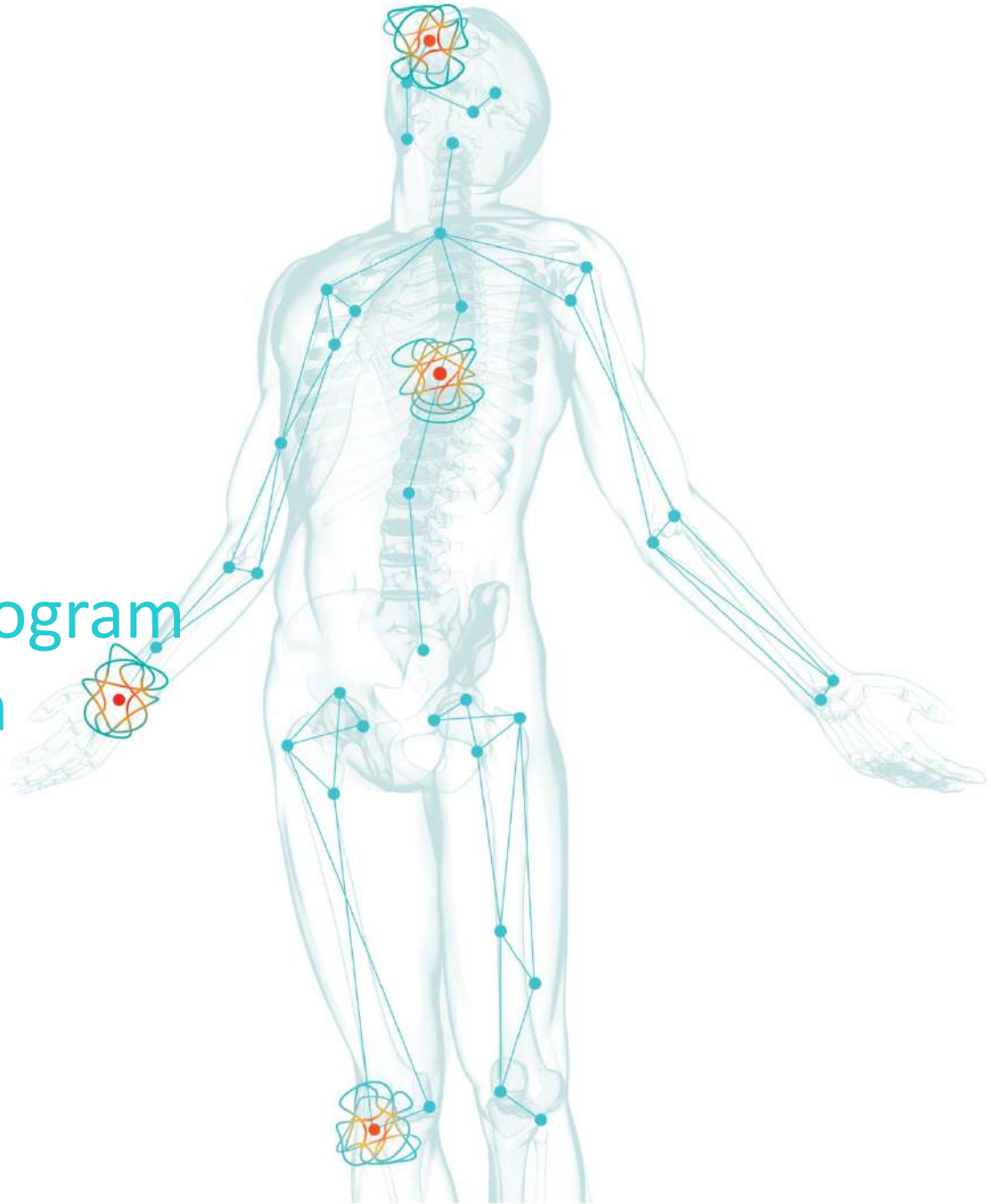
Knee OA/BMEL Expanded Access Program Results Presentation



30th July 2020

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Osteoarthritis with Bone Marrow Edema Lesions

Osteoarthritis – Facts and Figures

- **Most common form of joint disease** and **the leading cause of disability** for people greater than 65 years of age[1]
- **OA is a progressive disease strongly correlated with bone marrow edema lesions,** affecting the entire joint, including synovial inflammation, cartilage loss and bone remodelling
- **Blockbuster market** – 31m Americans have been diagnosed with OA - ~10% of the total population[2]
- **Significant cost –** OA currently costs the US economy ~US128+ billion per annum[3]
- **Growing crisis –** Due to an aging population and high obesity rates the number of OA sufferers in the US is expected to exceed 67m (116% growth) by 2030[3]
- **Current Treatments -** are for symptomatic pain relief and may offer limited chronic pain relief, but also have many untoward effects
  - 81% of OA patients dissatisfied with current treatments[3]
- **Opioid Epidemic –** The US and Australia are experiencing unprecedented opioid addiction and overdoses. Opioid use for osteoarthritis pain is no longer recommended due to addition risks and minimal efficacy. Effective and well-tolerated non-opioid pain treatment for osteoarthritis represents and unmet medical need in the US and abroad.

Osteoarthritis is the last frontier of blockbuster diseases with unmet need

1.Neogi T. (2013). The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis and cartilage*, *21*(9), 1145-53.2. http://ard.bmj.com/content/annrheumdis/early/2017/07/12/annrheumdis-2017-211396.full.pdf
3. National Institute of Health; Emerging drugs for osteoarthritis; Hunter DJ and Matthews G 16(3): 479–491; 2011 September. 4. Neogi T. (2013). The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis and cartilage*, *21*(9), 1145-53.

Prevalence of osteoarthritis in retired NFL Players

Golightly et al Journal of Physical Activity and Health, 2009, 6, 638-643

- Self-reported arthritis prevalence and retrospectively- recalled injury history were examined in a cross-sectional survey of 2,538 retired football players.
- Football players reported a high incidence of injury from their professional playing days (52.8% reported knee injuries, 74.1% reported ligament/tendon injuries, and 14.2% reported anterior cruciate ligament tears).
- For those under 60 years, 40.6% of retired NFL players reported arthritis, compared with 11.7% of U.S. males (prevalence ratio =3.5, 95%CI: 3.3 to 3.7).
- Within the retired NFL player cohort, osteoarthritis was more prevalent in those with a history of knee injury (prevalence ratio = 1.7, 95%CI: 1.5 to 1.9) and ligament/tendon injury (prevalence ratio = 1.6, 95%CI: 1.4 to 1.9).
- In males under the age of 60, arthritis is over 3 times more prevalent in retired NFL players than in the general U.S. population. This excess of early-onset arthritis may be due to the high incidence of injury in football.

Opioid Epidemic – Demand for New Treatments

What is the Opioid Epidemic?

- The opioid epidemic is a crisis throughout North America and now in Australia, that involves the widespread use of prescription painkillers and subsequent popularity of illegal opioids, resulting in unprecedented addiction and consequential overdoses, many of which are fatal

Opioids:

- **A class of narcotic substances**, both legal and illicit, derived from the opium poppy plant (synthetic or naturally occurring)
- **Not disease modifying** (only mask pain)
- **Highly addictive** with significant withdrawals
- **Serious adverse effects**– significant risk of overdose/death
- **Are now considered by TGA to be inappropriate for use** in chronic non-cancer pain settings (i.e. Osteoarthritis)

Demand for new effective treatments

- **Former FDA Commissioner Scott Gottlieb -** "Our goal is to support more rational prescribing practices, as well as **identify and encourage development of new treatment options that don't have the addictive features of opioids."**[1]

Prescription opioid overdose is now the leading cause of accidental death in Australia

115

opioid overdose deaths per day in the United States[2]

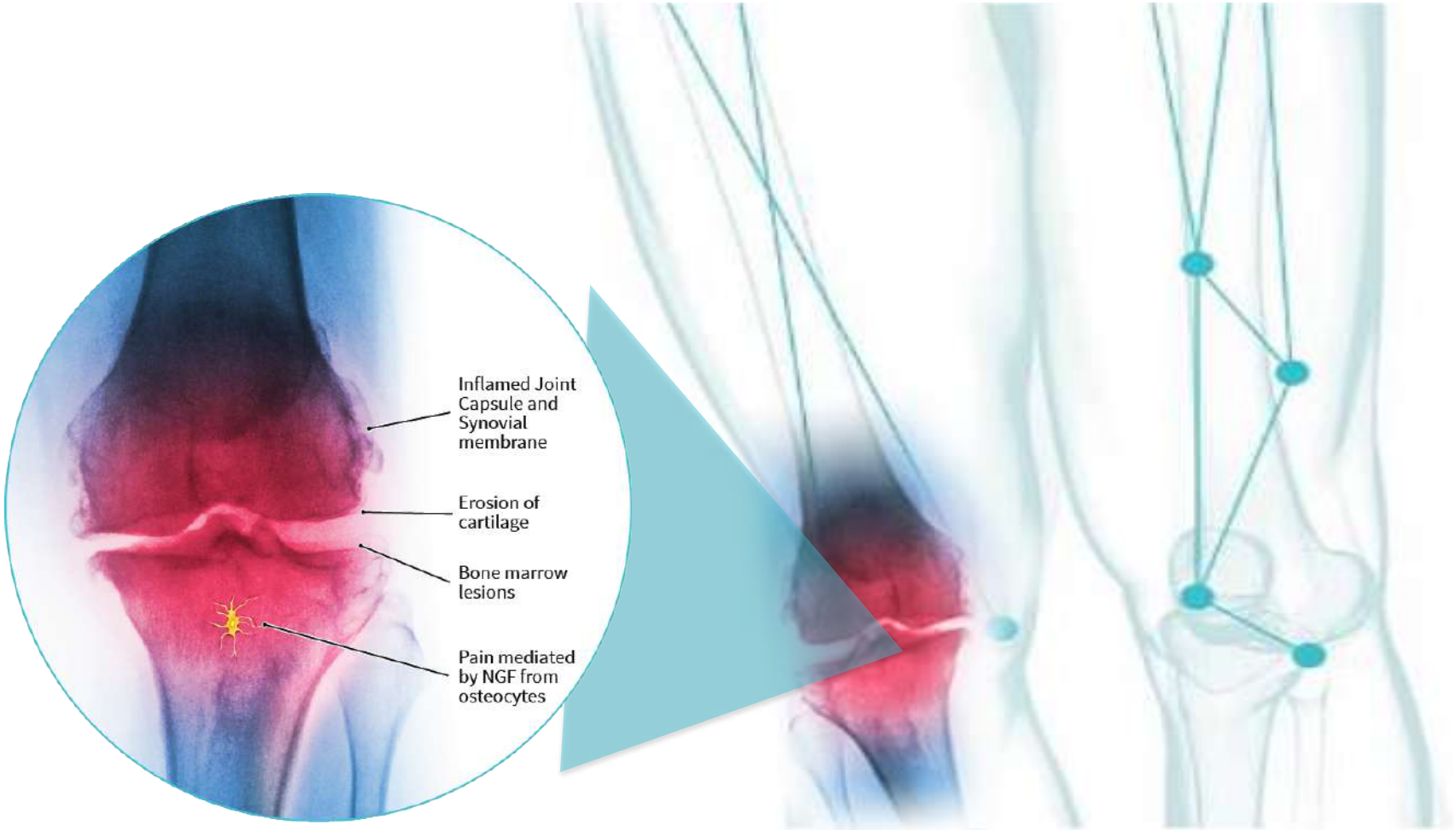
US$78.5 billion

total economic burden of prescription opioid misuse in the United States p.a.[3]

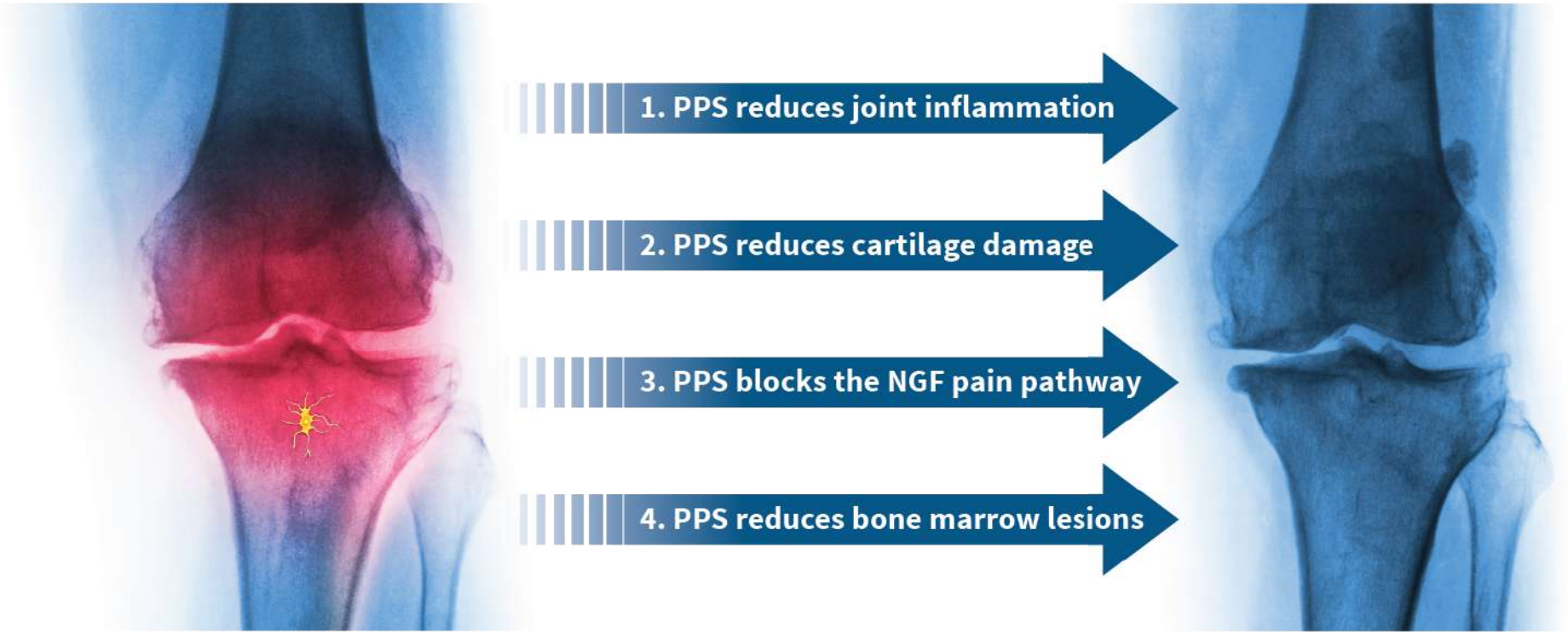
PPS has potential as a non-opioid treatment for osteoarthritis pain

1. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm612779.htm 2. CDC/NCHS, National Vital Statistics System, Mortality. CDC Wonder, Atlanta, GA: US Department of Health and Human Services, CDC; 2017. https://wonder.cdc.gov.
3. Florence CS, Zhou C, Luo F, Xu L. The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. *Med Care*. 2016;54(10):901-906. doi:10.1097/MLR.0000000000000625.

Pathogenesis in Knee Osteoarthritis



PPS Mechanisms of Actions



NGF = Nerve Growth Factor

Expanded Access Program[1]

- *Sometimes called "compassionate use", expanded access is a potential pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.*
- *Expanded access may be appropriate when all the following apply:*
  - *Patient has a serious disease or condition, or whose life is immediately threatened by their disease or condition.*
  - *There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.*
  - *Patient enrollment in a clinical trial is not possible.*
  - *Potential patient benefit justifies the potential risks of treatment.*
  - *Providing the investigational medical product will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication.*
- *Investigational drugs, biologics or medical devices have not yet been approved or cleared by FDA and FDA has not found these products to be safe and effective for their specific use. Furthermore, the investigational medical product may, or may not, be effective in the treatment of the condition, and use of the product may cause unexpected serious side effects*

1. Food and Drug Administration (2020, 27th April) *Expanded Access,* https://www.fda.gov/news-events/public-health-focus/expanded-access accessed 17072020

FDA Expanded Access Protocol Design

Intermediate-size Patient Population Expanded Access (Compassionate Use) Protocol Using Pentosan Polysulfate Sodium in patients with Osteoarthritis (OA) of the Knee with Bone Marrow Lesions (BML)

Efficacy Measures	**WOMAC® Osteoarthritis Index (NRS) and NRS Pain (24 hour recall) at week 12**
Safety Measures	Adverse Events, Lab changes, Vital signs
No. Participants	10
Active : Placebo	Open Label
Dosing	2mg/kg Pentosan Polysulfate Sodium (100mg/ml injectable solution), administered by subcutaneous injection, twice weekly for 6 weeks.
Recruitment Sites	1 Site (Texas, USA)

OA Expanded Access Program – Subject Population

Key Inclusion Criteria

- Subjects with a Diagnosis of Osteoarthritis according to the American College of Rheumatology criteria and with Bone Marrow Lesions (BML) on MRI
- Symptomatic pain for at least 12 months
- Males and females aged 18+ years
- Alternative therapies failed to provide adequate relief : ex; Acetaminophen/paracetamol, Oral and topical NSAIDS, IA Corticosteroids and Physiotherapy

Baseline Statistics

	PPS
Age, yrs. (mean) (min,max)	57.4 (43, 70)
Sex (M:F)	M **10** : F **0**
Total (n)	10

WOMAC® Pain Results Week 12

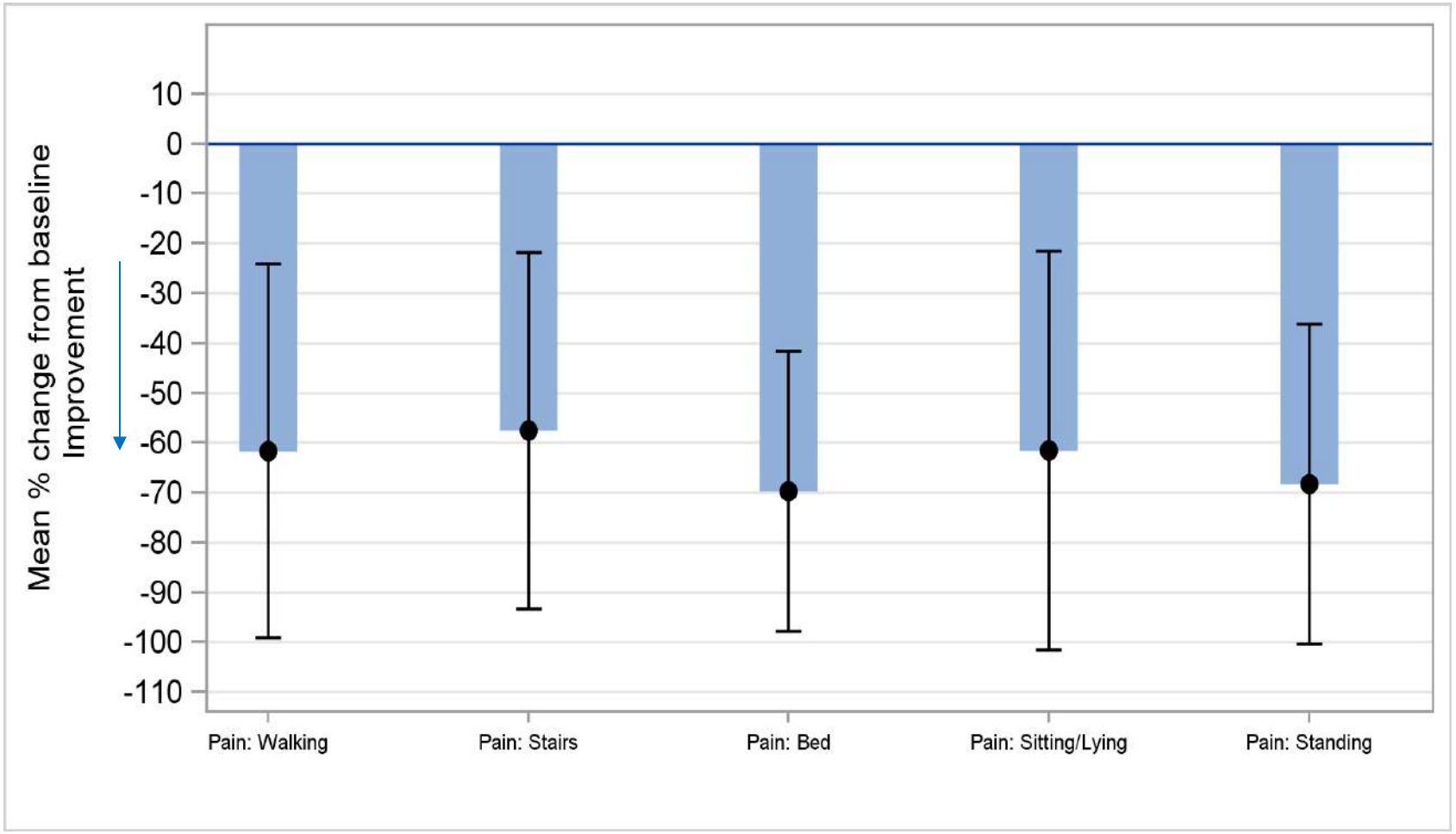
Summary of WOMAC Osteoarthritis Pain

WOMAC Pain Questionnaire (N=10 patients)	Mean Baseline value (95% CI)	Mean Post-treatment value (95% CI)	Mean % Reduction in Pain (95% CI)
1. Pain Walking on flat surface	5.5 (3.8, 7.2)	1.8 (0.3, 3.3)	61.64 (99.10, 24.18)
2. Pain Going up/downstairs	7.5 (5.9, 9.1)	2.8 (1.3, 4.3)	57.59 (93.39, 21.79)
3. Pain At night	4.5 (2.7, 6.3)	1.1 (-0.1, 2.3)	69.67 (97.76, 41.58)
4.Pain Sitting/lying	4.9 (3.0, 6.8)	1.3 (-0.2, 2.8)	61.57 (101.59, 21.55)
5. Pain Standing upright	5.8 (4.1, 7.5)	1.7 (0.4, 3.0)	68.27 (100.31, 36.23)
WOMAC Pain Subscale	28.2 (20.3, 36.1)	8.7 (2.2, 15.2)	**65.73** (97.08, 34.38)

CI = Confidence Interval

PPS treatment demonstrated reduction in WOMAC Pain Scores at 12 weeks after the initiation of treatment

Relative (%) Change from Baseline in WOMAC Pain Scores



Safety Profile

Medical History / Concurrent Diseases:

All subjects (100%) had minimal to severe bone marrow edema, with the most prevalent in the 5mm-20mm moderately sized grade.

50% of the subjects had medical history with highest being surgical/medical procedures (30% subjects and 7 procedures reported prior to IMP), 20% had previous knee arthroscopies and 10% had arthroplasty and meniscus surgeries

80% of the subjects had concurrent diseases (ongoing on or after first dose of IMP), with 14 ongoing conditions reported during the study. Highest (50% subjects) were Vascular Disorders (Hypertension) and Metabolic Disorders (30%) which is consistent with high BMI seen in baseline characteristics.

Prior and Concomitant Medications:

100% of subjects had previously used Acetaminophen‘ and Oral NSAIDs. Also, 50% of subjects had utilized topical, 20% Intraarticular corticosteroid injections, 20% Anti-inflammatories and 10% Physiotherapy.

Subjects had therapy ranging from less than a year to 40 years, with average of 14 years.

80% of subjects reported concomitant medications (ongoing on or after first dose of IMP). 30% were Renin-Angiotensin agents for vascular disorders, 30% calcium channel blockers, and 30% diabetic medications, which are all consistent with concurrent diseases reported.

Safety Profile (cont'd)

Adverse Events

50% subjects had reactions post-IMP (TEAEs), all of them related to the IMP received. The AEs were Mild or Moderate, no serious or severe AEs were reported.

Erythema and swelling at the injection site were the most frequently reported events (8 out of 16).

Laboratory Assessments

There were no clinically significant results reported in the study.

INR, Platelets, APTT, AST, and specific gravity means were all within normal ranges through the duration of the study

CPK (UL) was elevated at screening and baseline with a mean of 377 and 365, respectively and remained elevated throughout the course of the study. The elevated ranges were attributed to intense exercise and often seen in competitive athletes.

ALT mean increased from normal range to elevated. All patients were asymptomatic, and PI deemed it non-clinically significant

Change in vital signs between pre-IMP and post-IMP were reported at scheduled visits. Subjects did not report any significant change from pre-IMP in any parameters.

Safety Conclusion

PPS was well tolerated by all 10 patients. All AEs were mild to moderate and self limiting. There were no SAEs or discontinuations.

WOMAC® and NRS

Summary of WOMAC Index and NRS

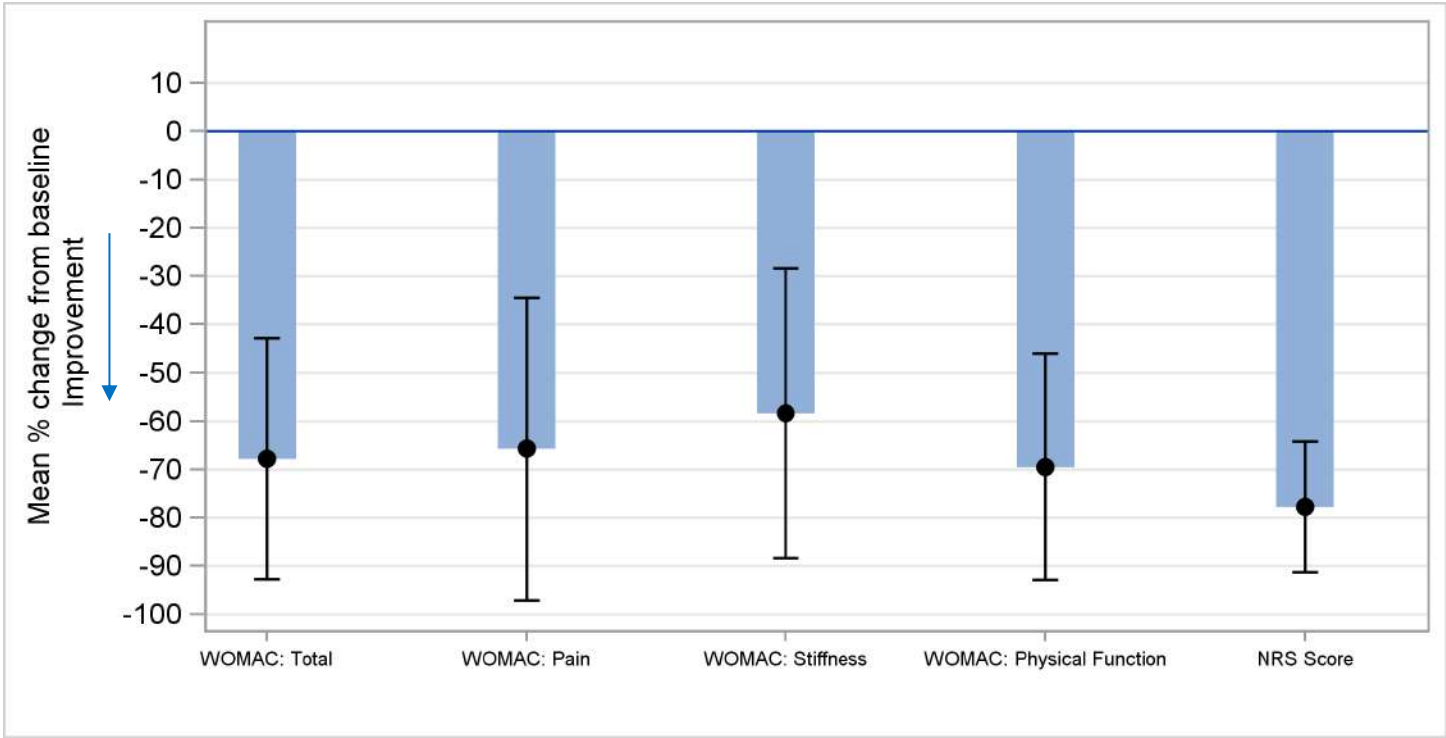
Scale (N= 10 patients)	Mean Baseline value (95% CI)	Mean Post-treatment value (95% CI)	Mean % Reduction (95% CI)
WOMAC Pain Subscale	28.2 (20.3, 36.1)	8.7 (2.2, 15.2)	65.73 (97.08, 34.38)
WOMAC Function Subscale	102.3 (77.8, 126.8)	31.6 (8.7, 65.4)	69.44 (92.93, 45.95)
WOMAC Stiffness Subscale	15.1 (12.2, 18.0)	5.9 (2.4, 9.4)	58.39 (88.40, 28.38)
WOMAC Total Score	145.6 (111.3, 179.9)	46.2 (13.9, 78.5)	67.76 (92.70, 42.82)
NRS (24 hour recall)	6.1 (4.4, 7.8)	1.4 (0.6, 2.2)	77.79 (91.37, 64.21)

CI = Confidence Interval

WOMAC® Scales and NRS Pain

Improvement seen across pain, function, and stillness subscales. NRS responses consistent with Womac pain

Relative (%) Change from Baseline in WOMAC and NRS Scores



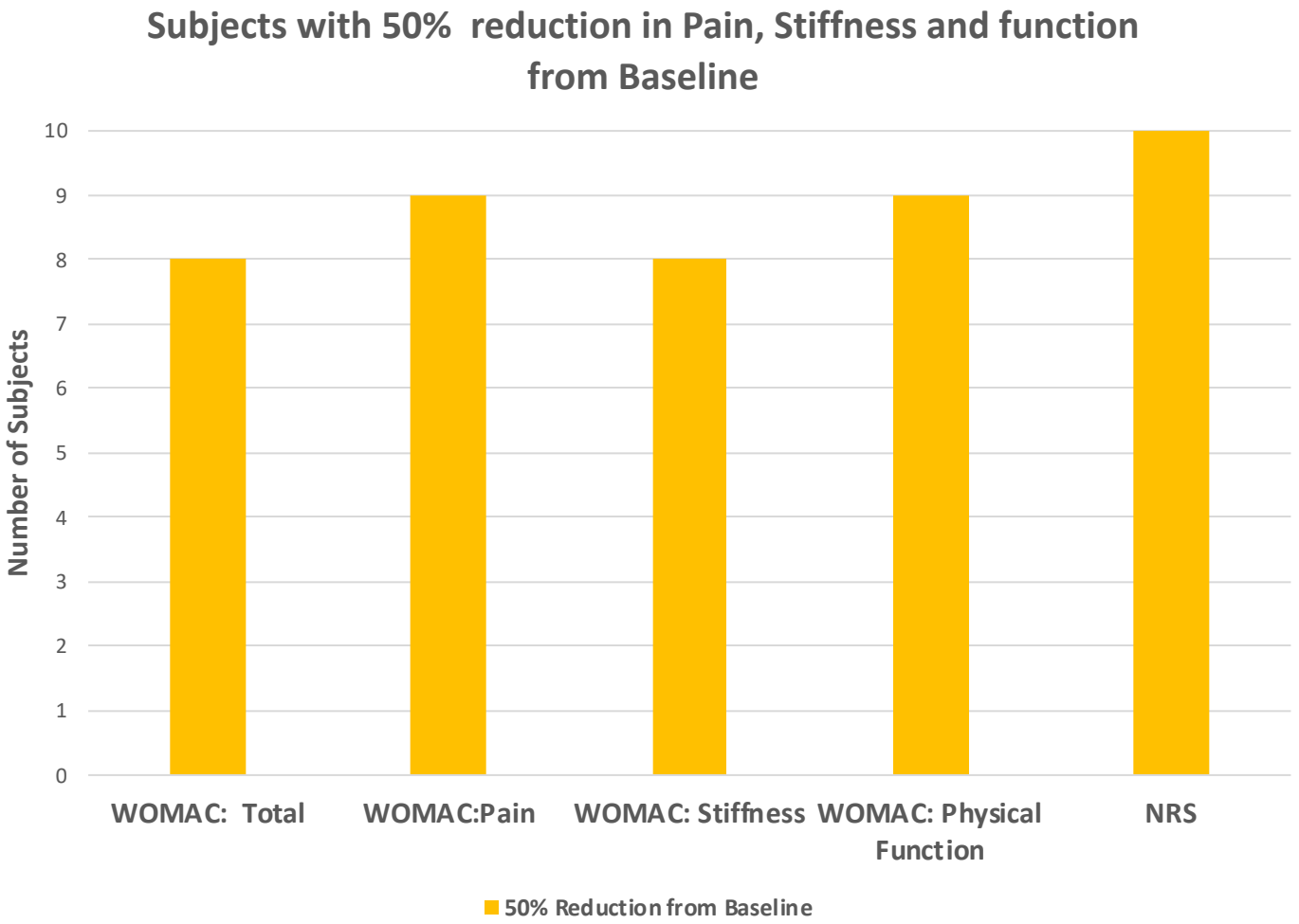
WOMAC® and NRS - Responders

Subjects with At least 25% and 50% Reduction in Symptoms from Baseline

Scale	Responder	N	% Responders	95% CI
WOMAC Total Score	At least 25% reduction	9	90%	0.5550, 0.9975
	At least 50% reduction	8	80%	0.4439, 0.9748
WOMAC Pain	At least 25% reduction	9	90%	0.5550, 0.9975
	At least 50% reduction	9	90%	0.5550, 0.9975
WOMAC Function	At least 25% reduction	9	90%	0.5550, 0.9975
	At least 50% reduction	8	80%	0.4439, 0.9748
WOMAC Stiffness	At least 25% reduction	9	90%	0.5550, 0.9975
	At least 50% reduction	9	90%	0.5550, 0.9975
NRS	At least 25% reduction	10	100%	0.6915, 1.0000
	At least 50% reduction	10	100%	0.6915, 1.0000

CI = Confidence Interval

Clinically meaningful reduction in WOMAC® and NRS Pain Scores – Percentage Responders



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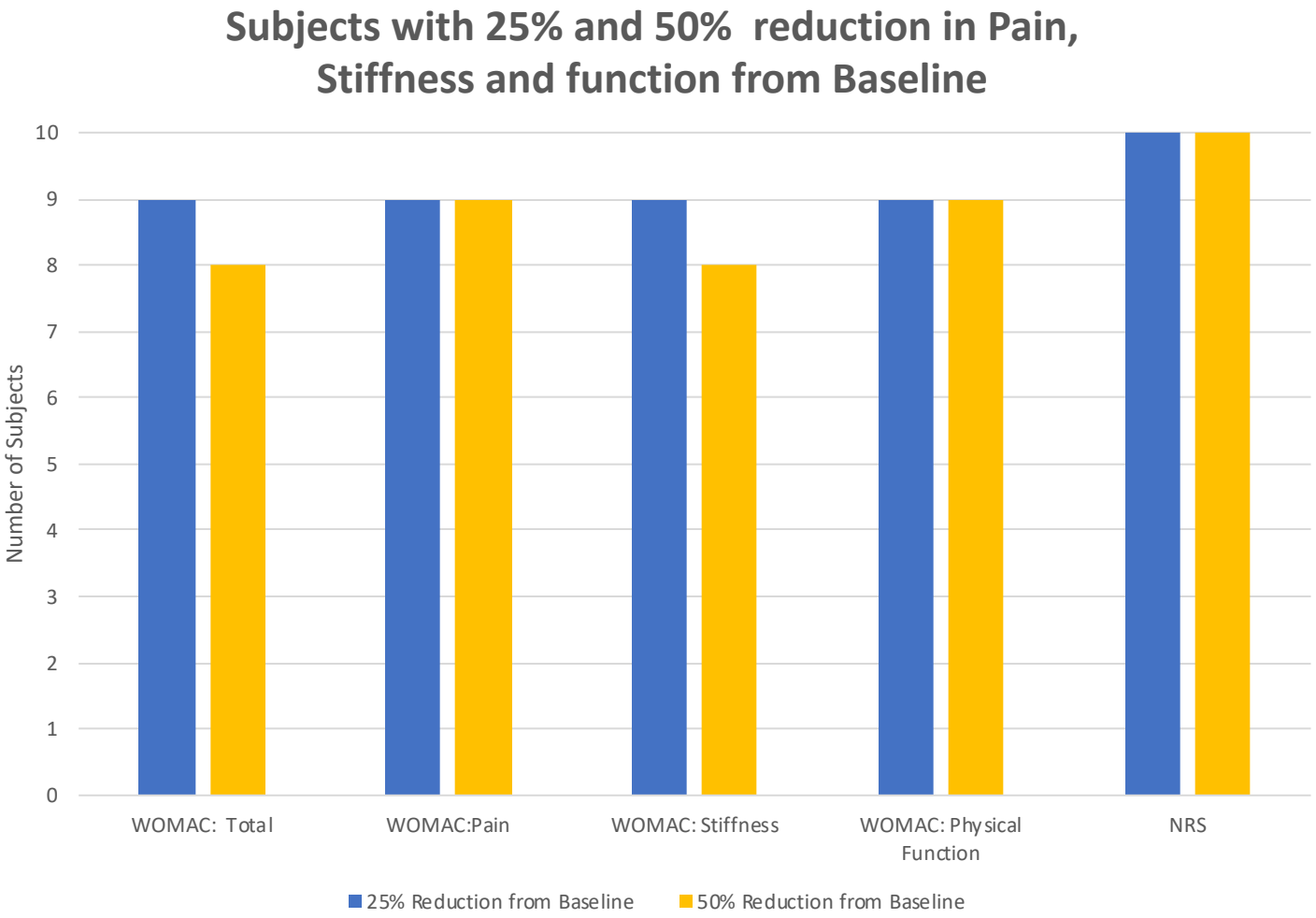

Acknowledgements

Paradigm would like to thank Dr East and all his staff in Dallas, for all their work and assistance with this program. We would also like to thank the 10 participants in the program and wish them all the best in returning to many activities that had previously been limited due to the pain associated with OA.

Disclosure

Dr East does not have any conflict of interest and is not a paid consultant nor a Shareholder in Paradigm.

Paradigm paid an independent (USA based) CRO to monitor the program. Paradigm reimbursed out of pocket expenses to participants such as travel to and from the treatment centre.

Paradigm paid an independent CRO to manage the data and a paid consultant was paid to undertake the statistical review of the clinical data.

In line with EAP or compassionate use programs, other costs such as clinical site set up costs and medical treatment expenses were provided by Paradigm and no participant was paid to participate in the program (save for travel costs in point 2 above