

The logo for 'flexion' features the word in a lowercase, sans-serif font. The 'x' is stylized with three green dots connected by thin grey lines, forming a path that starts at the bottom left of the 'x', goes up and right to the top of the 'x', then down and right to the top of the 'i', and finally down and left to the top of the 'o'.

flexion

*Transformative Medicine...*

*Where It Matters*

# Safe-Harbor Statement

This presentation contains “forward-looking” statements, including, without limitation, statements relating to: the future of Flexion; the ongoing development of our product candidates; our interpretation of the results of our clinical trials for Zilretta™; our plans to commercialize, and the market potential for, Zilretta; our plans and expected timing for our regulatory submissions; our anticipated clinical, regulatory and other milestones (including the timing of such milestones); and the potential benefits and commercial potential of Zilretta. Forward-looking statements also include all statements that are not historical facts.

Forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by such forward-looking statements. These risks and uncertainties include, without limitation, those associated with the process of developing, obtaining regulatory approval for, and commercializing pharmaceutical products; our ability to finance continued operations; competition in our target markets; the fact that results of past clinical trials may not be predictive of subsequent trials; the risk that the FDA and foreign regulatory authorities may not agree with our interpretation of the data from our clinical trials of Zilretta and may require us to conduct additional clinical trials; our reliance on third parties to manufacture our product candidates and conduct our clinical trials, which could delay or limit the future development or regulatory approval of our product candidates; the fact that we will require additional capital, including prior to commercializing Zilretta or any of our other product candidates, and may be unable to obtain such additional capital in sufficient amounts or on terms acceptable to us; the risk that our patents may be challenged or invalidated; and other risks and uncertainties described in our filings with the Securities and Exchange Commission (SEC), including under the heading "Risk Factors" in our most recent Annual Report on Form 10-K and subsequent filings with the SEC. These forward-looking statements represent our beliefs and assumptions only as of the date of this presentation, and we assume no obligation to update or revise any of these statements. We caution investors not to place considerable reliance on these forward-looking statements.

# Flexion: Investment Highlights

## Novel, Targeted Therapeutics – Initial Focus Osteoarthritis

- Designed to achieve effective concentrations locally and minimize systemic exposures
- Lead product candidate Zilretta (also known as FX006): potential first sustained release, intra-articular, non-opioid treatment for moderate to severe OA pain
- Patent protection into 2031

## Zilretta: Phase 3 Asset with Strong Efficacy and Safety Data

- Clinical results suggest rapid, powerful, durable pain relief that differentiates from standard of care (SOC)
  - Supports premium pricing
- Clinical trial data demonstrate adverse event profile comparable to placebo and SOC
- Facilitated 505(b)(2) regulatory pathway with FDA Fast Track designation

## Large, Growing, Unsatisfied Market

- ~27M in the U.S. have OA pain
  - ~12M see their MD for knee OA pain annually and ~5M of these receive IA injections
  - HA market approximately \$700M- \$800M
- Progressive disease: 50% with knee OA ultimately require total joint replacement

## Near Term Value Inflection Points

- Key milestones for Zilretta in 2016
  - Report Phase 3 topline data (February, 2016)
  - Initiate trial in OA knee patients with Type 2 Diabetes (Q2)
  - Hold pre-NDA meeting with FDA (Q2)
  - Report topline data from Diabetes trial (H2)
  - Initiate repeat-dose safety trial (H2)
  - Submit NDA (H2)

# Current OA Therapies: All Provide Inadequate Pain Relief and Many are Associated with Serious Side Effects

	TYPE	EFFICACY	TOXICITY
ORAL:	Acetaminophen	Limited pain relief	Liver/GI
	NSAIDs	Limited pain relief	GI/Cardiovascular
	COX II inhibitors	Limited pain relief	Cardiovascular
	Duloxetine	Limited pain relief	Suicidality/Liver
	Opioids	Limited pain relief	Addiction Fracture (elderly) Cardiovascular Mortality
INTRA-ARTICULAR (joint injection)	Steroids	Effect wanes after 2 – 4 weeks	Generally well tolerated
	Hyaluronic acid (HA)	Barely separates from placebo in controlled clinical trials	Generally well tolerated
		<ul style="list-style-type: none"> <li>American Academy of Orthopedic Surgeons guidelines (2013): “cannot recommend using HA” for “lack of efficacy”<sup>1</sup></li> </ul>	

# Zilretta: Potential First Sustained Release IA Treatment for OA of Knee

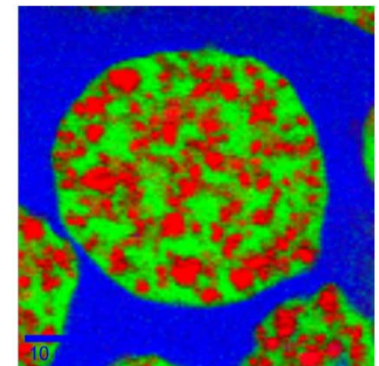
## Extending the potential of an established therapy

- Immediate Release (IR) IA steroids are effective, but short lived
  - Majority of injected drug has left joint in 3 – 5 days
  - Pain relief wanes after 2 – 4 weeks
  - Steroids are not injected more often than every 3 months
- Injection is straightforward and fast, ~1 minute start to finish
- Typically performed by physician assistants, no imaging



## Zilretta is designed to provide sustained release of Triamcinolone Acetonide (TCA) from PLGA<sup>1</sup> microspheres for at least 3 months

- Lower plasma exposures
  - Potentially reduce systemic issues seen with current standard of care immediate-release TCA
    - For example: hyperglycemia in diabetic patients
  - Value proposition: same procedure, same drug, same dose; just formulated for better, longer pain relief



Zilretta microsphere  
(45 micron diameter)

<sup>1</sup>PLGA: poly(lactic-co-glycolic acid)

# Phase 3 Study Design

## Ph 3 Pivotal Study (n= 486)

5ml IA single-dose knee injection

Location: International, US

- 161 OA patients on Zilretta (40mg)
- 162 OA patients on TCA-IR (40mg)
- 163 OA patients on Placebo (saline)

Zilretta 40mg (161)	TCA-IR 40mg (162)	Placebo Saline (163)
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### Study Objective

- Determine if Zilretta (40mg) is safe, well-tolerated, & demonstrates superiority to placebo in magnitude of pain relief at 12 weeks

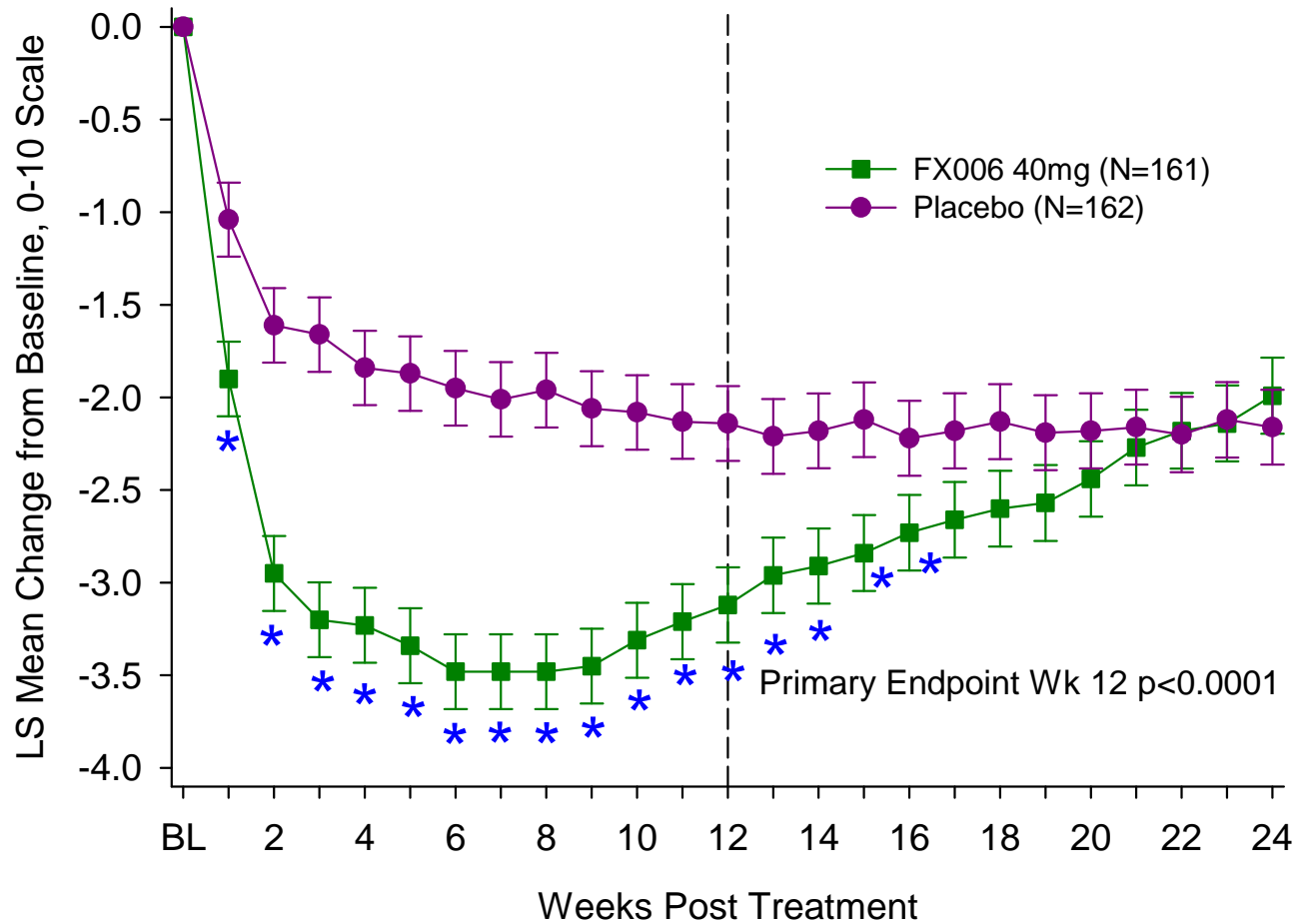
## Pain measured on 0 – 10 Numeric Rating Scale

- 0 = no pain; 10 = pain as bad as you can imagine
- Baseline index knee pain between 5 and 9
- Primary outcome measure - weekly mean of average daily pain (ADP) intensity score
- Primary endpoint: 12 week landmark analysis vs. placebo
- Patients will be evaluated for a total of 24 weeks

## Secondary outcome measures

- AUE at 12 and 24 weeks
- WOMAC A (pain), B (stiffness), C (function)
- KOOS quality of life
- Time to onset of pain relief
- Responder status
- Patient and clinical global impression of change
- Rescue medication consumption

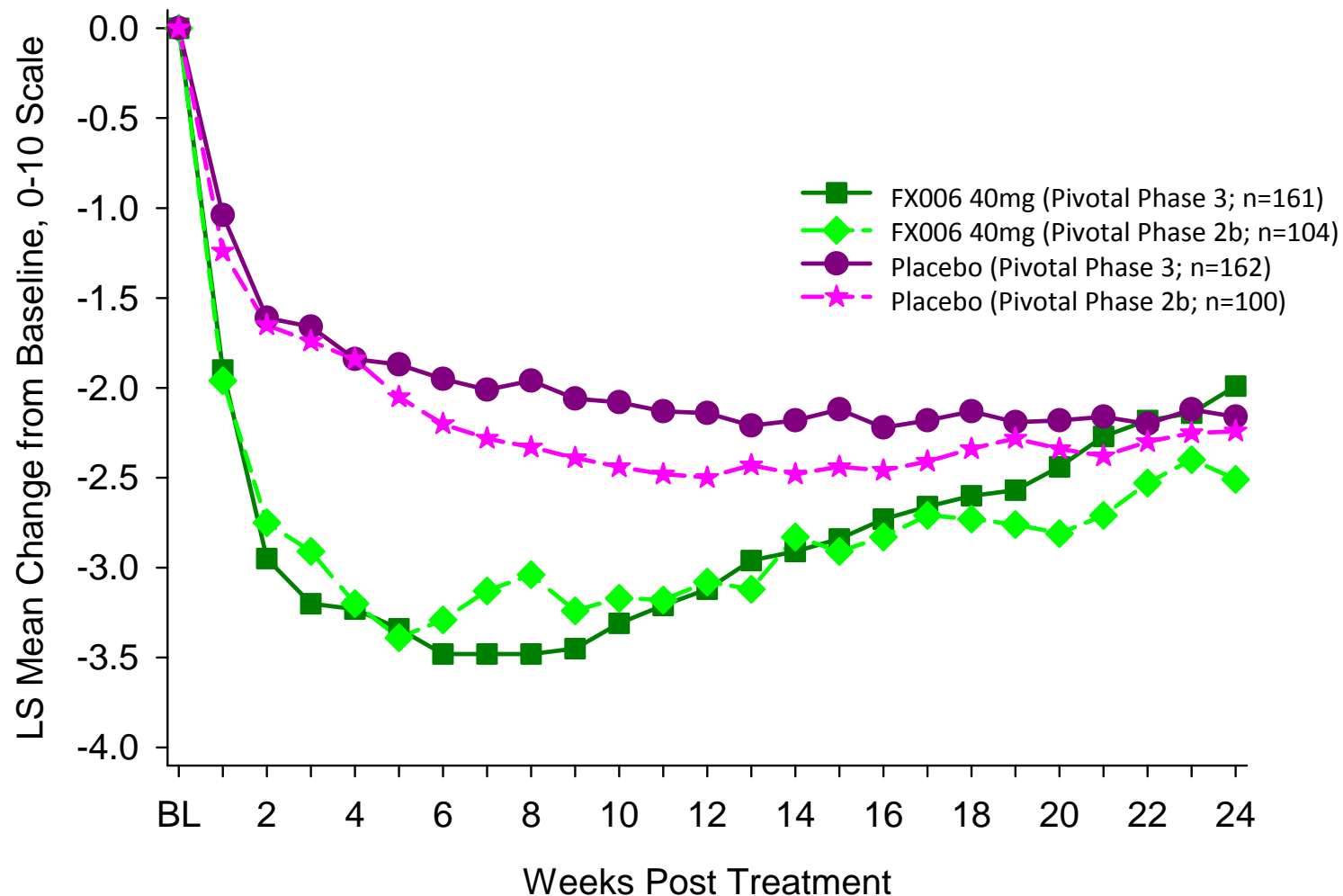
# Phase 3 Data Suggest Rapid, Powerful and Durable Pain Relief



\* p<0.05 Difference from Placebo



# Effect Consistent Across Both Pivotal Clinical Trials



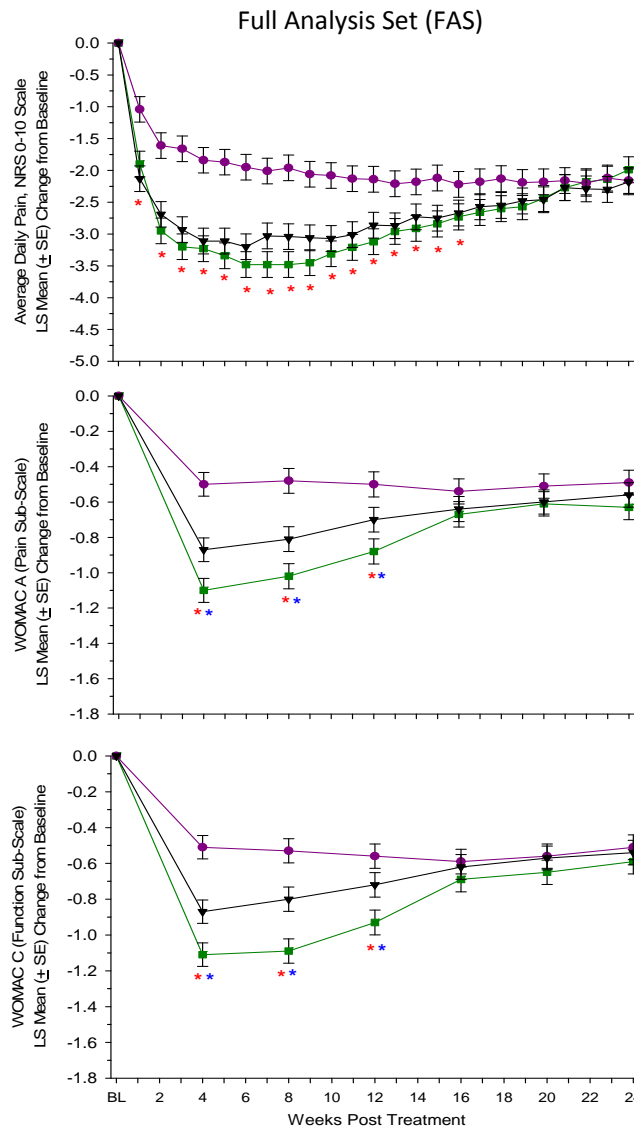


# Phase 3 Efficacy Results Demonstrate Advantages over TCA-IR



# Phase 3 Data Demonstrating Advantage Over TCA-IR: ADP and WOMAC

Weekly Mean Avg. Daily Pain



\*p<0.05, 2-sided FX006 vs. placebo  
 \*p<0.05, 2-sided FX006 vs. TCA

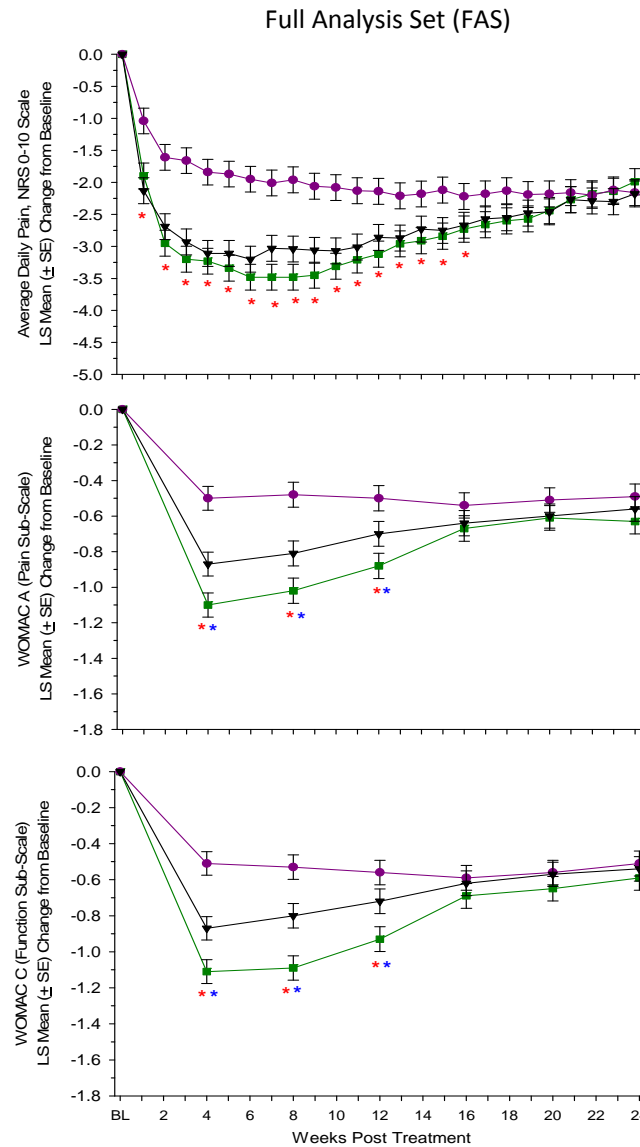


## Further Understanding the Phase 3 Data

- **Patients with bilateral knee pain were eligible for the study if the pain in the contralateral knee was less than that in the study knee**
- **Given that treatment was applied unilaterally it is reasonable to expect that patients with unilateral knee pain might experience better pain relief**
  - Patients with bilateral knee pain could have their perceptions of pain relief confounded by ongoing/worsening pain in the contralateral knee
- **There is precedent for IA studies demonstrating enhanced pain relief in patients with unilateral knee pain**

# Phase 3 Data Demonstrating Advantage Over TCA-IR : ADP and WOMAC

Weekly Mean Avg. Daily Pain

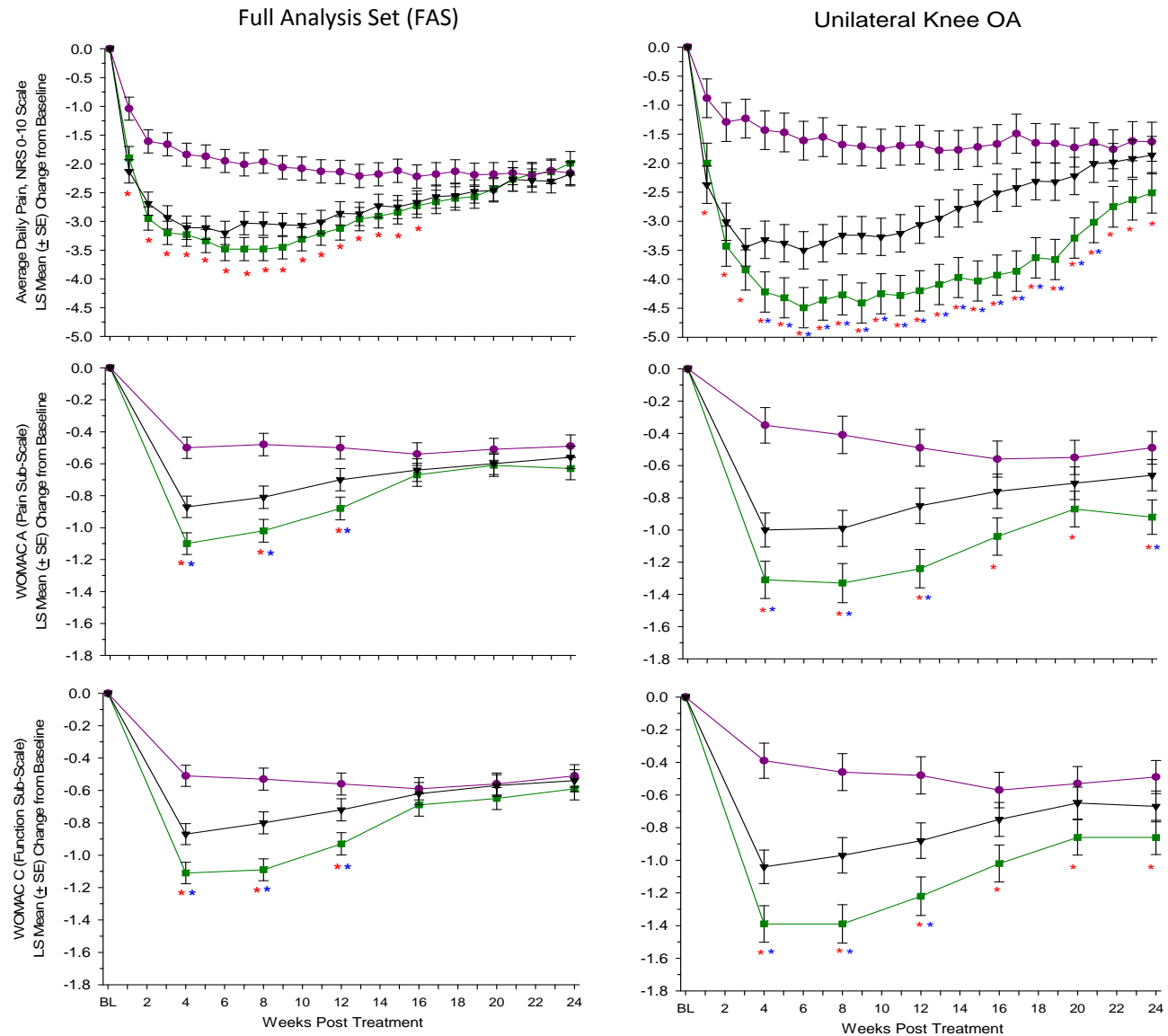


Unilateral Knee OA

WOMAC A (Pain)

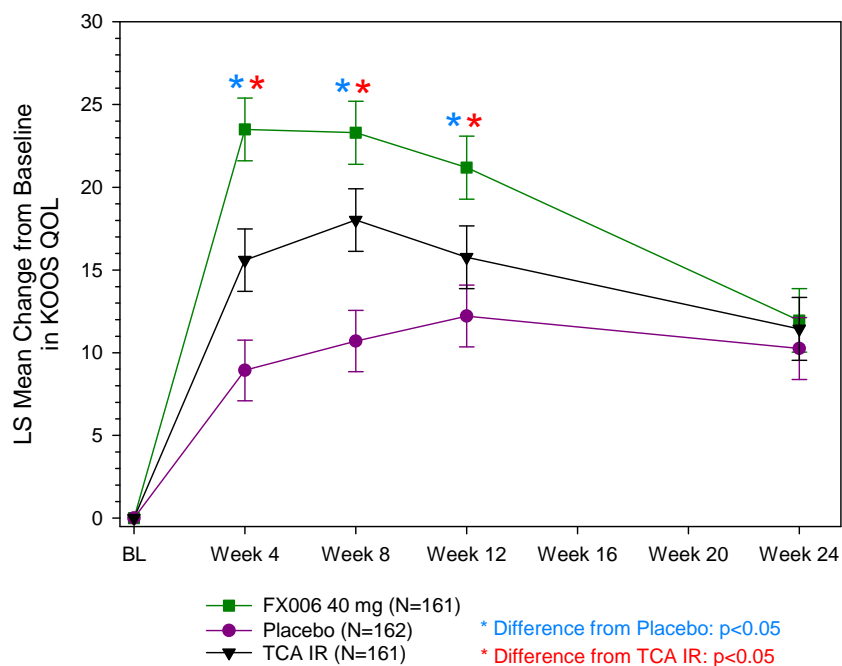
WOMAC C (Function)

\*p<0.05, 2-sided FX006 vs. placebo  
\*p<0.05, 2-sided FX006 vs. TCA

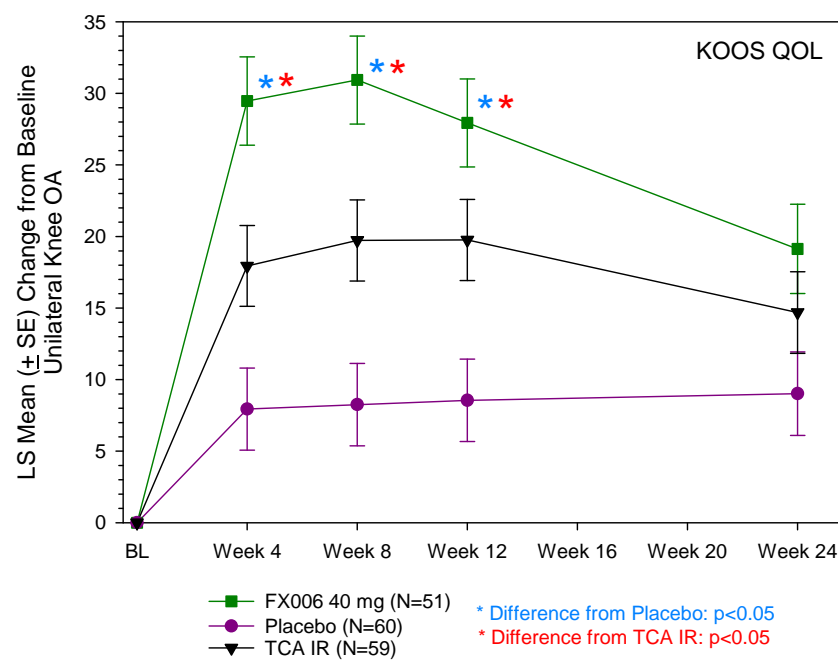


# Phase 3 Data Demonstrating Advantage Over TCA-IR: KOOS QoL

## Full Analysis Set



## Unilateral Knee OA



# Determining Clinical Relevance of OA Therapies

## American Academy of Orthopedic Surgeons (AAOS) Review of OA Therapies

- In 2013, the AAOS conducted and published an extensive review<sup>1</sup> of available OA therapies with the purpose of defining therapeutic value
- In addition to statistical differentiation relative to placebo, AAOS established the Minimal Clinically Important Improvement (MCII) measure
- MCII specifies a minimal magnitude of effect relative to placebo that constitutes a clinically important effect

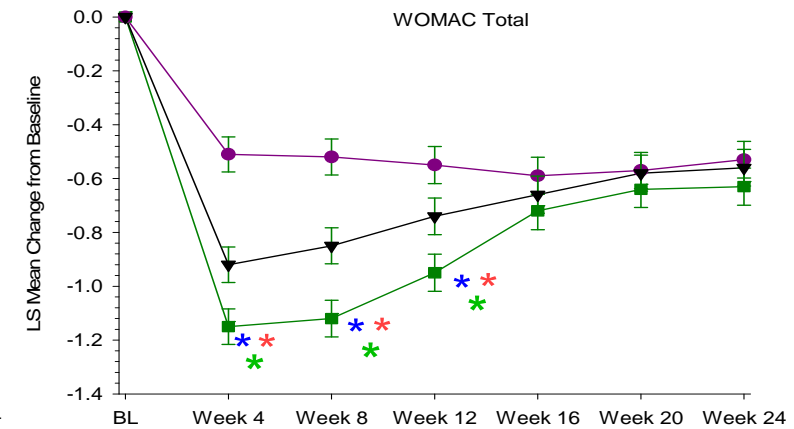
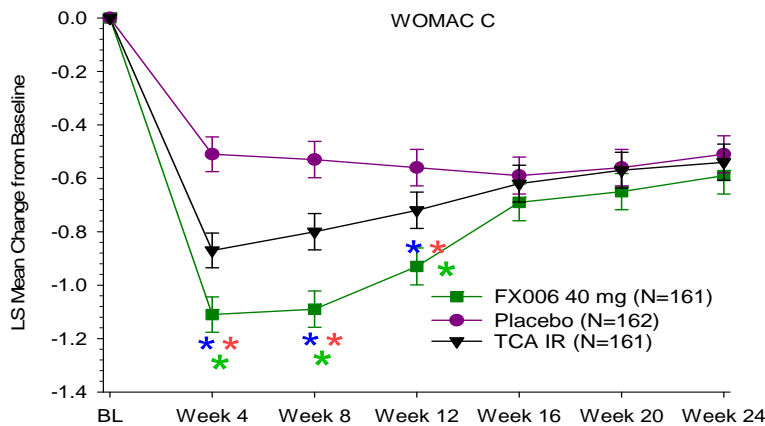
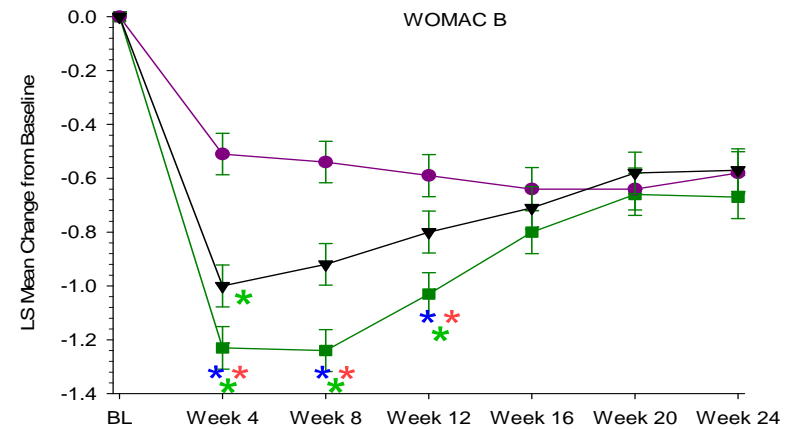
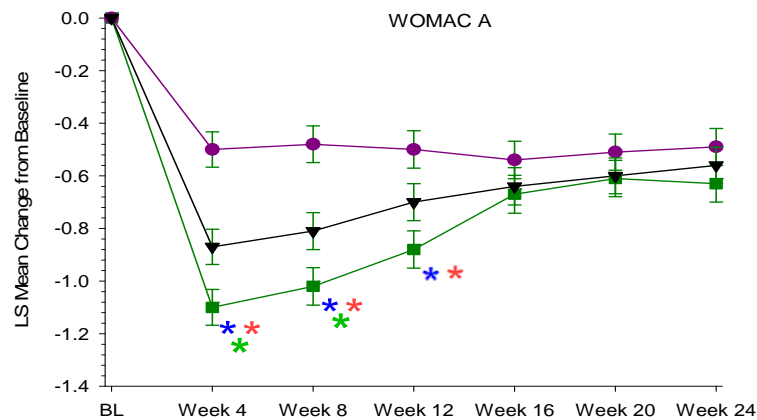
**“The MCII reflects the smallest clinical change that is important to patients and recognizes that there are some treatment-related statistically significant improvements that are too small to be relevant. “**

- These are the criteria that they used:

Outcome	WOMAC VAS MCII (scale 0 to 100mm)	WOMAC likert MCII
WOMAC pain	8.3mm (0 to 100mm scale)	1.66 (on 0 to 20 scale)
WOMAC physical function	8mm (0 to 100mm scale)	5.44 (on 0 to 68 scale)
WOMAC stiffness	10mm (0 to 100mm scale)	.8 (on 0 to 8 scale)
WOMAC total	8.2mm (0 to 100mm scale)	7.9 (on 0 to 96 scale)

- By these criteria, the AAOS determined:
  - HA’s were ineffective (“...lack of efficacy...”)
  - IA corticosteroids could not be assessed as effective or ineffective – the data were equivocal

# In Phase 3 FX006 Consistently Exceeds MCII – TCA IR Does Not



\* p<0.05 Difference from Placebo \* p<0.05 Difference from TCA IR  
 \* Meets AAOS Minimal Clinically Important Effect (MCII) Criteria



## Adverse Event Profile Comparable to Placebo and TCA-IR - Combined Phase 2b and Phase 3 Data

<b>TEAE [N (%)]</b>	<b>FX006 20 mg (N=102)</b>	<b>FX006 40 mg (N=265)</b>	<b>Placebo (N=262)</b>	<b>TCA (N=161)</b>
TEAEs	43 (42.2%)	135 (50.9%)	129 (49.2%)	91 (56.5%)
SAEs	1 (1.0%)	8 (3.0%)	3 (1.1%)	4 (2.5%)
Index Knee-related TEAEs	15 (14.7%)	44 (16.6%)	37 (14.1%)	16 (9.9%)
TEAEs Related to Injection Procedure	2 (2.0%)	5 (1.9%)	11 (4.2%)	3 (1.9%)

- SAEs: No deaths; all SAEs assessed as ‘unrelated to study drug’
- Lab assessments and vital signs were unremarkable and similar across groups

## Overall Adverse Event Profile Comparable to Placebo and TCA-IR

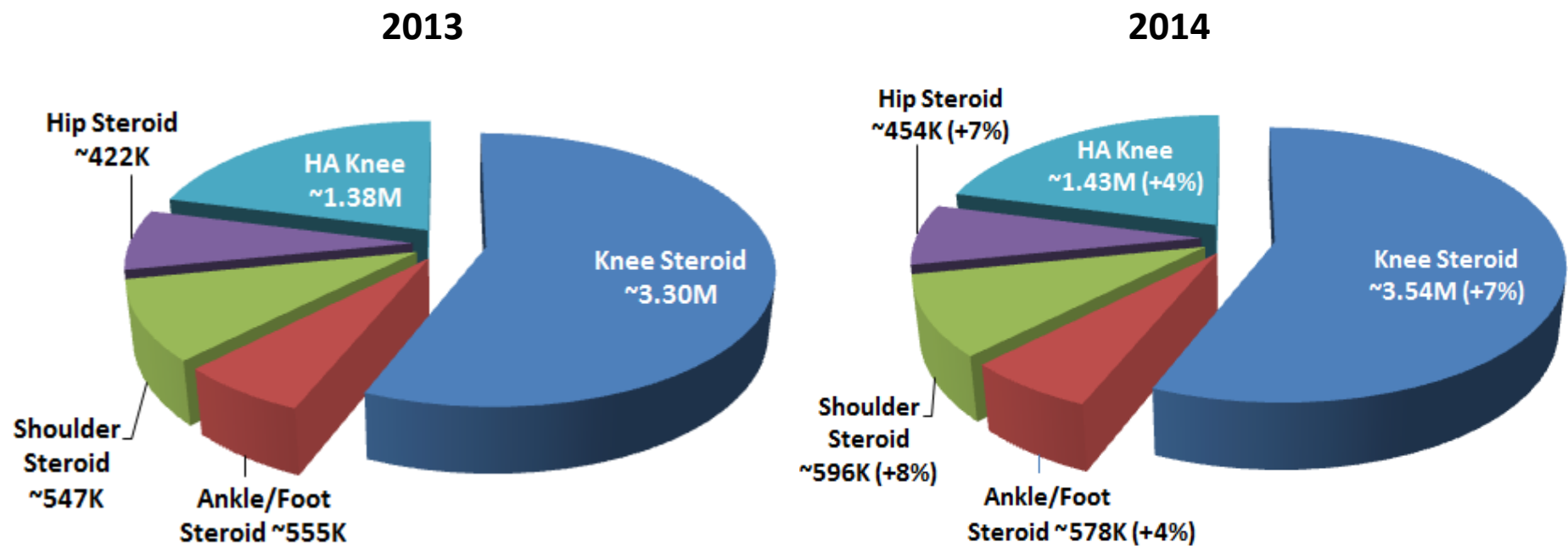
More than 600 clinical trial patients treated with Zilretta to date

- No drug related serious adverse events
- No clinically significant dose-related trends in incidence of overall adverse events or index knee related adverse events
- No remarkable changes in laboratory parameters, vital signs, or ECG parameters

# Zilretta: Large Commercial Opportunity in OA

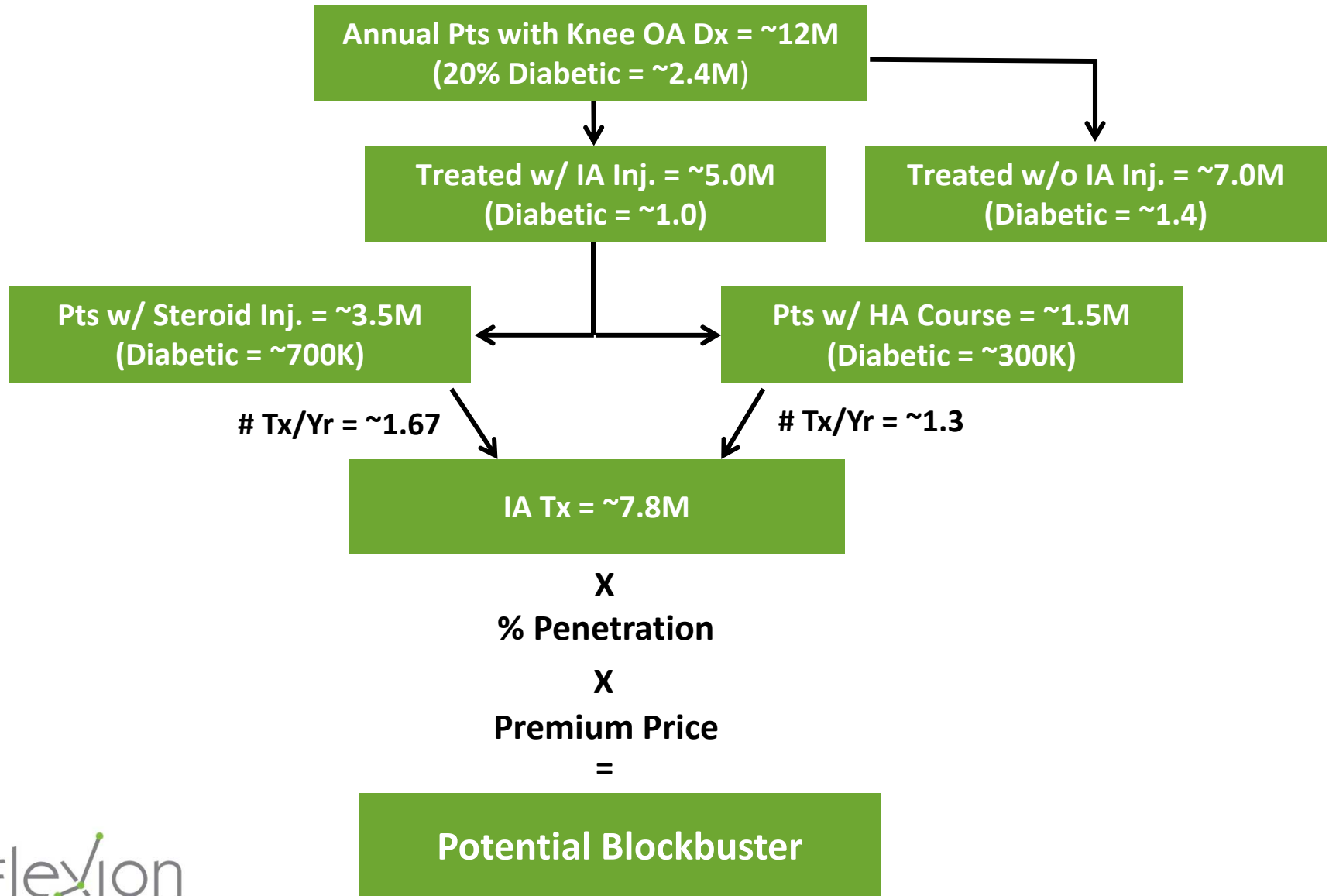
## Many OA patients receive IA injections annually

- ~7% YoY growth of OA knee steroid injections (vs. ~4% YoY growth in HA)
- ~7.5% YoY growth in other joint steroid injections (hip, shoulder, foot, ankle)



2013 & 2014 IMS Sales & Claims Data (85 health plans, 70MM patients, ~40% of total medical claims)

# Zilretta's™ Blockbuster Potential in OA of the Knee



# Pricing Research and Costs of Commonly Used OA Treatments

## Pricing Research Summary

- Seven studies, with six different independent research firms, spanning 2012-2015
- Conservatively represent >100M covered lives
- All assessments support a price in the range of \$500/dose

## Commonly Used OA Treatments

Class	Selected Products	Monthly Cost	3 Month Cost	Annual Cost
NSAIDs <sup>1,2</sup>	Celecoxib (200mg q.d.)	\$221.99	\$665.97	\$2,663.88
SNRIs <sup>1,2</sup>	Duloxetine (30mg q.d.)	\$215.37	\$646.11	\$2,584.44
HA Injections <sup>1,3</sup>	Synvisc/Synvisc-One (3/1 injection(s)/6 months)	\$96.98	\$575.86 (6mo)	\$1,151.72
	Monovisc (1 injection/6 months)	\$151.54	\$909.25 (6mo)	\$1,818.50
Opioids <sup>1,2</sup>	Oxycontin ER (10mg q 12h)	\$219.99	\$659.97	\$2,639.88

### References:

1. Dosing schedule for products as per package inserts
2. NSAID, SNRI, and Opioid pricing reflects suggested retail price as per CVS Pharmacy 3/2016
3. HA pricing reflects manufacturer reported Average Selling Price (ASP) across all distribution channels as per CMS.gov 10/2015

## Keys to Successful Commercial Launch of Zilretta™

- **Build on a foundation of successful Synvisc commercialization**
- **Focus on compelling, clinically relevant product attributes**
- **Command premium price**
- **Drive adoption through experienced, dedicated sales force**
  - 60 – 110 reps targeting the 9,000 orthopedists/rheumatologists = > 75% of injections
- **Apply deep insight into all relevant stakeholders**
- **Provide world-class customer support**
  - Reimbursement, office support

## Proven Management Team

- **Michael Clayman MD, President & Chief Executive Officer-** 20+ yrs of pharma exp.  
Eli Lilly, Advanced Cardiovascular Systems, Chorus
- **Neil Bodick MD PhD, Chief Medical Officer-** 15+ yrs of pharma development  
Eli Lilly, Chorus
- **Fred Driscoll, Chief Financial Officer-** 35+ yrs of pharma/financial experience  
Novavax, Genelabs, OXiGENE, Instrumentation Laboratory
- **Dan Deardorf, SVP Commercial-** 20 yrs of commercial biopharmaceutical experience  
Genzyme (BioSurgery Division)- Led the successful launch of Synvisc-One



# Flexion Financial Position

Cash 12/31/15    \$119 million    Total Shares Outstanding    21.5 million



CAPITAL WORLD  
INVESTORS



BLACKROCK



KINGDON



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