

Genzyme Biosurgery

P940015/S12

(Synvisc-One)

**Orthopaedic and Rehabilitation Devices
Advisory Panel Meeting
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PMA Review Team

- Kyung Lee, M.D. – Lead reviewer
- Chang Lao, Ph.D. – Statistical review
- Cunlin Wang, M.D. – Post-Approval Study
- Amy Skrzypchak – Manufacturing review
- Patty L Jahnes, Ph.D. – BIMO Review
- Mary Ann Wollerton – Patient labeling

FDA Presentation

- Introduction
- Summary of Non-Clinical Studies
- Clinical Study
- Statistical Overview
- Post-Approval Study
- Panel Questions

Proposed Indications for Use

- 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 non-pharmacologic therapy and simple analgesics, e.g., acetaminophen.

Rationale for Panel Meeting

- Single dosing regimen for intra-articular injection of hyaluronic acid (HA) is based on viscosupplementation
- FDA is presenting Synvisc-One to the Panel primarily to comment on the clinical effectiveness of the device in relieving pain in patients who have OA of the knee.
- Panel questions will be presented

Device Description

- Synvisc-One™ (hylan G-F 20) is a single IA injection supplied in a 10-mL glass syringe containing 6-mL hylan G-F 20 and is administered as a single IA injection.
- Hylan G-F 20 is a hyaluronic acid (HA)-based viscosupplementation device.
- Synvisc was approved for a total of three injections (2mL of Synvisc per each injection supplied in a 2.25mL glass syringe) for the treatment of OA in the knee for patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics on August 8, 1997 in the US (P940015).
- Synvisc and Synvisc-One contain the identical composition hylan G-F 20 and the manufacturing process for hylan G-F 20 is unchanged.

Non-clinical testing

- An evaluation of the non-clinical tests by FDA was based in large part on the previous device approval (for three injections).
- There were no unresolved safety issues.

Clinical Study Summary

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Initial Phase (Pivotal) &
Repeat Treatment Phase Study

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Study Design

- Primary study was conducted to evaluate the safety and efficacy of a single 6-mL IA dose of Synvisc-One injected into the knee from baseline for a 26 week period.
- Study was conducted as a randomized, double-blind, placebo-controlled, concurrent and multi-center study.
- Study was conducted at 21 sites in 6 European countries (Belgium, Czech Republic, France, Germany, the Netherlands and the United Kingdom.)
- *Study was not conducted in US under IDE so FDA did not review protocol prior to its conduct.*

Study Design (continued)

- 253 patients were randomized
[1 :1 (Synvisc-One: n=124, Placebo: n=129)]
 - Group 1: Arthrocentesis followed by a 6-mL IA injection of Synvisc-One on Day 0
 - Group 2: Arthrocentesis followed by a 6-mL IA injection of Placebo on Day 0
- The Evaluator and the patient were blinded to the treatment group assignment.

Study Design: Follow-up Phase

- All patients were scheduled to return for follow-up within specified visit windows: at Day 0 (baseline) 1, 4, 8, 12, 18 and 26 weeks following the single injection.
- For 48 hours prior to each visit, patients were to forego those pain or their OA medications that were otherwise permitted during the study (i.e., those with a half-life of ≤ 5 hours).

Key Inclusion Criteria

- Patients were required to have a documented diagnosis of OA of the target knee made at least 3 months prior to screening.
- All patients met the American College of Rheumatology (ACR) criteria for OA (Altman, 1986, *Arthritis Rheum*).
- The main initial treatment phase inclusion criteria were the following:
 - 40 years or older;
 - Documented diagnosis of primary OA of the target knee;
 - Radiographic evidence of OA in the tibio-femoral compartment of the target knee;
 - Continued OA pain in the target knee despite conservative treatments;
 - Score of 2 or 3 (0 to 4 scale) on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC LK 3.1) A1 (pain while walking on flat surface); and
 - A mean score of 1.5 to 3.5 on all five questions of the WOMAC LK 3.1 A (pain)

Key Exclusion Criteria

- The main initial phase exclusion criteria were the following:
 - Grade IV radiographic stage of the target knee according to the system of Kellgren and Lawrence (K-L) (Kellgren, 1957, *Ann Rheum Dis*);
 - Clinically apparent tense effusion of the target knee;
 - Significant valgus/varus deformities;
 - Viscosupplementation in any joint in the past 9 months;
 - Previous surgery at the target knee in the past 6 months;
 - Symptomatic OA of the contralateral knee or either hip that is not responsive to acetaminophen; and
 - Systemic or IA injection of corticosteroids in any joint within 3 months prior to screening.

Primary Efficacy Objective

- To demonstrate that 1 x 6-mL injection of Synvisc-One provides superior pain relief (using the WOMAC* LK 3.1 A scale) over a 26 week period as compared to a 1 x 6-mL IA injection of Placebo (Phosphate-buffered saline) in treating patients with symptomatic primary OA of the knee.

* *Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index*

Primary Effectiveness Endpoint

WOMAC Likert Scale* of subscore pain (WOMAC A)

5-point scale: 0 = none, 1 = mild, 2 = moderate,
3 = severe, and 4 = extreme

For each of five questions (each for 5 point scale):

- pain walking on flat surface (WOMAC A1)
- up and down
- at night in bed
- sitting or lying down
- standing

**Refer to Section 9 of Panel Pack*

Rescue Medications

- Patients were allowed to take rescue medication (paracetamol, not to exceed 4000 mg/day):
 - for target knee pain relief throughout the duration of the trial, including during the screening phase (with the exception of within 48 hours prior to study evaluations)
 - Additionally permitted pain medications (i.e., those with half-lives ≤ 5 hours) are listed in the protocol (*Section 8 of Panel Pack*).

Patient Demographic Characteristics

Initial Treatment Study (ITT)

	Synvisc-One (N=124)	Placebo (N=129)	Total (N=253)
Age			
n	124	129	253
Mean (SD)	63.6 (9.64)	62.5 (9.17)	63.0 (9.40)
Sex, n			
Male, n (%)	32 (25.8)	41 (31.8)	73 (28.9)
Female, n (%)	92 (74.2)	88 (68.2)	180 (71.1)
Weight (kg)			
n	123	129	252
Mean (SD)	79.38 (14.049)	82.35 (16.120)	80.90 (15.188)
Body Mass Index (kg/m²)			
n	123	129	252
Mean (SD)	29.08 (4.814)	29.77 (5.742)	29.43 (5.310)

Safety

- Safety was determined using the incidence of treatment-emergent adverse events (AEs), vital signs, and physical examination findings.
- The AEs were categorized using a standardized coding dictionary (e.g., Medical Dictionary for Regulatory Activities [MedDRA]).

Adverse Events (Initial Treatment Phase)

Patients	Synvisc-One (N = 123)		Placebo (N = 130)		Overall (N = 253)	
	n (%)	No. of Events	n (%)	No. of Events	n (%)	No. of Events
With an AE	70 (56.9)	177	79 (60.8)	224	149 (58.9)	401
With an Injection Procedure-Related AE	7 (5.7)	7	5 (3.8)	5	12 (4.7)	12
With a Treatment- Related AE	4 (3.3)	5	2 (1.5)	2	6 (2.4)	7
Who Prematurely Discontinued Because of an AE	1 (0.8)	1	3 (2.3)	7	4 (1.6)	8
With a Target Knee AE	44 (35.8)	77	44 (33.8)	82	88 (34.8)	159
With an Injection Procedure-Related Target Knee AE	6 (4.9)	6	4 (3.1)	4	10 (4.0)	10

Adverse Events (continued)

Patients	Synvisc-One (N = 123)		Placebo (N = 130)		Overall (N = 253)	
	n (%)	No. of Events	n (%)	No. of Events	n (%)	No. of Events
With a Target Knee Serious AE	0	0	0	0	0	0
Whose Highest Severity of AE is:						
Mild	26 (21.1)	40	35 (26.9)	81	61 (24.1)	121
Moderate	36 (29.3)	64	39 (30.0)	75	75 (29.6)	139
Severe	8 (6.5)	11	5 (3.8)	6	13 (5.1)	17

Adverse Events in the Target Knee Occurring in >1 Patient in Either Group - Safety Population

Preferred Term	Synvisc-One N =123 n (%)	Placebo N =130 n (%)	Total N = 253 n (%)
Any Treatment- Emergent Adverse Event	44 (35.8)	44 (33.8)	88 (34.8)
Arthralgia	31 (25.2)	28 (21.5)	59 (23.3)
Joint stiffness	10 (8.1)	13 (10.0)	23 (9.1)
Joint effusion	7 (5.7)	7 (5.4)	14 (5.5)
Joint swelling	5 (4.1)	7 (5.4)	12 (4.7)
Joint warmth	2 (1.6)	5 (3.8)	7 (2.8)
Post-traumatic pain	0	3 (2.3)	3 (1.2)
Synovial cyst	0	2 (1.5)	2 (0.8)

Safety and Effectiveness

- The Panel will be asked a question about the overall safety and efficacy of this device

Key Efficacy Results

- The following slides will demonstrate that for the primary endpoint there was a statistically significant difference in the least square mean of change in the WOMAC A scale from baseline through 26 weeks using Analysis of Covariance (ANCOVA).
- The clinical significance of this change will be a question for the panel.
- There were a number of evaluations of secondary endpoints that were variable in result.
- The panel will be asked a question on the results of secondary endpoints by various methods.

Primary endpoint

WOMAC LK 3.1 A Pain Subscore Overall Change From Baseline: ITT Population (Using a fixed effects model of ANCOVA)

	Baseline Mean (SE)	Overall Mean (SE)	Estimated Change (SE)	Estimated least square mean difference between Synvisc-One and Placebo (SE)	2-sided 95% Confidence Interval for the difference (δ) of two mean changes from baseline	p-value
Synvisc-One (n=124)	2.30 (0.038)	1.43 (0.060)	-0.84 (0.060)	-0.15 (0.076)	-0.3 < δ < -0.002	0.047
Placebo (n=129)	2.25 (0.036)	1.59 (0.058)	-0.69 (0.058)			

Summary of Results

(From the Previous Table)

- The least square mean difference from the baseline between the two groups through 26 weeks on the WOMAC A Scale was 0.15 on a 5-point scale
- The primary endpoint had a p-value of 0.047
- The Panel will be asked questions about the effectiveness of the device based primarily on these two findings.

Introduction of Pre-determined (Applicant's)

Secondary Efficacy Endpoints*:

1. The differences between the treatment and control groups in the WOMAC A subscore from Baseline at the single endpoint of the Week 26.
2. The difference over 26 weeks (repeated measures) and from Baseline to single point Week 26 assessment between the two groups in the following subscores:
 - WOMAC AI
 - WOMAC C
 - PTGA
 - COGA
 - Responder analysis according to the responder criteria of OMERACT-OARSI set

****There was no pre-specified adjustment for Type 1 error, and/or fixed sequence for sequential testing.***

Secondary Effectiveness Endpoints

- **WOMAC A1**
 - walking pain on a flat surface, 5 ordinal categories (0-4)
- **WOMAC C**
 - physical function (17 questions)
- **PTGA**
 - patient global assessment (very well, well, fair, poor, very poor)
- **COGA**
 - clinical observer global assessment (very well, well, fair, poor, very poor)
- **OMERACT-OARSI**
 - Outcome measures in Rheumatology-Osteoarthritis Research Society international; a binary responder/non-responder outcome

WOMAC A at 26 Weeks (Secondary Endpoint)

	Synvisc-One (n=124) baseline	Placebo (n=129) baseline	Synvisc-One (n=124) (SE) change from baseline	Placebo (n=129) (SE) change from baseline	Estimated Difference in (Placebo – Synvisc- One) from baseline	2-sided 95% CI for the difference of two mean changes at 26 weeks from baseline	p-value
WOMAC LK A at 26 weeks	2.25	2.30	76 (0.074)	0.58 (0.073)	-0.18 (0.097)	- 0.372 < δ <0.0109	0.064

Secondary Endpoints

Categorical analyses of Efficacy Endpoints (proportional odds analysis) – PTGA

	Synvisc-One n (%)	Control n (%)	Week 26 Estimate of Odds Ratio (95% CI)	Overall 26 weeks Estimate of Odds Ratio (95% CI)
PTGA	Week 26		0.51 (0.31, 0.82) p = 0.005	0.69 (0.50, 0.96) p = 0.029
Very Well	9 (7.3%)	2 (1.6%)		
Well	33 (26.6%)	27 (20.9%)		
Fair	50 (40.3%)	54 (41.9%)		
Poor	21 (16.9%)	31 (24.0%)		
Very Poor	2 (1.6%)	3 (2.3%)		

Secondary Endpoints

Categorical analyses of Efficacy Endpoints (proportional odds analysis) – COGA

	Synvisc-One N(%)	Placebo N(%)	Week 26 Estimate of Odds ratio (95% CI)	Overall 26 weeks Estimate of Odds ratio (95% CI)
COGA	Week 26			
Very Well	13 (10.5%)	8 (6.2%)	0.56 (0.34, 0.93) p = 0.025	0.71 (0.50, 0.99) p=0.041
Well	37 (29.8%)	31 (24.0%)		
Fair	38 (30.6%)	38 (29.5%)		
Poor	22 (17.7%)	34 (26.4%)		
Very Poor	5 (4.0%)	6 (4.7%)		

Secondary Endpoints

Categorical analyses of Efficacy Endpoints (proportional odds analysis) – WOMAC A1

	Synvisc-One n(%)	Placebo n(%)	Week 26 Estimate of Odds ratio (95% CI)	Overall Weeks 26 Estimate of Odds ratio (95% CI)
WOMAC A1	Week 26			
None	17 (13.7%)	13 (10.1%)	0.56 (0.35, 0.92) p = 0.022	0.64 (0.45, 0.91) p=0.013
Mild	45 (36.3%)	39 (30.2%)		
Moderate	41 (33.1%)	42 (32.6%)		
Severe	11 (8.9%)	19 (14.7%)		
Extreme	1 (0.8%)	4 (3.1%)		

Secondary endpoint

**OMERACT-OARSI over all 26 weeks for the Responder Analysis
as prespecified in the SAP**

OMERACT-OARSI	Week 26		Week 26 Estimate of Odds ratio (95% CI)	Overall Weeks 26 Estimate of Odds ratio (95% CI)
	Synvisc-One	Placebo		
Responder	73 (58.9%)	66 (51.2%)	0.69 (0.41, 1.16) p = 0.156 at 26 weeks	0.66 (0.44, 1.02) p = 0.059 Over all
Non-Responder	50 (40.3%)	63 (48.8%)		
Based on Criteria	43	52		
Due to Withdrawal	7	11		

Secondary Study: Applicant's Repeat Treatment Phase of the Study

- After the completion of safety and effectiveness assessments at the Week 26 visit, patients were offered participation in the Repeat Treatment Phase of the study, which lasted for an additional 4 weeks.
- Study was conducted to monitor only safety after the initial 26 week study.

Secondary Study: Applicant's Repeat Treatment Phase of the Study (continued)

- Second injection of the same dosage of Synvisc One
- Observational Study
- N=77 for Synvisc One – Synvisc One treatment
- N=83 for Placebo - Synvisc One treatment

Adverse Events

Patients in the Repeat Treatment Phase Only

	Synvisc One - Synvisc One (n=77) n (%)	Placebo- Synvisc One (n=83) n (%)
With an AE	9 (11.7)	13 (15.7)
With a Procedure- Related AE	4 (5.2)	7 (8.4)
With a Treatment-Related AE	1 (1.3)	6 (7.2)
With an Injection Procedure-Related “Other” AE and/or a Treatment-Related AE	0	0
With a Serious AE	0	2 (2.4)
Who Died	0	1 (1.2)
With a Target Knee AE	4 (5.2)	7 (8.4)
With an Injection Procedure-Related Target Knee AE and/or a Treatment-Related Target Knee AE	4 (5.2)	7 (8.4)
With a Procedure- Related Target Knee AE	4 (5.2)	7 (8.4)
With a Treatment-Related Target Knee AE	1 (1.3)	6 (7.2)
With a Serious AE in the Target Knee	0	0

Thank You!

**Orthopedic and Rehabilitation Devices Advisory
Panel Meeting (December 9, 2008)**

**Statistical Perspective for PMA P940015/S12,
Synvisc-One, Genzyme Biosurgery**

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FDA/CDRH

Outline

- **Sample Size**
- **Statistical Models (Repeated Measures)**
- **Effectiveness Results (FDA)**
- **Summary**

Sample Size

- **Superiority trial with primary endpoint based on the mean difference in the change from baseline of WOMAC A pain score, Synvisc-One vs. Placebo**
- **Applicant's Assumptions**
 - Two-sided type I error rate = 5%, power = 80%
 - Overall treatment difference (mean change from baseline) = 0.297
 - Common standard deviation = 0.725 (effect size = $0.297/0.725 = 0.41$)
 - Expected dropout rate ~25%
- **N = 93 subjects per group (unadjusted for 25% dropouts)**
- **N=124 subjects per group (adjusted for 25% dropouts)**

Note: Sample size calculation was based on t-test.

Table 1. Sample Size by Country and Site

Country	# Investigators	Synvisc-One	Placebo
UK	5	14	14
France	5	28	29
Czech Republic	4	37	38
Germany	1	9	10
Belgium	4	23	27
The Netherlands	2	12	12
Total	21	123	130

Statistical Models

- **Mixed Models - Repeated-Measures**

- Applicant modeled mean change from baseline over 26 weeks on treatment, site, visit, treatment-by-visit interaction, baseline WOMAC A score (all fixed effects)
- FDA modeled mean pain score over 26 weeks on treatment, visit, treatment-by-visit interaction, baseline WOMAC A score
- (site: random effect)

- **FDA Analysis of Covariance (ANCOVA)**

- Tests null hypothesis (no difference in overall least square means (LSMEANS) in WOMAC A pain score and other WOMAC scores averaged over 26 weeks, between Synvisc-One and Placebo groups)

Criteria for Model Selection

- **PURPOSE**: Find the model which fits best to the observed WOMAC A (and others) data by jointly modeling mean and variance-covariance structure
- Find a better Variance-Covariance structure among repeated measures of visits
 - Residual maximum likelihood, or REML; i.e., Auto-Regressive of order one (AR(1))
- Likelihood ratio (LR) test for comparing full and reduced (nested) models
- Akaike Information Criterion (AIC) or LR for selection of different models (same data set); sufficiently complex to fit data best, but also a parsimonious model

Applicant's Original Analyses

- **ANCOVA on Change from Baseline (CFB), Site: fixed effect**

MODEL: $CFB_{ij} = \beta_1 + \beta_2 \text{Group}_i + \beta_3 \text{Visit}_{ij} + \beta_4 \text{Group}_i \times \text{Visit}_{ij} + \beta_5 \text{Site} + \beta_6 \text{Baseline WOMAC A pain Score}_i + \text{error}_{ij}$ (for Subject i, Visit j)

Statistical Models (Repeated Measures)

- FDA Model: Repeated-Measure Analysis of Covariance (ANCOVA):
 - Model: MEAN pain score (Y_{ij}) over 26 weeks on treatment group, visit, treatment-by-visit interaction, baseline WOMAC A pain score.

$$E(Y_{ij}) = \beta_1 + \beta_2 \text{Group}_i + \beta_3 \text{Visit}_{ij} + \beta_4 \text{Group}_i \times \text{Visit}_{ij} + \beta_5 \text{Baseline WOMAC A pain Score}_i + e_{ij}$$

(β_1 = intercept , e_{ij} = error term)

The above parameters (β_1, \dots, β_5) are estimated by generalized least squares (SAS PROC MIXED software)

Different Questions Answered by Change from Baseline vs. ANCOVA on Mean

- Change from Baseline (Applicant: either in randomized or observational study):
 - Are the profiles of the average change over all visits equal between the two groups?
- ANCOVA on Mean (FDA: appropriate for randomized trial):
 - What's the expected true treatment effect on means over all visits given that each subject has the same baseline value? (assume that population distributions of baseline values are equal between groups)

Comparison of Models: Applicant versus FDA

- The ANCOVA Model on means over 26 weeks (FDA) always has smaller variance of treatment difference (more efficient or more powerful) than that of mean Change From Baseline (CFB) model (Applicant), except when correlation between repeated visits reaches 1.0 (very rare!).
 - The relative efficiency, $[\text{Var}(\text{ANCOVA})/\text{Var}(\text{CFB})] = (1+\rho)/2$ (if # post-treatment visits = 1, compound symmetry correlation among visits).
 - General case: depends on the number of repeated visits and correlation.
- With the FDA model, the treatment effect, averaged over all 26 weeks and at each visit, is measured by the difference in the estimated least square means (LSMEANS) between the two groups, a more powerful approach.
- However, no matter what the model, testing the null hypothesis of ZERO difference (superiority test) does not guarantee a clinically meaningful difference.

Table 2. FDA ANCOVA for Primary Endpoint on Mean Results (ITT, Over 26 weeks, Site Random; Same Covariates, AR(1) Correlation)

Outcome	LSMEANS (Synvisc-1)	LSMEANS (Placebo)	Difference (S – P)	SE (Diff.)	2-Sided 95% CI	p- value
WOMAC A: (<u>Primary</u> pain score)	1.40	1.55	-0.15	0.072	(-0.30, -0 .013)	0.032

**Table 3. FDA’s Analysis for Primary Endpoint of Observed and Fitted Mean WOMAC A Pain Scores
(Repeated-Measures Mixed Model, Random Site, ITT Population, over all 26 Weeks)**

Week	Synvisc-1 Observed MEANS (O)	Synvisc-1 Fitted (F) LSMEANS	Synvisc-1 Residual (O – F)	Placebo Observed Means (O)	Placebo Fitted (F) LSMEANS	Placebo Residual (O – F)
Baseline	2.30 (N=124)	-	-	2.25 (N=129)	-	
4	1.45 (N=119)	1.48	-0.03	1.54 (N=128)	1.58	-0.04
8	1.32 (N=121)	1.35	-0.03	1.44 (N=126)	1.49	-0.05
12	1.33 (N=117)	1.38	-0.05	1.48 (N=123)	1.55	-0.07
18	1.22 (N=114)	1.30	-0.08	1.41 (N=121)	1.48	-0.07
26	1.41 (N=115)	1.47	-0.06	1.58 (N=117)	1.65	-0.07

**Table 4. FDA ANCOVA For Secondary Endpoints on Mean Results
(ITT, Over 26 weeks, Site Random; Same Covariates, AR(1)
Correlation)**

Outcome	LSMEANS (Synvisc-1)	LSMEANS (Placebo)	Difference (S – P)	SE (Diff.)	2-Sided 95% CI	p- value
WOMAC A1: (Walking pain)	1.44	1.63	-0.19	0.078	(-0.34, -0.03)	0.017
PTGA: (Patient global assessment)	1.77	1.90	-0.13	0.070	(-0.27, 0.007)	0.06
COGA: (Clinical global assessment)	1.78	1.91	-0.13	0.076	(-0.28, 0.02)	0.09
WOMAC C: (physical function)	1.58	1.61	-0.03	0.074	(-0.18, 0.11)	0.65

Secondary Effectiveness Endpoint Issues **(WOMAC A1, WOMAC C, PTGA, COGA, OMERACT-OARSI)**

- **In original submission, the Applicant prepared a different approach for each endpoint:**
 - **MIXED model for change from baseline**
 - **WOMAC C**
 - **Proportional Odds Model**
 - **cumulative logit for other 3 secondary endpoints (WOMAC A1, PTGA, COGA)**
 - **Binary analysis for OMERACT-OARSI**
 - **non-significant Odds Ratio = 0.66 overall, p=0.059**

Secondary Effectiveness Endpoint Issues

(cont'd)

- **At FDA's request, the Applicant prepared a MIXED model on change from baseline for WOMAC A1, PTGA, COGA**
 - **Only WOMAC A1 was statistically significant**
 - **p = 0.029 (Applicant: on Mean change from baseline)**
 - **p = 0.017 (FDA: On mean score over 26 weeks)**
- **For proportional odds model, the Applicant provided graphical results for PTGA, COGA and WOMAC A1, by various cutoff points, to show validity of proportional odds model.**
- **It appears that no existing computer software is available to test proportionality or parallelism assumption of slopes from different cutoff points.**

Comments on the Applicant's Generalized Estimating Equation (GEE) Model based on Proportional Odds Assumption,

- Let $Y_j = \Pr(Y \leq j | \underline{X})$, the j th cumulative response (Y_j) probability given a set of covariates \underline{X} (Group, site, visit, visit*Group, baseline).
- **By Logistic Regression** (for p covariates):
 - $\text{Logit}(Y_j) = \text{Log}[P(Y \leq j)/P(Y > j)] = \alpha_j + \beta_1 x_1 + \dots + \beta_p x_p$
 - $j = 0$ (no pain), 1 (mild), 2 (moderate), 3 (severe), 4 (extreme);
 $x_1 = \text{Treatment Group}$
 $\beta_1 = \text{Regression coefficient for Group}$
- **Odds Ratio (OR) = e^{β_1}** ($\text{Log}_e \text{OR} = \beta_1$)

- **Question to ask: Are slopes parallel?**
Does $\beta_1 = \beta$? [i.e., Does cutoff point (j) matter?]
- **Applicant's Response:** Graphical visual inspection of Odds Ratios and their 95% confidence intervals from different cutoff points (j=0,1,2,3,4) shows overlapping of 95% CIs (i.e., Applicant believes cutoff does not matter).
- **Problem:** No formal hypothesis testing. Most 95% CIs contain unity, for COGA, PTGA, WOMAC A1.

Figure 1. Applicant's Justification of Proportional Odds Model

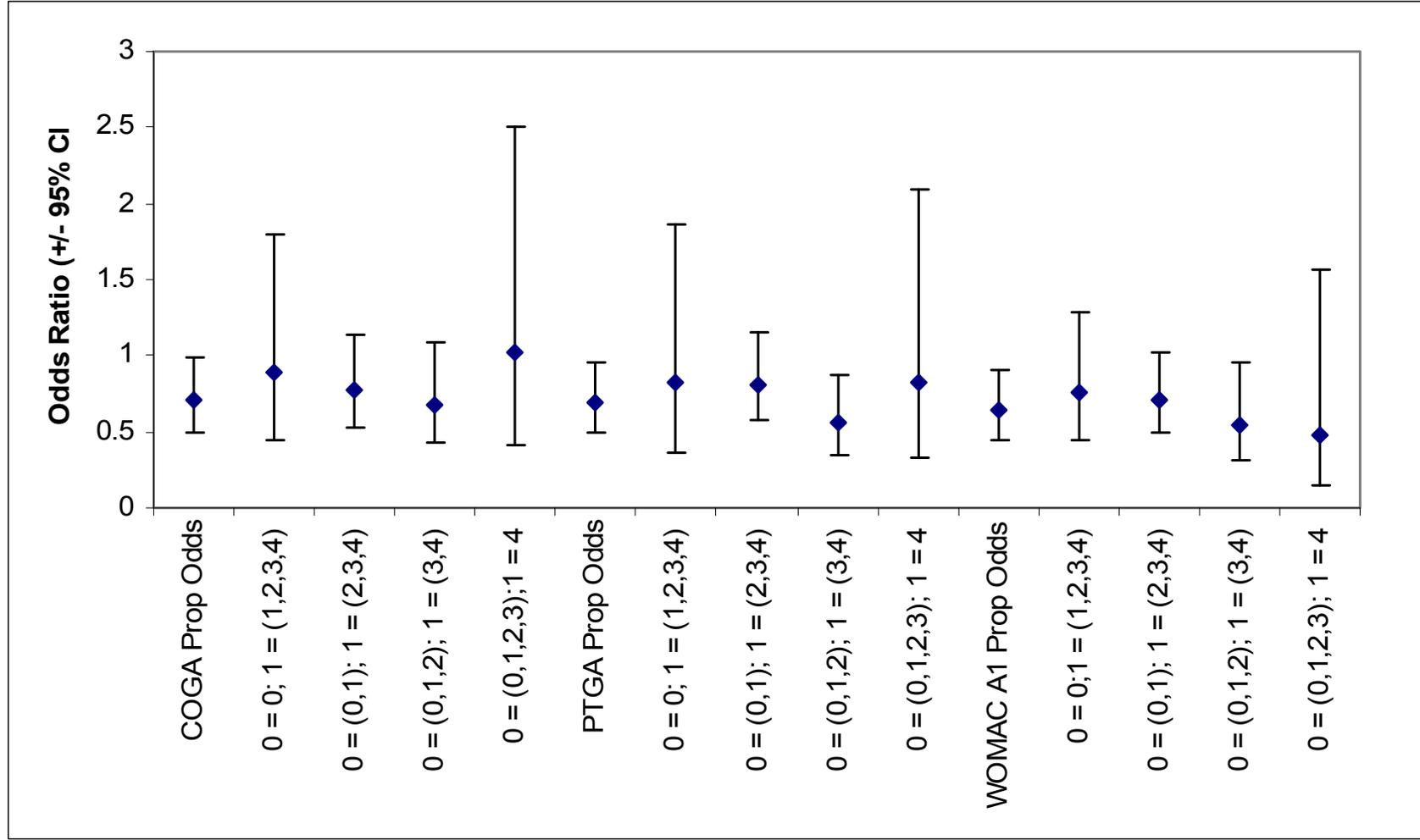


Table 5. Summary of Statistical Significance Testing Over 26 Weeks (Synvisc-One vs Placebo) As Reported by Applicant and FDA, ITT)

	Applicant (Mixed Model on Change from Baseline; Site Fixed)	Applicant's Original (Proportional Odds: GEE Model)	FDA (Mixed Model ANCOVA on Least Square Means; Site: Random)
Primary Endpoint:			
WOMAC A	Yes (p= 0.047)	N/A	Yes (p=0.032)
Secondary Endpoints: (no multiplicity adjustment)	(*) = FDA Requested		
WOMAC A1	Yes (p = 0.03)*	Yes (p = 0.013)	Yes (0.017)
PTGA	No (p = 0.10)*	Yes (p=0.029)	No (p=0.06)
COGA	No (p =0.10)*	Yes (p=0.041)	No (p=0.09)
WOMAC C	No (p=0.68)	N/A	No (p=0.65)
OMERACT-OARSI	Binary Responder Analysis – Odds Ratio not significant (p=0.059, Applicant)		

Summary

- **Primary WOMAC A Pain Score:**
 - Tx difference (Synvisc-One – Placebo) = -0.15
 - Applicant and FDA agree statistically significant
 - Is it clinically significant? (panel question)
- **Secondary Endpoints**
 - **WOMAC A1 (ANCOVA):**
 - Tx difference (Synvisc-One–Placebo) = -0.19
 - Applicant and FDA agree statistically significant
 - No multiplicity adjustment
 - **PTGA, COGA not significant by ANCOVA Model**
 - **PTGA, COGA , WOMAC A1 (Proportional Odds)**
 - All 3 significant by Applicant's proportional odds model
 - No multiplicity adjustment (panel question)

Thank You!

Post-Approval Study Considerations Synvisc-One Genzyme Biosurgery, Inc.

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Office of Surveillance and Biometrics / CDRH

Orthopaedic and Rehabilitation Devices Panel

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Reminder

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.
- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

General Principles for PAS

- Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable device safety and effectiveness.
- Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

Need for Post-Approval Studies

- Gather postmarket information
 - Longer-term performance
 - Community performance
 - Effectiveness of training programs
 - Sub-group performance
 - Rare adverse events and real world experience
- Account for Panel recommendations

Issues for PAS Consideration

- The clinical study supporting this PMA supplement was solely conducted in Europe; study has shown that patient's characteristics may be associated with the treatment effects of the device ¹.

Kemper F, et al. Curr Med Res Opin. 2005; 21(8): 1261-9

Issues for PAS Consideration

- The follow-up of this PMA study was 26 weeks for initial phase and 4 additional weeks for repeat phase, while intra-articular injection of similar devices has demonstrated the treatment effects extended to 12 month after the injection ².

Clarke S, et al. Knee. 2005; 12(1): 57-62

Issues for PAS Consideration

- Literature suggested that cross-linked hylan G-F 20 used by Synvisc may be associated with increased risk of severe acute inflammatory reaction, the exact mechanism and long-term consequences of which remain unclear³.

Goldberg VM, Coutts RD, Clin Orthop 2004; (419):130-7

Issues for Panel Discussion

- Please comment on the need to evaluate the device in US population in a post-approval study (PAS).
- If a PAS is recommended, please discuss:
 - the objectives
 - clinical endpoints
 - study size
 - comparison group
 - duration of follow -up of study subjects
 - other specific issues that you would like to be addressed in PAS