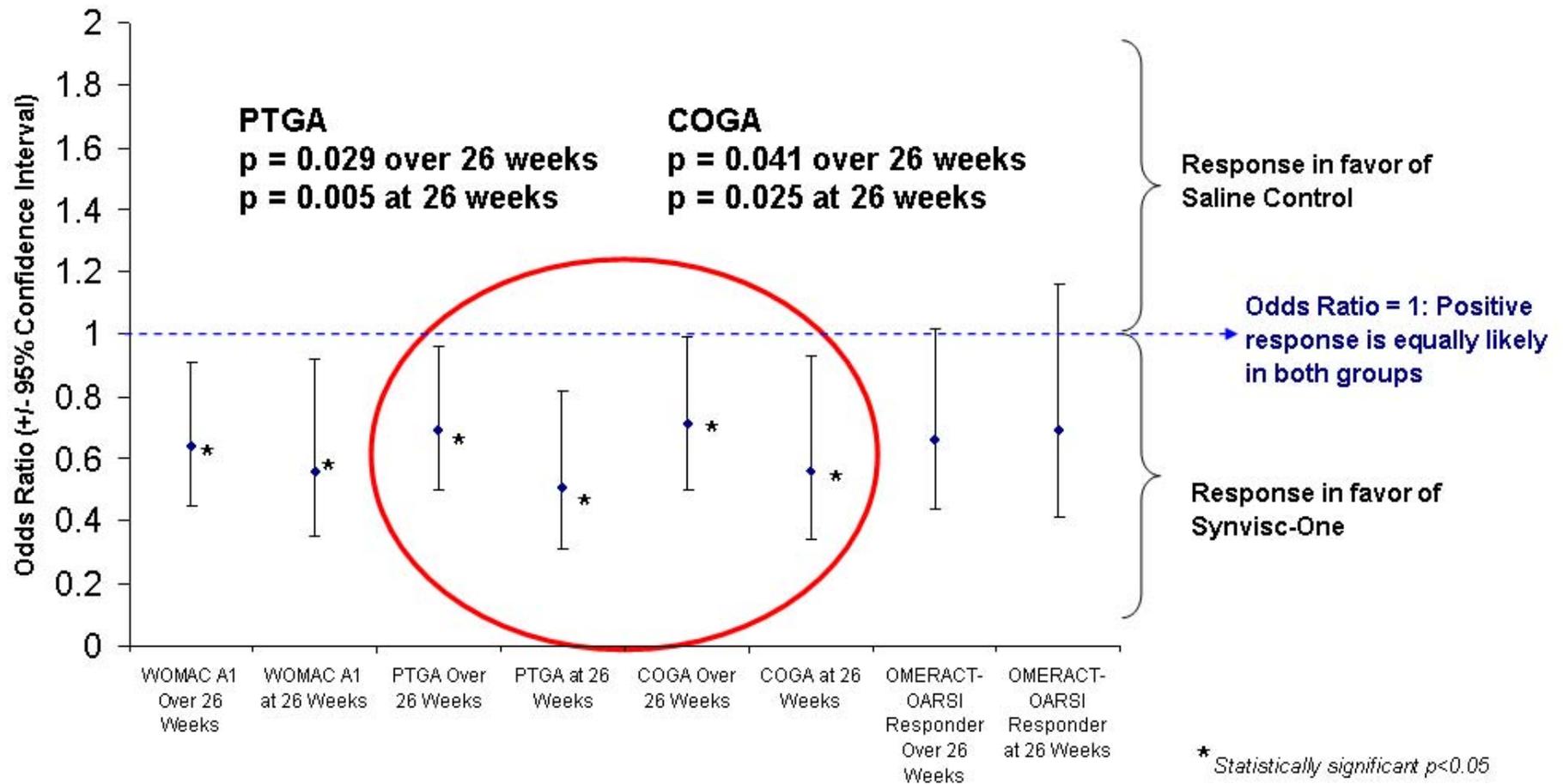
# Secondary Endpoints: WOMAC A1 (Pain on Walking)



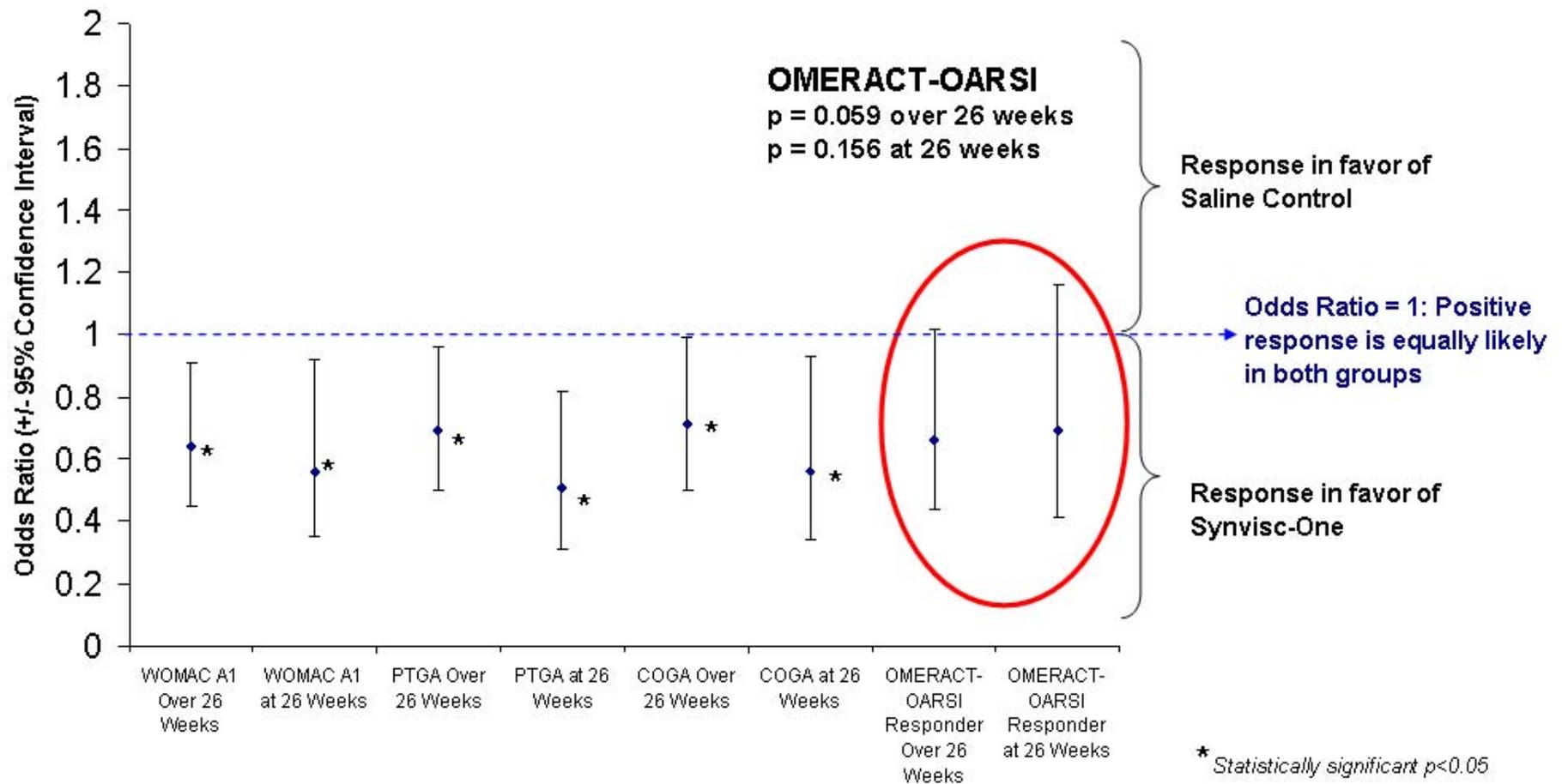
# Secondary Endpoints: PTGA



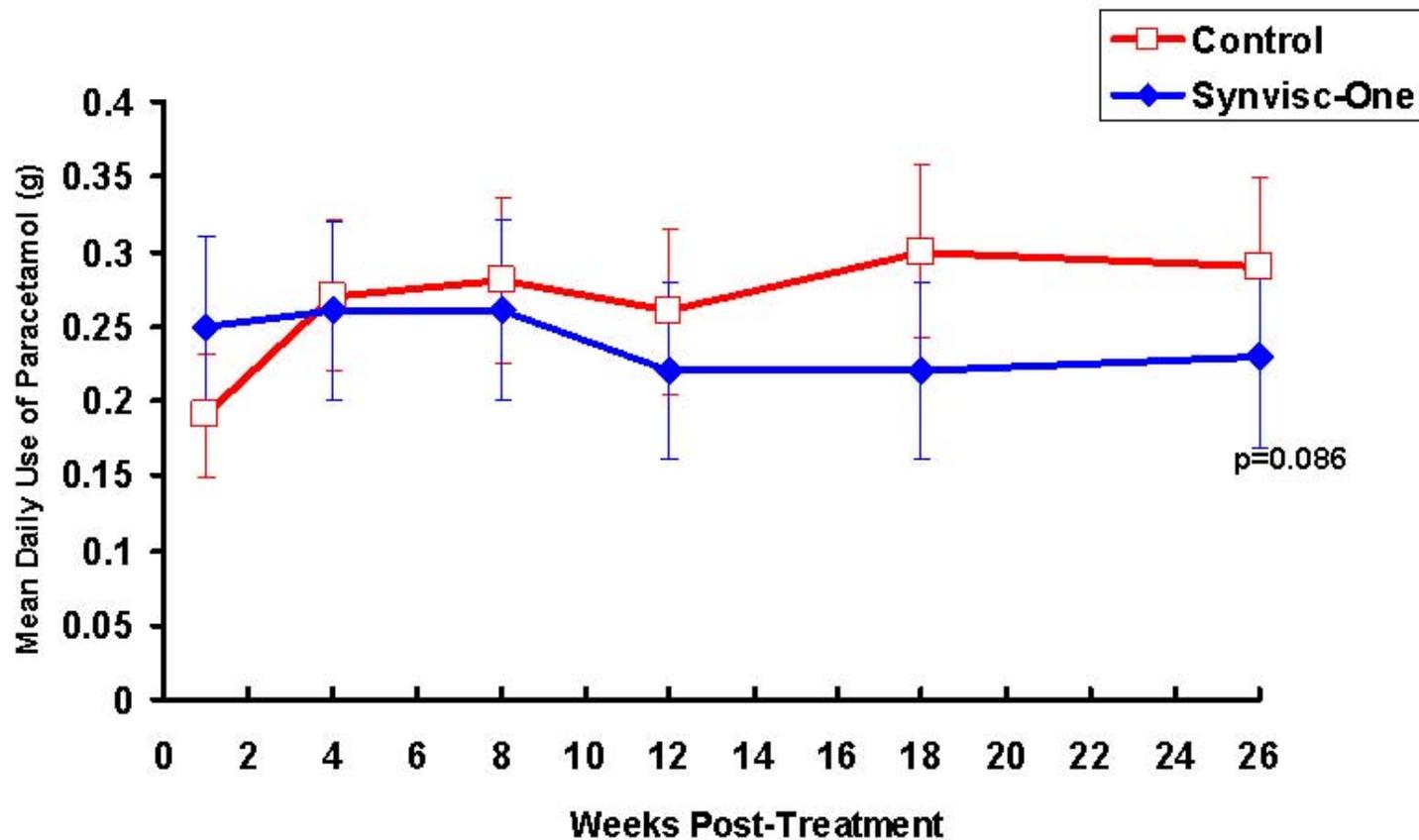
# Secondary Endpoints: COGA



# Secondary Endpoints: OMERACT-OARSI

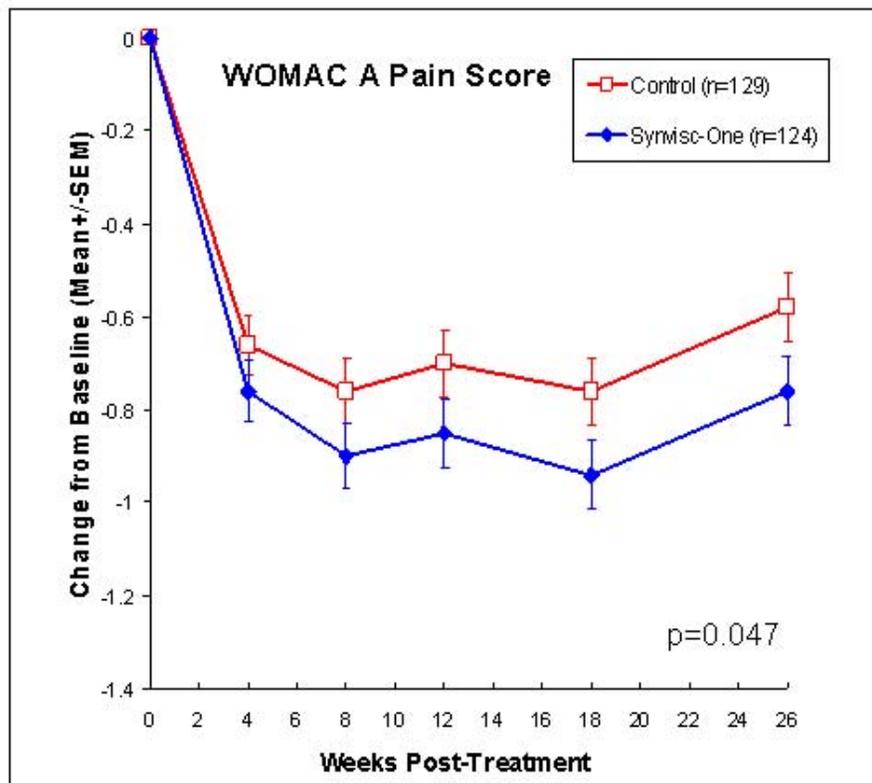


# Rescue Medication: Average Daily Consumption

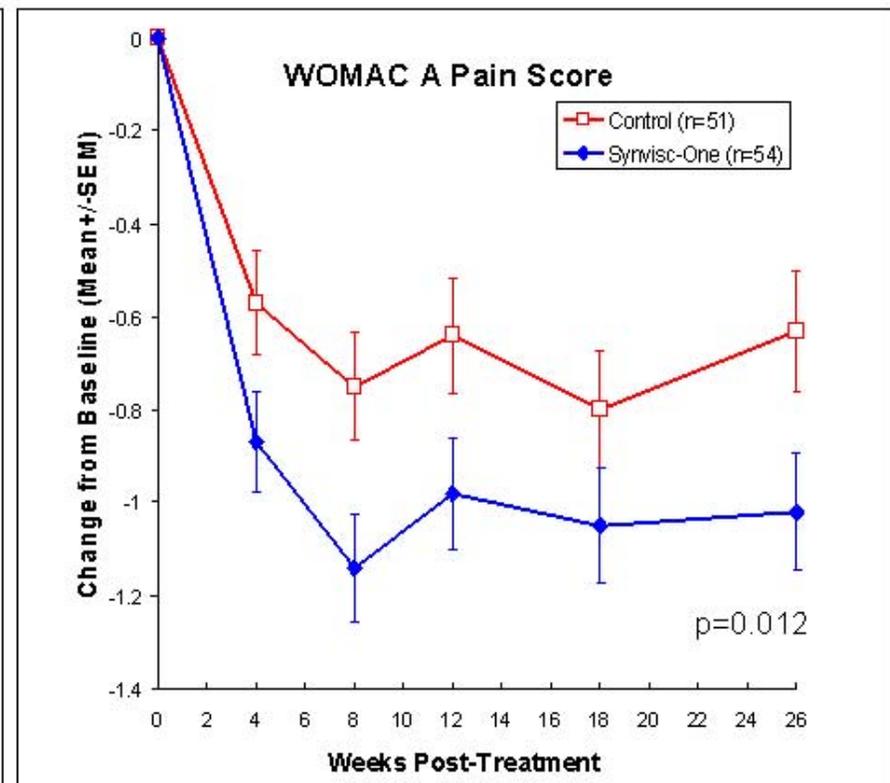


# Local Therapy Works in a Single Joint

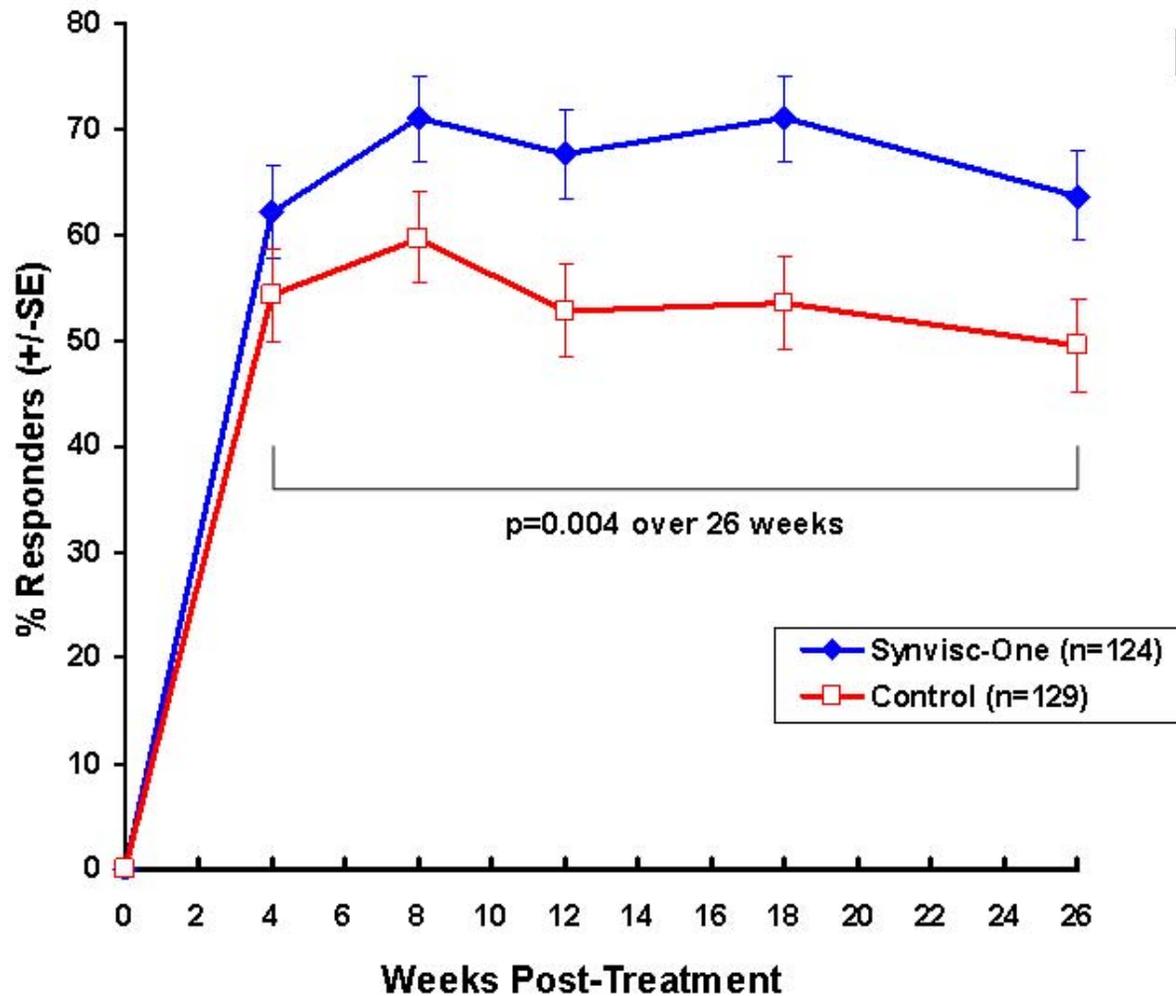
*In all patients*



*In patients without  
concomitant lower limb OA*



# WOMAC A1 Responder Rate



## Responder:

- Improvement of at least 1 category on the Likert scale
- Did not withdraw due to lack of efficacy

# Efficacy Summary

- Synvisc-One is effective at reducing pain compared to control – primary endpoint was met and was supported by several secondary endpoints
- Synvisc-One is effective at reducing pain compared to baseline
- Patients were more likely to feel better
- Patients were more likely to be assessed as being better



Synvisc-One



## What We Found: Safety Results

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# Initial Treatment Phase Safety: Similar Profile to Approved Treatment

	Synvisc-One N = 123 n (% of patients)	Control N = 130 n (% of patients)	
All patients with an AE	70 (56.9%)	79 (60.8%)	
In target knee			} •Short duration •Symptomatic treatment
Target knee AE	44 (35.8%)	44 (33.8%)	
Target knee Serious AE	0	0	
With a device-related AE	7 (5.7%)	4 (3.1%)	
Outside target knee			
Outside target knee	47 (38.2%)	54 (41.5%)	
With a Serious AE	5 (4.1%)	3 (2.3%)	
With a device-related AE	1 (0.8%)	1 (0.8%)	
Discontinued due to AE	1 (0.8%)	3 (2.3%)	
Deaths	0	0	

# Patients with Severe Target Knee AE Initial Double Blind Phase

Preferred Term	Synvisc-One Initial Treatment n=123	Control N=130
	Severe n (%)	Severe n (%)
Any AE – Regardless of Causality	7 (5.7%)	3 (2.3%)
Joint pain	6 (4.9%)	2 (1.5%)
Joint Stiffness	1 (0.8%)	1 (0.8%)
Joint Effusion	0	0
Joint Swelling	0	1 (0.8%)
Related to device	0	0

**No patients experienced severe, acute, local inflammatory reactions**

# Device-related Target Knee AEs Repeat Phase (Treatment Arm)

Preferred Term	Synvisc-One – Synvisc-One (N = 77) n (% of patients)
Any Device-related Target Knee AE	4 (5.2%)
Arthralgia	2 (2.6%)
Injection site pain	1 (1.3%)
Synovial cyst	0
Arthritis	1 (1.3%)
Arthropathy	0
Hypoaesthesia	0
Injection Site Hematoma	1 (1.3%)
Joint Swelling	0

# Safety Summary

- Injection of Synvisc-One results in a similar safety profile as injection of saline
- No new safety signals were observed with a single injection of a larger volume of Synvisc
- Repeat treatment with Synvisc-One does not change the safety profile



Synvisc-One



# Statistical Considerations

**Clare Elkins, MSc**  
Director, Biostatistics



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# Statistical Considerations Related to FDA Questions

- Efficacy Analyses Methods
- Controlling for Type I Error
- Power of the Study

# Statistical Considerations Related to FDA Questions

- Efficacy Analyses Methods
- Controlling for Type I Error
- Power of the Study

# All Analyses were Specified Prior to Database Lock and Unblinding

<b>Protocol Finalized</b>	<b>November 15, 2004</b>
<b>SAP Finalized</b>	<b>October 10, 2006</b>
<b>Database Lock and Unblinding</b>	<b>November 7, 2006</b>
<b>Pre-Specified Analyses Performed</b>	<b>November 14, 2006</b>
<b>sPMA Submitted to FDA</b>	<b>June 18, 2007</b>
<b>FDA Re-Analyses Performed</b>	<b>November 10, 2007 to November 14, 2008</b>

**No Interim Analyses**

**Statistical Analysis Plan was not changed  
once the data was unblinded**

# Primary Efficacy Endpoint: Difference in Genzyme and FDA Analyses

- Genzyme:
  - Investigator site was treated as a fixed effect
  - Analyzed **change from baseline**
- FDA:
  - Investigator site treated as a random effect
  - Analyzed **absolute value**

No difference in interpretation of results  
p-value changed from 0.047 (Genzyme) to 0.032 (FDA)

# Ordinal Secondary Endpoints were Collected as Discrete Categorical Data

- WOMAC A1 (shown), PTGA, and COGA

The screenshot shows a survey form titled "Genzyme WOMAC 1A" with a timestamp of "4/17/2008 3:31 PM". The main heading is "PAIN". The instruction reads: "Think about the pain you felt during the last 48 hours caused by the arthritis in your knee to be injected." The question is "How much pain have you had... when walking on a flat surface?". Below the question are five radio button options: "None", "Mild", "Moderate", "Severe", and "Extreme". Each option has a small radio button icon below it. At the bottom right of the form is an "OK" button.

# Modern Statistical Techniques Provide Robust Methods for Analyzing Ordinal Data

## Genzyme Analysis

Generalized estimating equations (GEE) for a proportional odds logistic regression

Appropriate for ordinal data

## FDA Final Analysis

Repeated Measures Analysis of Covariance (ANCOVA)

Appropriate for continuous data

# The Proportional Odds Model is Appropriate to Use with Ordinal Data

- Commonly used to analyze ordinal data from a Likert scale
  - Pre-specified prior to unblinding in Statistical Analysis Plan
- WOMAC A: **Mean of 5** potential data points (5 item x 5 responses)
  - Therefore, can assume continuous endpoint and use methods designed for continuous data
- WOMAC A1: **5** potential data points (1 item x 5 responses)
  - Therefore use methods designed for ordinal data
- Formal testing (Score test) of the proportional odds assumption was performed
  - The p-values from these tests were not significant the proportional odds assumption was met
  - **WOMAC A1 p=0.48; PTGA p=0.11; COGA p=0.26**

# FDA Re-analysis History

	Genzyme sPMA	FDA Analysis 1	FDA Analysis 2	FDA Analysis 3	FDA Analysis 4	FDA Analysis 5	FDA Analysis 6
<b>Date</b>	<b>Nov 15<sup>th</sup> 2006</b>	<b>June 25<sup>th</sup> 2008</b>	<b>Oct 27<sup>th</sup> 2008</b>	<b>Nov 4<sup>th</sup> 2008</b>	<b>Nov 6<sup>th</sup> 2008</b>	<b>Nov 13<sup>th</sup> 2008</b>	<b>Nov 13<sup>th</sup> 2008</b>
<b>WOMAC A</b>	<b>0.047</b>	<b>0.047</b>	<b>0.022</b>	<b>0.02</b>	<b>0.021</b>	<b>0.032</b>	<b>–</b>
<b>WOMAC A1</b>	<b>0.013</b>	<b>0.029</b>	<b>0.003</b>	<b>0.01</b>	<b>0.011</b>	<b>0.0172</b>	<b>0.150</b>
<b>WOMAC C</b>	<b>0.679</b>	<b>0.679</b>	<b>0.502</b>	<b>0.655</b>	<b>0.866</b>	<b>0.6515</b>	<b>–</b>
<b>PTGA</b>	<b>0.029</b>	<b>0.099</b>	<b>&lt;0.001</b>	<b>0.052</b>	<b>0.064</b>	<b>0.0633</b>	<b>0.053</b>
<b>COGA</b>	<b>0.041</b>	<b>0.101</b>	<b>0.175</b>	<b>0.655</b>	<b>0.086</b>	<b>0.0918</b>	<b>0.11</b>

Note: FDA analyses 1 and 2 were run by Genzyme at FDA request, FDA analyses 3, 4, 5, and 6 were run by FDA

# FDA Re-analysis History

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WOMAC A	0.047	0.047	0.022	0.02	0.021	0.032	–
WOMAC A1	0.013	0.029	0.003	0.01	0.011	0.0172	0.150
WOMAC C	0.679	0.679	0.502	0.655	0.866	0.6515	–
PTGA	0.029	0.099	<0.001	0.052	0.064	0.0633	0.053
COGA	0.041	0.101	0.175	0.655	0.086	0.0918	0.11

Note: FDA analyses 1 and 2 were run by Genzyme at FDA request, FDA analyses 3, 4, 5, and 6 were run by FDA

# FDA Re-analysis History

	Genzyme sPMA	FDA Analysis 1	FDA Analysis 2	FDA Analysis 3	FDA Analysis 4	FDA Analysis 5	FDA Analysis 6
Date	Nov 15 <sup>th</sup> 2006	June 25 <sup>th</sup> 2008	Oct 27 <sup>th</sup> 2008	Nov 4 <sup>th</sup> 2008	Nov 6 <sup>th</sup> 2008	Nov 13 <sup>th</sup> 2008	Nov 13 <sup>th</sup> 2008
WOMAC A	0.047	0.047	0.022	0.02	0.021	0.032	–
WOMAC A1	0.013	0.029	0.003	0.01	0.011	0.0172	0.150
WOMAC C	0.679	0.679	0.502	0.655	0.866	0.6515	–
PTGA	0.029	0.099	<0.001	0.052	0.064	0.0633	0.053
COGA	0.041	0.101	0.175	0.655	0.086	0.0918	0.11

Note: FDA analyses 1 and 2 were run by Genzyme at FDA request, FDA analyses 3, 4, 5, and 6 were run by FDA

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# Statistical Considerations Related to FDA Questions

- Efficacy Analyses Methods
- Controlling for Type I Error
- Power of the Study

# ICH E9 Statistical Principles in Clinical Trials Provides Guidance on Multiplicity

- Multiplicity may arise from
  - Multiple primary variables
  - Multiple comparisons of treatments for the primary endpoint
  - Repeated evaluation over time for the primary endpoint
  - Interim analyses of the primary endpoint
- Methods to avoid or reduce multiplicity include
  - Identification of the key primary variable (multiple variables)
  - The choice of a critical treatment contrast (multiple comparisons)
  - The use of a summary measure such as 'area under the curve' (repeated measures)

# Statistical Considerations: Controlling of Type I Error

- **Primary Efficacy Endpoint**
  - In order to maintain the overall Type I Error for the WOMAC A, the overall change from baseline over all timepoints was calculated and used as the primary efficacy endpoint
- **Secondary Efficacy Endpoints**
  - Secondary efficacy analyses are considered supportive to the primary analysis there is no requirement under ICH to adjust for multiplicity
  - Genzyme is not asking for any additional indication statements based on the secondary endpoints

# Statistical Considerations Related to FDA Questions

- Efficacy Analyses Methods
- Controlling for Type I Error
- Power of the Study

# Study Power

- Power calculations
  - Are performed in the design phase of the study
  - Based on assumptions, including subject drop-out rate
  - Used for sample size calculation
- Analysis method
  - Independent of power and sample size calculations

A retrospective power calculation attempts to determine the power of a study after data has been collected and analyzed and is not relevant to the interpretation of the results

# Statistical Conclusions

- Primary efficacy results are robust – confirmed by all FDA re-analyses
- Proportional odds model for ordinal data is appropriate
- Multiplicity is not an issue for this study design
- Study was powered correctly

# Clinical Meaningfulness in Randomized Trials of Chronic Pain Treatments

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**Robert H. Dworkin, PhD**

**Professor of Anesthesiology, Neurology, Oncology, and Psychiatry**

**Director, Anesthesiology Clinical Research Center**

**University of Rochester School of Medicine and Dentistry**

*Financial disclosure: I am receiving consulting fees and reimbursement of my travel expenses from Genzyme Biosurgery.*

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## ***By way of introduction...***

- **Research focus: (1) clinical trials of acute and chronic pain treatments; (2) studies of methodologic aspects of clinical trials for acute and chronic pain.**
- **Former consultant to and member of Anesthetic and Life Support Drugs Advisory Committee.**
- **Member of the OARSI-FDA Osteoarthritis Initiative Claim of Symptomatic Relief Working Group.**
- **Co-Chair of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)**
  - **Consortium with representatives from academia, regulatory agencies (FDA, EMEA), NIH, VA, patient advocacy groups, and industry.**

# Objectives

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- **To address FDA Question 1: is the 0.15 difference between treatment groups clinically meaningful?**
  - **Discuss the clinical meaningfulness of *patient improvements* in chronic pain trials**
  - **Discuss the clinical meaningfulness of *group differences* in chronic pain trials**
- **Given the critical differences between patient improvements and group mean differences, discuss approaches for determining the clinical meaningfulness of group differences.**



Pain 113 (2005) 9–19

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**PAIN**

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[www.elsevier.com/locate/pain](http://www.elsevier.com/locate/pain)

Topical Review and Recommendations

## Core outcome measures for chronic pain clinical trials: IMMPACT recommendations

Robert H. Dworkin<sup>a,\*</sup>, Dennis C. Turk<sup>b</sup>, John T. Farrar<sup>c</sup>, Jennifer A. Haythornthwaite<sup>d</sup>,  
Mark P. Jensen<sup>b</sup>, Nathaniel P. Katz<sup>e</sup>, Robert D. Kerns<sup>f</sup>, Gerold Stucki<sup>g</sup>, Robert R. Allen<sup>h</sup>,  
Nicholas Bellamy<sup>i</sup>, Daniel B. Carr<sup>j</sup>, Julie Chandler<sup>k</sup>, Penney Cowan<sup>l</sup>, Raymond Dionne<sup>m</sup>,  
Bradley S. Galer<sup>n</sup>, Sharon Hertz<sup>o</sup>, Alejandro R. Jadad<sup>p</sup>, Lynn D. Kramer<sup>q</sup>, Donald C. Manning<sup>r</sup>,  
Susan Martin<sup>s</sup>, Cynthia G. McCormick<sup>t</sup>, Michael P. McDermott<sup>u</sup>, Patrick McGrath<sup>v</sup>,  
Steve Quessy<sup>w</sup>, Bob A. Rappaport<sup>o</sup>, Wendye Robbins<sup>x</sup>, James P. Robinson<sup>b</sup>,  
Margaret Rothman<sup>y</sup>, Mike A. Royal<sup>z</sup>, Lee Simon<sup>o</sup>, Joseph W. Stauffer<sup>aa</sup>,  
Wendy Stein<sup>ab</sup>, Jane Tollett<sup>ac</sup>, Joachim Wernicke<sup>ad</sup>, James Witter<sup>o</sup>



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## Consensus Statement

### Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations

Robert H. Dworkin,<sup>\*</sup> Dennis C. Turk,<sup>†</sup> Kathleen W. Wyrwich,<sup>‡</sup> Dorcas Beaton,<sup>§</sup>  
Charles S. Cleeland,<sup>||</sup> John T. Farrar,<sup>¶</sup> Jennifer A. Haythornthwaite,<sup>#</sup> Mark P. Jensen,<sup>†</sup>  
Robert D. Kerns,<sup>\*\*</sup> Deborah N. Ader,<sup>††</sup> Nancy Brandenburg,<sup>‡‡</sup> Laurie B. Burke,<sup>§§</sup>  
David Cella,<sup>|||</sup> Julie Chandler,<sup>¶¶</sup> Penny Cowan,<sup>##</sup> Rozalina Dimitrova,<sup>\*\*\*</sup>  
Raymond Dionne,<sup>†††</sup> Sharon Hertz,<sup>§§</sup> Alejandro R. Jadad,<sup>‡‡‡</sup> Nathaniel P. Katz,<sup>§§§</sup>  
Henrik Kehlet,<sup>||||</sup> Lynn D. Kramer,<sup>¶¶¶</sup> Donald C. Manning,<sup>###</sup> Cynthia McCormick,<sup>\*\*\*\*</sup>  
Michael P. McDermott,<sup>††††</sup> Henry J. McQuay,<sup>‡‡‡‡</sup> Sanjay Patel,<sup>§§§§</sup> Linda Porter,<sup>|||||</sup>  
Steve Quessy,<sup>¶¶¶¶</sup> Bob A. Rappaport,<sup>§§</sup> Christine Rauschkolb,<sup>####</sup>  
Dennis A. Revicki,<sup>\*\*\*\*\*</sup> Margaret Rothman,<sup>####</sup> Kenneth E. Schmader,<sup>†††††</sup>  
Brett R. Stacey,<sup>‡‡‡‡‡</sup> Joseph W. Stauffer,<sup>§§§§§</sup> Thorsten von Stein,<sup>|||||||</sup>  
Richard E. White,<sup>¶¶¶¶¶</sup> James Witter,<sup>§§</sup> and Stojan Zavisic<sup>#####</sup>

# Provisional Benchmarks for Interpreting Changes from Baseline in Chronic Pain Clinical Trial Outcome Measures

<i>OUTCOME DOMAIN AND MEASURE</i>	<i>TYPE OF IMPROVEMENT*</i>	<i>METHOD†</i>	<i>CHANGE</i>
Pain intensity			
0–10 numerical rating scale	Minimally important	Anchor	10–20% decrease
	Moderately important	Anchor	≥30% decrease
	Substantial	Anchor	≥50% decrease
Physical functioning			
Multidimensional Pain Inventory			
Interference Scale	Clinically important	Distribution	≥0.6 point decrease
Brief Pain Inventory			
Interference Scale	Minimally important	Distribution	1 point decrease
Emotional functioning			
Beck Depression Inventory	Clinically important	Distribution	≥5 point decrease
Profile of Mood States			
Total Mood Disturbance	Clinically important	Distribution	≥10–15 point decrease
Specific subscales	Clinically important	Distribution	≥2–12 point change‡
Global rating of improvement			
Patient Global Impression of Change	Minimally important	Anchor	Minimally improved
	Moderately important	Anchor	Much improved
	Substantial	Anchor	Very much improved

\*Because few studies have examined the importance of worsening on these measures, benchmarks are only provided for improvement in scores.

†Specific method used in determining benchmark provided in final column; distribution-based methods were based on use of 0.5 standard deviation or 1.0 standard error of measurement or both.

‡The magnitude of a clinically important change depends on the specific subscale, as does the direction of change that reflects an improvement.

# Provisional Benchmarks for Interpreting Changes from Baseline in Chronic Pain Clinical Trial Outcome Measures

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<i>OUTCOME DOMAIN AND MEASURE</i>	<i>TYPE OF IMPROVEMENT*</i>	<i>METHOD†</i>	<i>CHANGE</i>
<b>Pain intensity 0-10 scale</b>	<b>Minimally important</b>	<b>Anchor</b>	<b>10-20% ↓</b>
	<b>Moderately important</b>	<b>Anchor</b>	<b>≥ 30% ↓</b>
	<b>Substantial</b>	<b>Anchor</b>	<b>≥ 50% ↓</b>

# Patient Global Impression of Change Scale

**Since the start of the study, my overall status is:**

- 1  Very Much Improved**
- 2  Much Improved**
- 3  Minimally Improved**
- 4  No Change**
- 5  Minimally Worse**
- 6  Much Worse**
- 7  Very Much Worse**

Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale.

Pain, 2001;94:149-158.

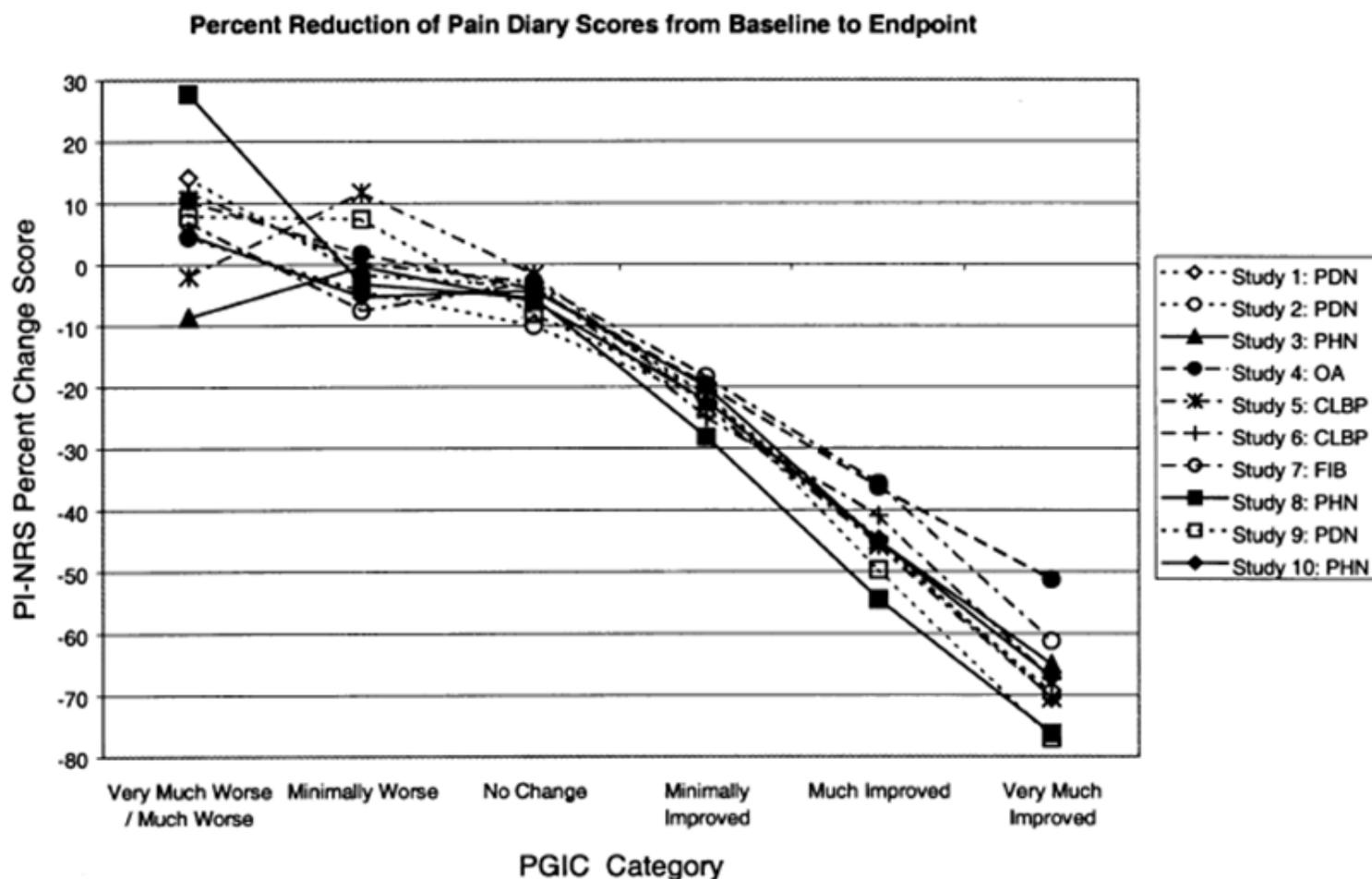


Fig. 3. Stratification by study – percent change (baseline to endpoint) in PI-NRS compared to PGIC assessment recorded at endpoint. PDN, peripheral diabetic neuropathy; PHN, postherpetic neuralgia; OA, osteoarthritis of the hip or knee; CLBP, chronic low back pain and Fib, fibromyalgia. Note: ‘very much worse’ and ‘much worse’ are combined because of low numbers in these groups.

**Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain, 2001;94:149-158.**

## *Determining Criteria for Important Changes for Groups*

**“It is crucial to recognize that criteria for clinically important change in individuals cannot be directly applied to the evaluation of clinically important group differences.**

**For example, in evaluating a new analgesic, if a 2 point decrease on a 0-10 NRS of pain intensity is considered a clinically important improvement for an individual, it should not be inferred that a 2 point difference in pain reduction between the analgesic and placebo must occur before the treatment benefit can be considered clinically important.”**

# Guidance for Industry

## Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Laurie Burke (CDER) 301-796-0700, Toni Stifano (CBER) 301-827-6190, or Sahar Dawisha (CDRH) 301-594-3090.

**“For many widely used measures (pain, treadmill distance, HamD), the ability to show *any* difference between treatment groups has been considered evidence of a relevant treatment effect.**

**When defining a meaningful change on an individual patient basis (i.e., a responder), that definition is generally larger than the minimum important difference for application to group mean comparisons.”**

*as illustrated in the following meta-analysis...*

# Individual Clinically Meaningful Improvements vs. Group Differences Between Treatment and Placebo

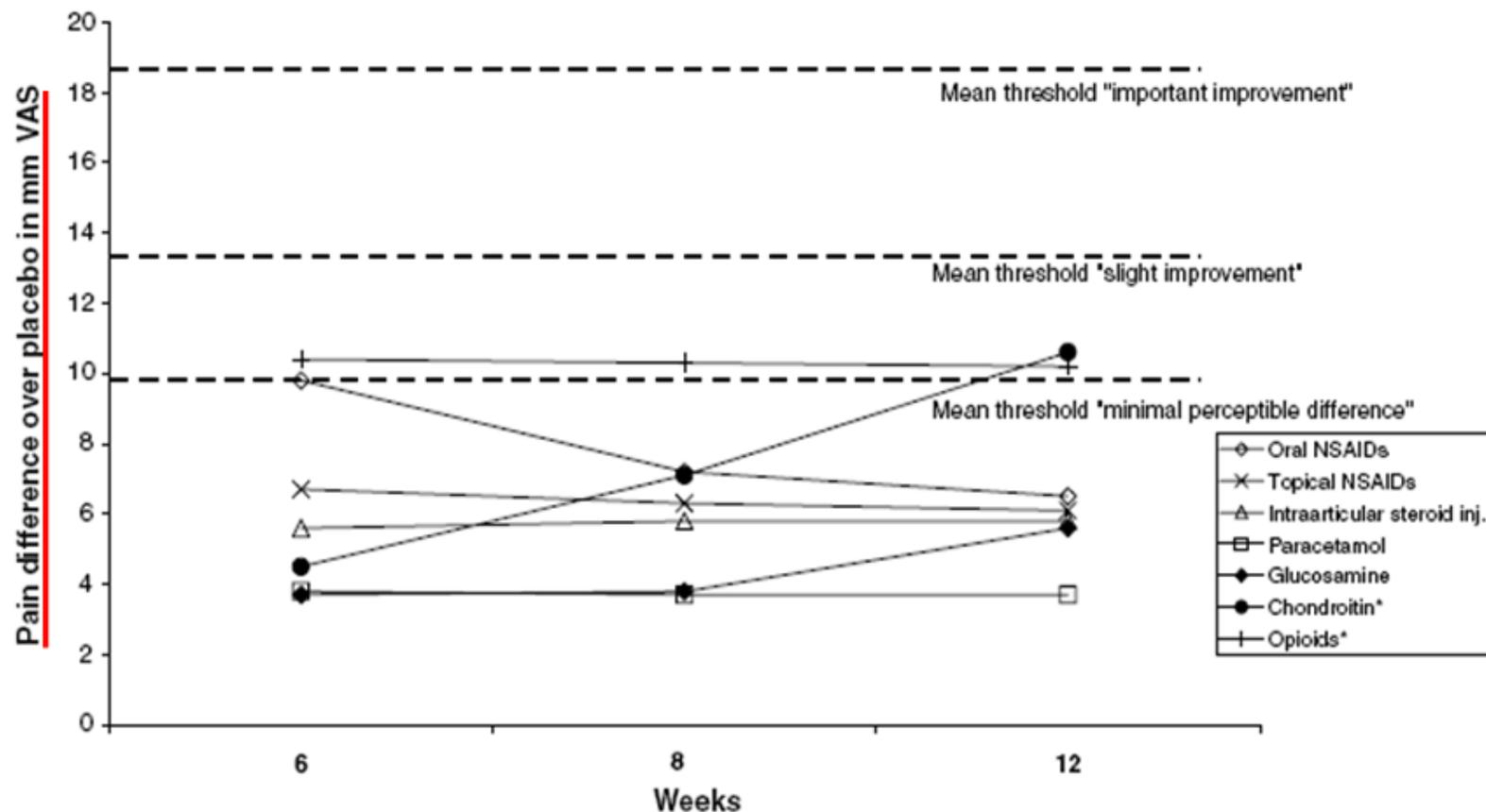
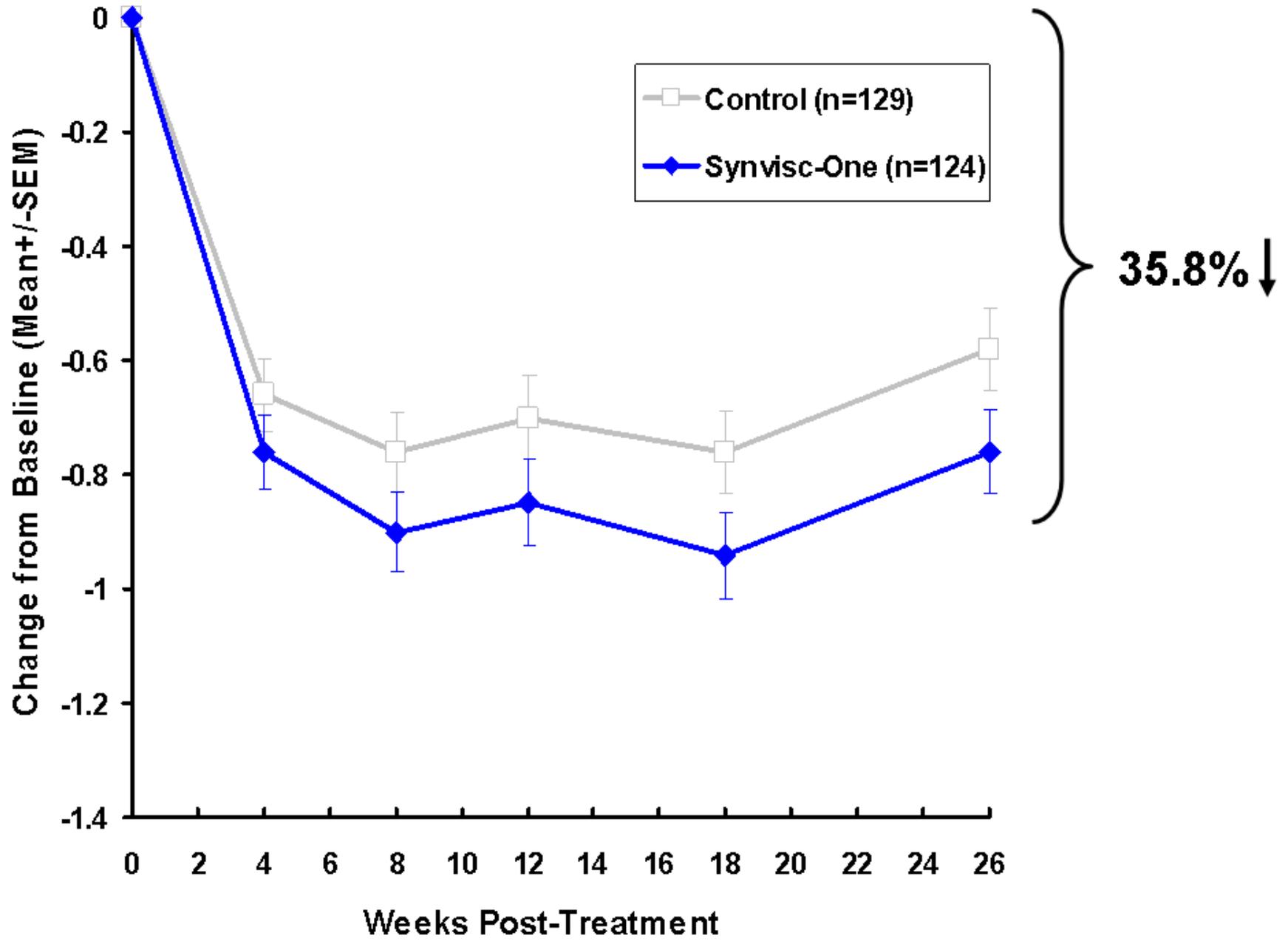


Fig. 2. The secondary outcome results by graph lines for efficacy at 6, 8 and 12 weeks for seven pharmacological interventions are shown. The stapled horizontal lines indicate mean thresholds for clinically important improvement (Tubach et al., 2005), for categorical shift from none to slight improvement (Angst et al., 2002), and threshold for the minimal perceptible threshold (Ehrich et al., 2000) in descending order. Asterisks for opioid therapy and chondroitin sulphate indicate that categorical data for these therapies contradict the positive results shown for continuous data.

**Bjordal JM, Klovning A, Ljunggren AE, Slørdal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: a meta-analysis of randomised placebo-controlled trials. Eur J Pain, 2007;11:125-138.**

**The previous figure illustrated that the improvement that patients with OA consider clinically meaningful is larger than the differences found between active treatment and control groups in OA knee pain clinical trials. Why?**

- 1. Meaningful change in individuals reflects treatment effects, placebo and other non-specific effects of the clinical setting, natural history and spontaneous resolution, and regression to the mean.**
  - Group differences between active treatment and control groups reflect the incremental benefits of active treatment that contribute to improvement.**



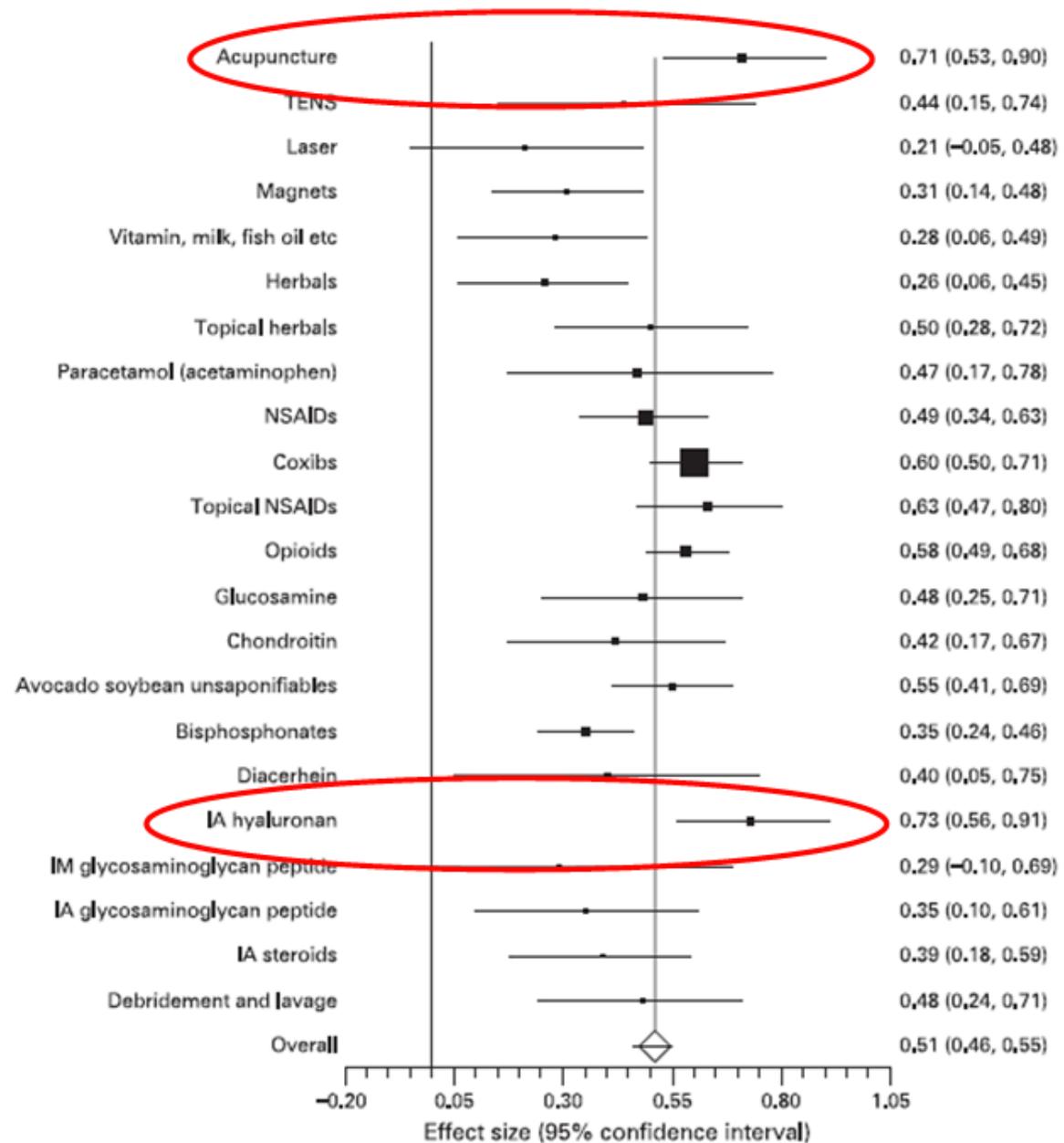
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**1. Meaningful change in individuals reflects treatment effects, placebo and other non-specific effects of the clinical setting, natural history and spontaneous resolution, and regression to the mean.**

- Group differences between active treatment and control groups reflect the incremental benefits of active treatment that contribute to improvement.**

**2. The differences between active treatment and control groups are also limited by the magnitude of placebo effects in chronic pain clinical trials, which can be substantial, and by the use of rescue and concomitant analgesics.**

**Figure 4** Placebo effect for pain categorised according to active treatment. IA, intra-articular; IM, intramuscular; NSAID, non-steroidal anti-inflammatory drug; TENS, transcutaneous electrical nerve stimulator.



Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials  
 Ann Rheum Dis, Dec 2008; 67:1716-1723.

## **Factors to consider in determining the clinical meaningfulness of group differences**

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**Evaluations of the clinical meaningfulness of group differences between chronic pain active treatment and control groups should not be based on criteria for evaluating clinically meaningful change in individuals.**

**Rather, they should be based on case-by-case considerations of various characteristics of the specific treatments.**

*What are these characteristics?*

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## Multiple factors must be considered to determine the clinical meaningfulness of group differences

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- ✓ **Statistical significance of primary efficacy analysis.**
- 1. **Results for secondary endpoints.**
- 2. **Results of responder analyses.**
- 3. **Magnitude of improvement with treatment.**
- 4. **Onset and durability of treatment benefit.**
- 5. **Plausibility of treatment benefits.**
- 6. **Safety and tolerability.**
- 7. **Treatment effect size compared to available treatments.**
- 8. **Limitations of available treatments.**
- 9. **Different mechanism of action vs. existing treatments**
- 10. **Convenience and patient adherence.**
- 11. **Other benefits, including improvements in physical and/or emotional functioning, few or no drug interactions, and cost.**

# Conclusions

---

- **The clinical meaningfulness of *patient improvements* in chronic pain trials can be determined by assessing what patients themselves consider meaningful improvement.**
- **The clinical meaningfulness of *group differences* in chronic pain trials, however, must be determined by a multifactorial evaluation of the benefits and risks of the treatment and of other available treatments for the disease.**

# Clinical Implications of Synvisc-One Study Results

Lee S. Simon, M.D.

# Clinical Implications of Synvisc-One Study Results

**Lee S. Simon, M.D.**

**Associate Clinical Professor of Medicine  
Harvard Medical School**

**Clinical Rheumatologist for 25 years**

**Executive Committee of OMERACT, “Outcome Measures in  
Rheumatic Disease Clinical Trials”**

**Co-Chair of OARSI committee to address RFP from FDA on  
updating the Draft Osteoarthritis Guidance of 1999**

**Former Division Director of Analgesic, Anti-inflammatory and  
Ophthalmologic Drug Products, CDER, FDA**

# Summary of Key Results for Synvisc-One

- The primary endpoint analysis of WOMAC A (pain) over 26 weeks demonstrated statistical superiority ( $p=0.047$ ) to the control arm (arthrocentesis plus 6 mL of IA saline)
- Synvisc-One was also statistically superior to the control arm in several key secondary endpoints measured over 26 weeks, including:
  - WOMAC A1 (pain on walking) ( $p=0.013$ )
  - Patient Global Assessment (PTGA) ( $p=0.029$ )
  - Clinical Observer Global Assessment (COGA) ( $p=0.041$ )

# Summary of Key Results for Synvisc-One

- Patients receiving Synvisc-One showed a significant decrease in pain from baseline (35.8%) over 26 weeks ( $p < 0.001$ ).
  - Significantly better ( $p = 0.033$ ) than control group (29%)
- This is consistent with literature on clinically important improvement in osteoarthritis (OA) and expected treatment benefits shown by other approved pharmaceutical and medical device products for treatment of OA pain.
- Observed treatment effect amplified in subset of patients without OA in non-target lower limbs
  - Expected finding for an effective local therapy

# Approval of Other Local OA Pain Treatments

- Hyalgan
  - VAS pain on 50 ft walk test demonstrated a 6 mm separation from saline
- Voltaren Gel (diclofenac)
  - Statistical superiority to vehicle alone on walking pain on VAS scale. Treatment difference was 7 mm at 12 weeks.
  - Primary endpoint adjusted
    - To exclude patients with pain in the contra-lateral knee.
    - To exclude patients whose pain spontaneously declined between screening and treatment
- Viscosupplements: Supartz, Orthovisc, and Euflexxa approved by various criteria
- **Level of evidence provided for Synvisc-One commensurate with these approved products**

# Improvements from Baseline for other OA Therapies are Similar to Synvisc-One

Type	Product	Reference	WOMAC A Percent Improvement from Baseline
<b>Systemic Effect/ Frequent Dosing</b>	Celecoxib	Bingham et al. 2007, Birbara et al. 2006, Gibofsky et al. 2003, Lehmann et al. 2005, McKenna et al. 2001, Rother et al. 2007	33.3% to 42.7%
	Diclofenac	Case et al. 2003, McKenna et al. 2001, Schnitzer et al. 2004	27% to 40.2%
	Morphine sulfate ER	Caldwell et al. 2002	17.2%
	Tramadol/acetaminophen	Emkey et al. 2004	29.6%
<b>Local Effect/ Frequent Dosing (2-3 times/day)</b>	Diclofenac topical	Bookman et al. 2004, Grace et al. 1999	36.9% to 42.9%
<b>Local Effect/ Multiple Injection (3-5 injections per course)</b>	Supartz®	Day et al. 2004	42%
	Orthovisc®	Brandt et al. 2001	30%
	Euflexxa®	Kirchner and Marshall 2006	30%
<b>Local Effect/ Single Injection</b>	Synvisc-One	sPMA (P940015/S012)	35.8%

## Effect Size of Synvisc-One Similar to Commonly-Used Approved OA Products

Product	Effect Size	Sources
acetaminophen	0.13 to 0.21	Zhang et al., 2004 Toweed et al., 2006
NSAIDs	0.32	Bjordal et al., 2004
celecoxib	0.14 to 0.50	Bensen et al., 1999 Zhao et al., 1999 Clegg et al., 2006 Bingham et al., 2007
“Synvisc-One”	0.23	Genzyme sPMA

# Synvisc-One: Positive Risk-Benefit Profile

- No serious adverse events reported
- No new safety signals observed
  - Types of AEs observed not different from that reported with 3-injection dosing
- No increase in incident local AEs with repeated 1-injection dosing
- The clinical benefit was consistent in multiple outcome measures
- Increased convenience and adherence

# Broader Implications

## Support Approval

- There is no cure for OA of the knee; multiple choices are important
- Viscosupplements
  - Similar treatment effect as observed with NSAIDs/COX-2 inhibitors, as well as other local therapies
    - While avoiding potential GI, CV and renal toxicity of NSAIDs and acetaminophen
    - Reduced need for chronic oral therapy
    - A needed option for OA patients who have failed oral meds, have risk factor(s) for them, and/or are not candidates for knee arthroplasty
- Synvisc-One
  - Clinically meaningful and statistically significant improvement from baseline
  - Acceptable risk-benefit
  - Proposed change to injection schedule has advantages for patients and providers



Synvisc-One



## Concluding Remarks

**Michael Halpin**

Vice President, Regulatory Affairs



genzyme



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# Summary

- OA – significant unmet medical need
  - New options needed
  - Local therapies have advantages
- Clinical Effectiveness
  - Primary endpoint met (treatment effect of 0.15, effect size of 0.23)
  - 3 of the key statistically significant supportive analyses
    - Within patient improvement from baseline of 0.84 (36%)
    - WOMAC A1 – pain on walking on a flat surface (effect size of 0.36)
    - Only the treated joint involved (effect size of 0.44)
- Pain Trials
  - Important to look at within patient improvement as well as between group differences

# Summary (Cont.)

- **Safety**
  - Same material as Synvisc
    - 16 year history in over 4.5 million patients
  - No new safety signals identified in Synvisc-One trials
  - 10,000 patients treated with Synvisc-One outside U.S.
    - Spontaneously reported adverse event rate 0.14%
- **Pre-specified appropriate analysis plan**
  - Multiple secondary endpoints support clinical benefit

# Conclusion

- The totality of the evidence demonstrates that Synvisc-One represents a clinically meaningful treatment option for patients suffering from osteoarthritis knee pain



Synvisc-One



Summation

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Synvisc-One



## Summation

**Alison Lawton**

Senior Vice President  
Global Regulatory Affairs  
& Corporate Quality Systems



genzyme



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# Summation

- OA is a significant unmet medical need
  - New options needed
  - Local therapies have advantages
- Synvisc One:
  - Packaging & administration change from Synvisc
    - 4.5 million patients treated
  - Safety
    - No new safety signals with Synvisc One

# Summation

- **Clinical Effectiveness:**
  - Agreement on statistical significance of primary endpoint
  - Secondary endpoints
    - Appropriate pre-specified statistical analysis
    - No adjustment required for multiplicity (ICH)
- **Clinical Meaningfulness**
  - Totality of evidence supports

## **Multiple Factors Must be Considered to Determine the Clinical Meaningfulness of Group Differences**

- ✓ **Statistical significance of primary efficacy analysis**
- 1. **Results for secondary endpoints**
- 2. **Results of responder analyses**
- 3. **Magnitude of improvement with treatment**
- 4. **Onset and durability of treatment benefit**
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- 10. **Convenience and patient adherence**
- 11. **Other benefits, including improvements in physical and/or emotional functioning, few or no drug interactions, and cost**

# Summation

- Secondary endpoints support Clinical benefit
  - 36% improvement from baseline in WOMAC A
  - Only the treated joint involved (effect size 0.44)
  - WOMAC A1 (effect size 0.36)
  - Patient and physician global assessments
- Comparable effect size to other OA products
- Published benchmarks for individual patient response in chronic pain outcomes

# Summation

- Synvisc One offers clinically meaningful and convenient treatment option for patients suffering from OA of the knee