Relieving Osteoarthritic Pain – Novel Biomaterials for Safer and Longer Acting Solutions

CRS 2023 Annual Meeting

Presented by Dr. George Mihov, Ph.D. and Gina Conti

25 July 2023

Presentation Focus

- Company overview
- Introduction to TheraPEA™ polymer platform
- Biodegradation and processing of TheraPEA™
- Extended-release solution for pain management
- Prospective safety and clinical efficacy study

About DSM Biomedical

Taking biomaterials FURTHER

As restorative healers who possess a true passion for improving patient outcomes and creating brighter lives for all, DSM Biomedical aspires to *solve the world's healthcare needs through sustainable science*

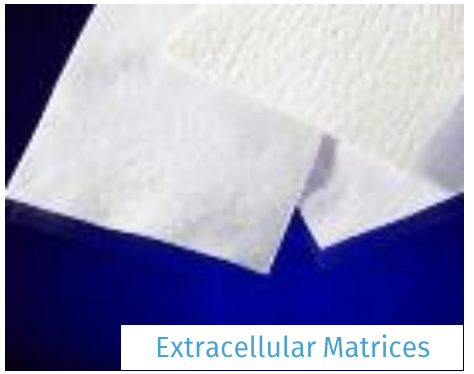
Through our extensive biomaterials portfolio and world-class capabilities, we empower our global partners to create and deliver transformative solutions that *elevate patient well-being, enable healthcare professionals, and foster sustainability*


Bioceramics


Hydrophilic Coatings


Collagen


Drug Delivery Solutions

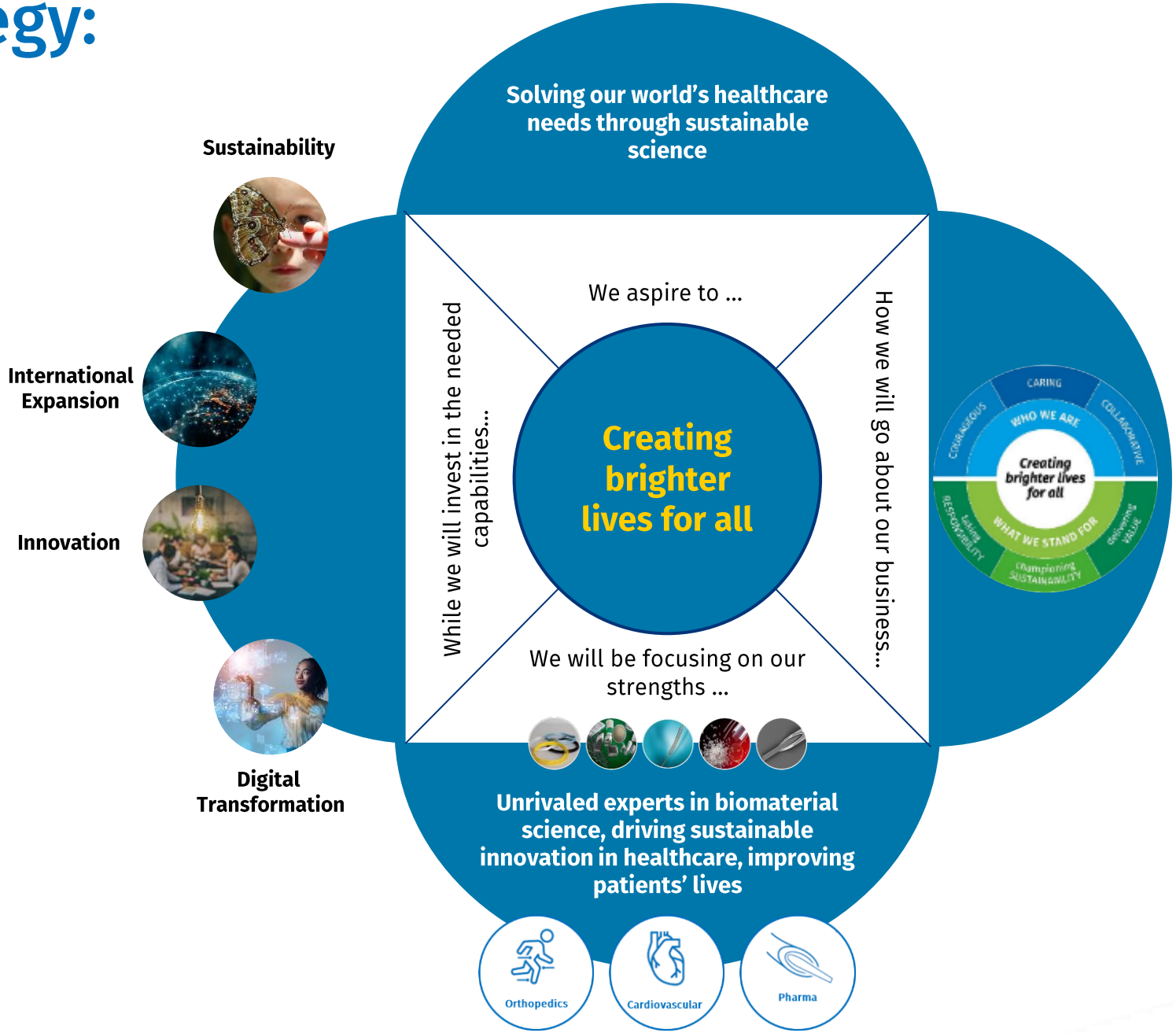

Extracellular Matrices


Polyethylenes


Polyurethanes


Polymer Processing Capabilities

DBM Strategy:



Additional Company Information

- **Effective May 9th, 2023** – DSM (formerly Royal DSM) and Firmenich merged to become dsm-firmenich

- Additional information can be found through the following links:
  - Website Link
  - Press Release Link

- Please note that DSM Biomedical is maintained in regulatory filings. There will be no immediate changes made to any financial links or documentation

Innovators in Nutrition, Health, and Beauty

- **dsm-firmenich: we bring progress to life**
  We're a trusted partner to global companies operating in high-growth and resilient markets

~30,000
passionate, talented, and diverse people in our global team

150+ years
of combined scientific discovery and innovation heritage

€12+ bn
combined revenue

DSM's Core Strengths in Polymeric Drug Delivery Solutions

Full support from feasibility to cGMP manufacturing

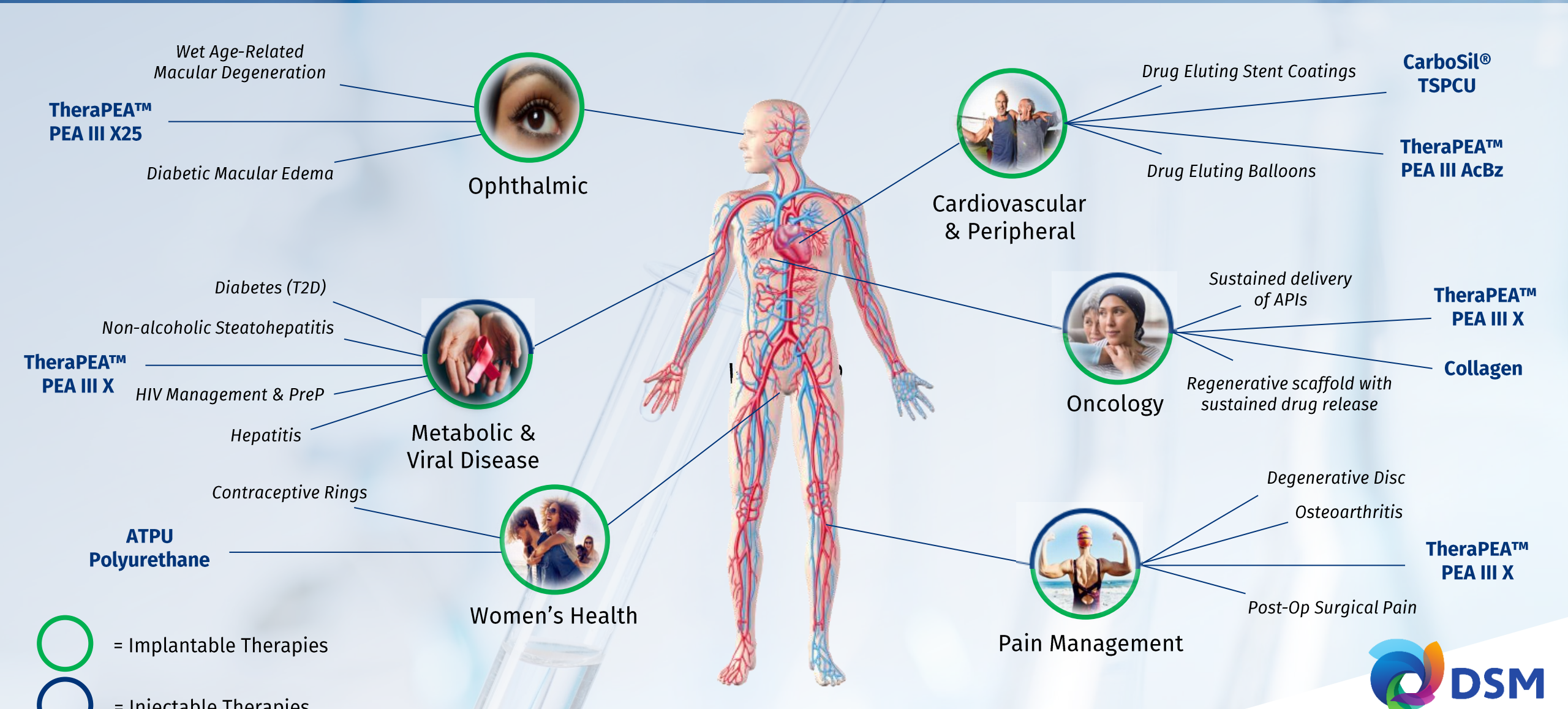
Extensive expertise in polymer technologies for biomedical applications

Formulation development with APIs to achieve the desired therapy profile

Custom process development for different polymeric drug delivery forms

A broad IP portfolio that enables life cycle management opportunities in branded products

DSM in Drug Delivery: An Application View



TheraPEA™ Drug Delivery Platform

Biodegradable Polyester Amide (PEA)
Technology Introduction

Impact of Sustained Delivery

Introduction of TheraPEA™ polymer platform

TheraPEA™ - A Proven Biodegradable Platform Solution for Sustained Drug Delivery

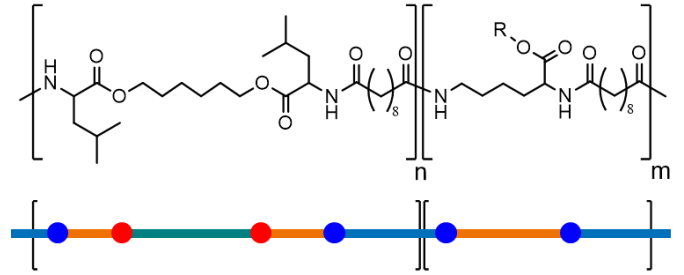
DSM Biomedical's Competitive Qualifiers

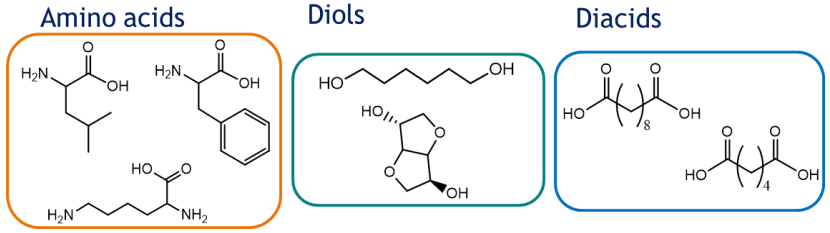
- Broad compatibility with wide range of small molecule and biological drugs due to low susceptibility to acylation (i.e., interaction of polymer with API's nucleophilic primary amines).
- Excellent biocompatibility proven in multiple settings including ophthalmic, intravascular, intra-articular applications.
- Material Master Files & GMP Manufacturing

Our Competitive Differentiators

- Near linear release from weeks to greater than 6 months.*
- Controlled degradation kinetics (weeks to multiple months); no acidification of micro-environment.
- Unique solubility properties (incl. low hydrocarbon alcohols) provides for ease of processing with active pharmaceutical ingredients incl. low temperature melt processing into multiple product forms (fibers, microparticles, films, foams, coatings).
- Broad IP protection provides opportunities for lifecycle extension.

TheraPEA™ Polyester Amide (PEA)





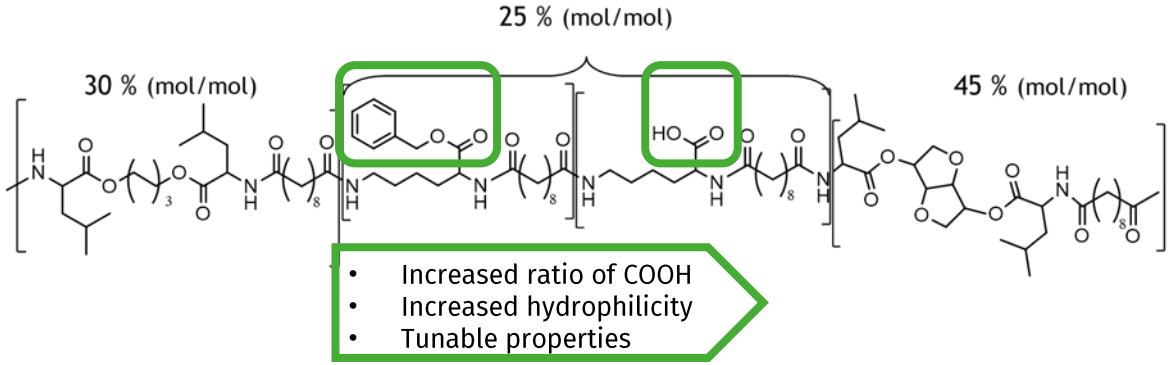
DSM offers polymer solutions tailored to sustain drug elution over the lifetime of the therapy, while allowing ease of processing with active pharmaceutical ingredients (APIs).

* Polymer-drug formulation dependent
** In case of adverse reactions for example; shape and time-dependent

Addressing Challenges in Sustained Delivery of Difficult to Formulate APIs

- **Random copolymer** – Product of catalyst-free polycondensation process at low temperature
- **Material Properties** – amorphous elastomers, Mn 40 – 70 kDa, Tg 55 – 65 ^{0}C
- **Bio-degradation** – Unique degradation mechanism controlled by the polymer's features
- **Shelf-life stability** – GLP data supported five years shelf-life
- **Solubility** – Unique solubility in low hydrocarbon alcohols opening new opportunities for processing and co-processing with other biomaterials

Enabling Features of TheraPEA™

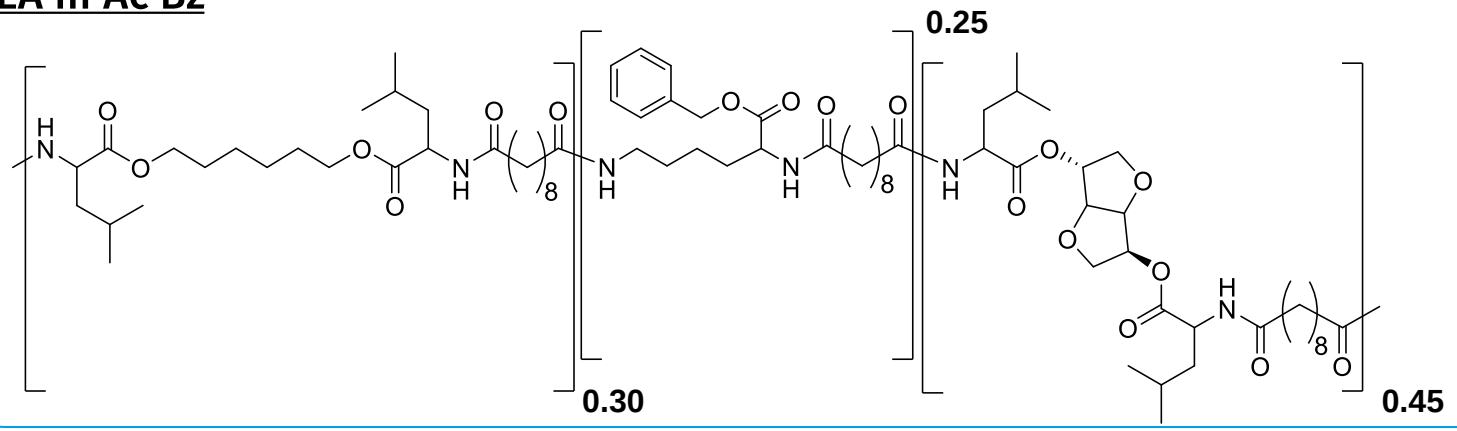


- Tunable hydrophilicity – next generation of PEA X Polymers
- Unique degradation mechanism (non-acidic degradation with zero order kinetics)
- Controlled water-uptake properties (“slow-hydrogel like“ behavior)
- Unique drug-release properties
- Protein inspired polymer structure preserves the intrinsic properties of the bio-therapeutics even at advanced stage of polymer degradation – provides a “buffering effect” during degradation

Biodegradation and Processing of TheraPEA™

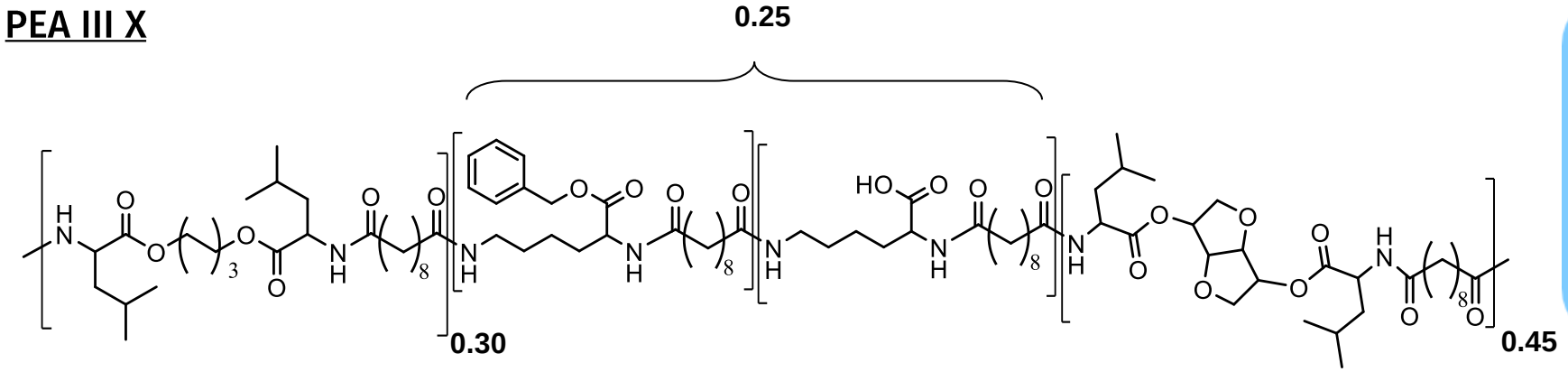
Structural Control on Degradation Mechanism

PEA III Ac Bz



Enzymatically degradable

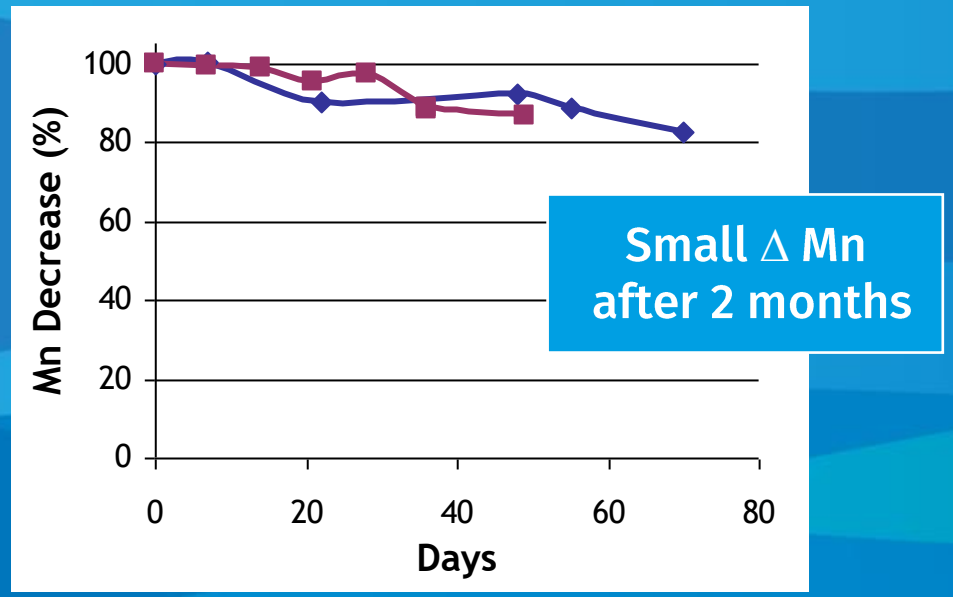
PEA III X

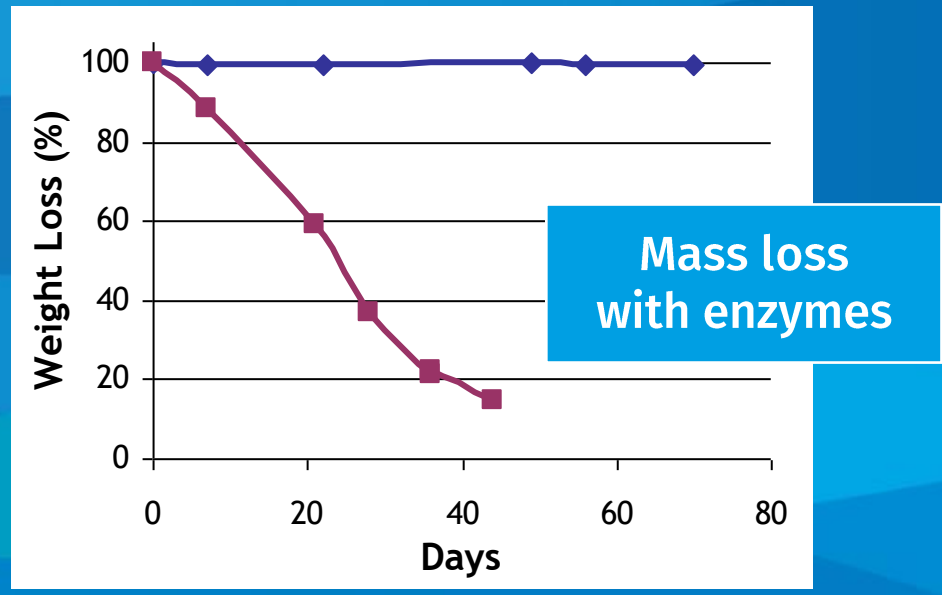


Hydrolytically degradable

TheraPEA™ Unique Degradation

Hydrolytic vs. Enzymatic

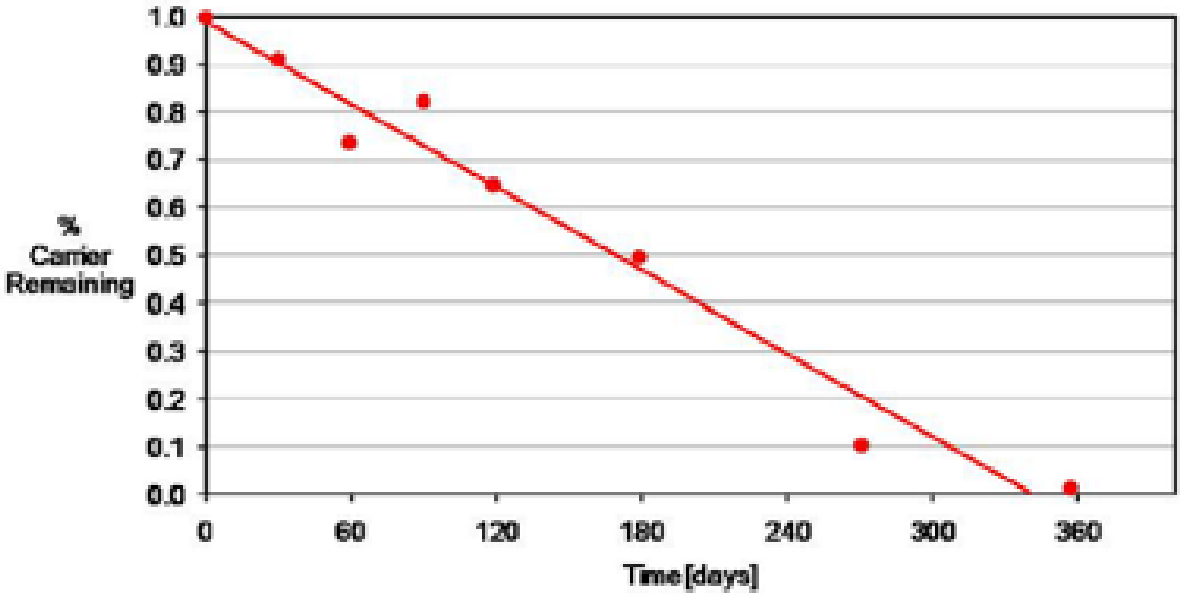




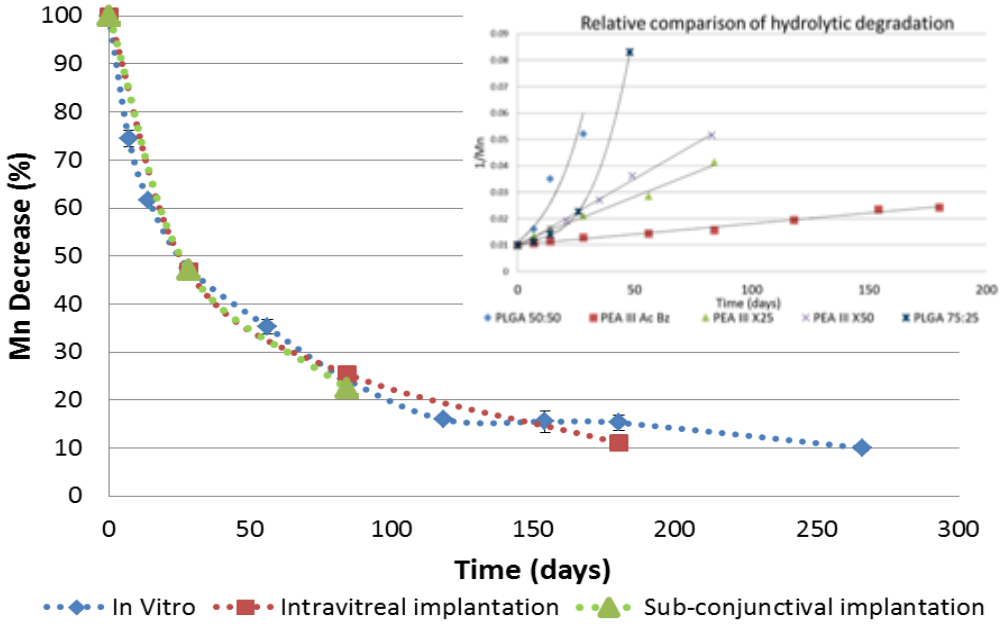
PEA incubated in PBS at 37 °C — w/ Chymotrypsin

- Hydrolytically stable TheraPEA™ polymers
- Enzyme-mediated polymer degradation

TheraPEA™ Biodegradation Verified in Pre-clinical Models



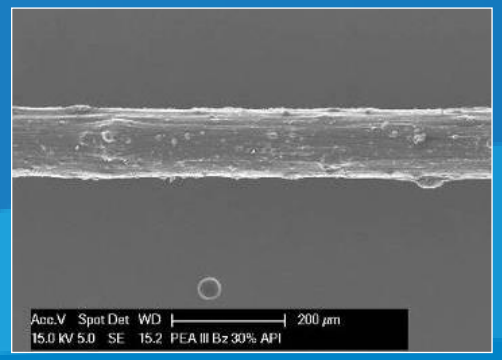
Bio-resorption of TheraPEA™ coating on DES
Preclinical data



Zero order bio-degradation kinetics in
ophthalmic models

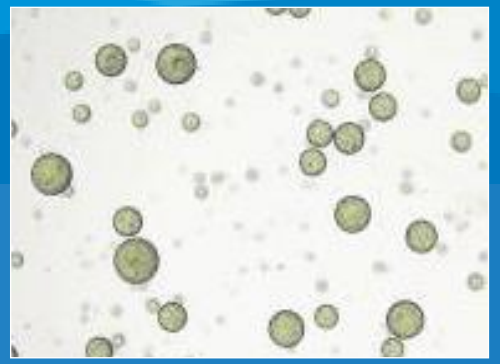
Our Versatility in Processing Forms

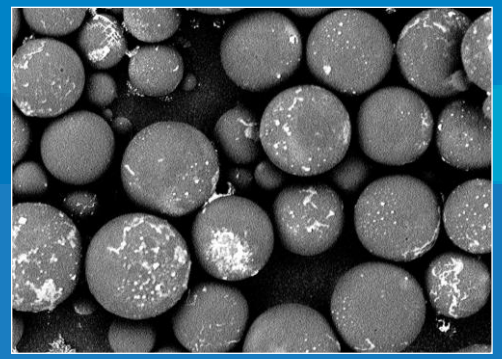
Fibers



- Microfiber diameter: 100µm – mm.
- API loading 10 – 50 wt% .
- Melt – Extrusion, Spinning (g) and Injection molding (mg).
- Solution - Film casting and cutting.

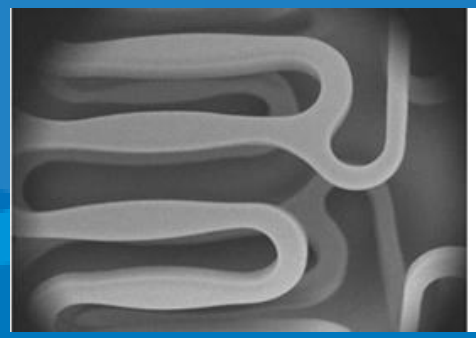
Microparticles

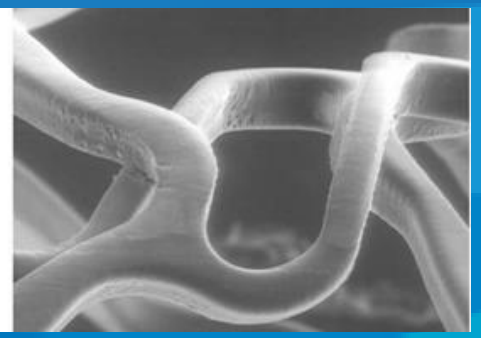




- Typical diameter can range from 10 – 100µm.
- API loading >10 wt%.
- Numerous: emulsification, spraying, etc.

Coatings and Films

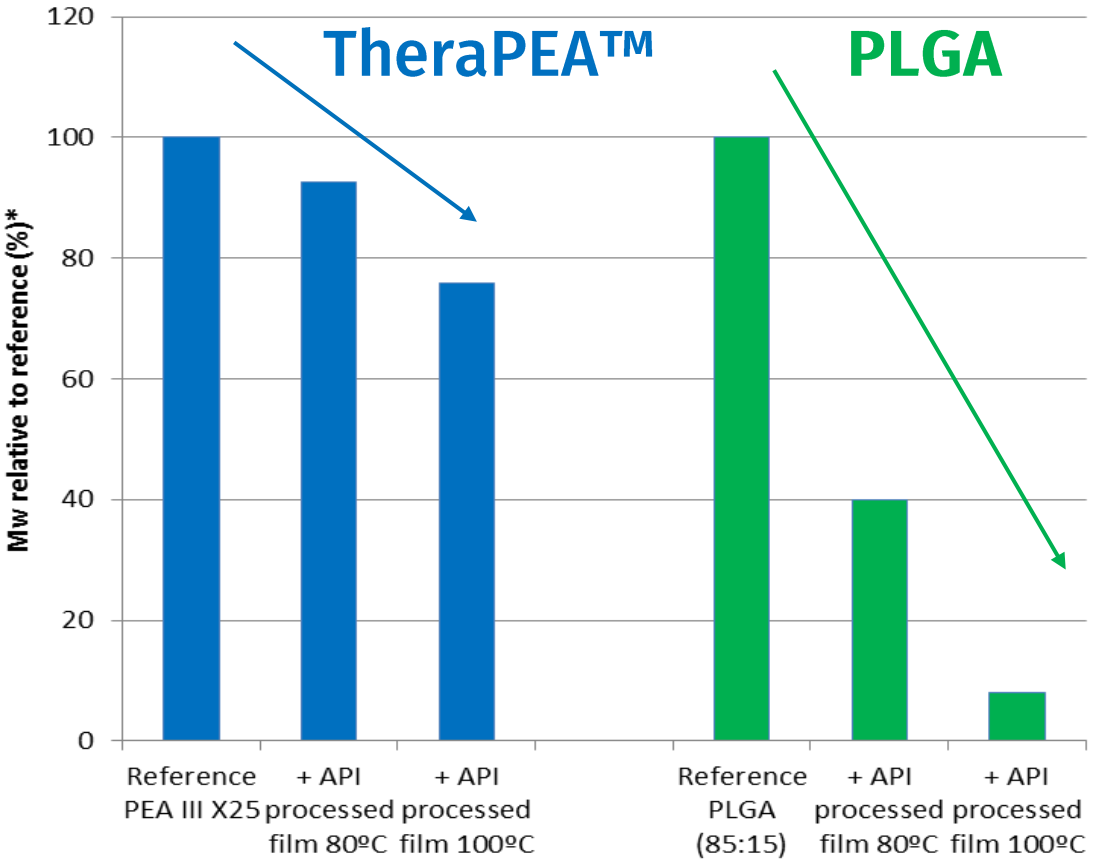




- Compatibility with number of substrates.
- Excellent adhesion to metals.
- Numerous options available.
- Excellent melt processability.
- Unique solubility properties.

- DSM Biomedical has continuously demonstrated the ability to process PEA into a variety of injectable and implantable forms
- Enables possibility of low temperature melt processing
- Compatible with challenging APIs (free amines, peptides)

Polyester amides differentiated chemistry enable where other biomaterials fail with nucleophilic pharmaceuticals

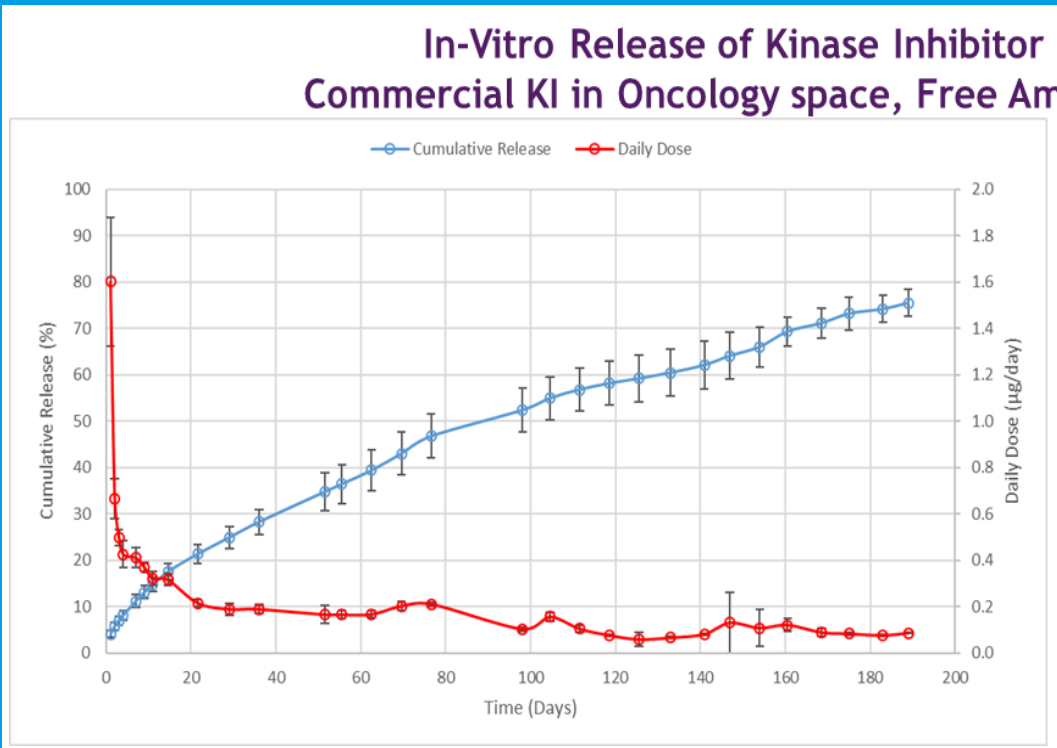


Example of formulation and processing with a nucleophilic kinase inhibitor

- Polyester shows rapid degradation during the hot-melt processing
- TheraPEA™ polymer retains its properties in a much more robust way

The differentiated polyester amide chemistry allows good processability in a melt processed polymer/drug application

Demonstrated Extended Release of Kinase Inhibitor



*Formulation / processing of free amine APIs with PolyEsters (PLGA) typically results in disintegration of implant in 2-7 days

- Injectable micro Fiber
- 100µg total weight
- 40µg total API load
- Past 21 days 80-200ng/day
- 6+ month release

Compatibility with “Challenging APIs”– free amines, free acids, peptides, large molecules

Extended-Release Solution for Pain Management

Case Study: Management of Pain Associated with Osteoarthritis (OA)

A HIGHLY DISABLING CONDITION WITHOUT EFFECTIVE TREATMENT

242 million

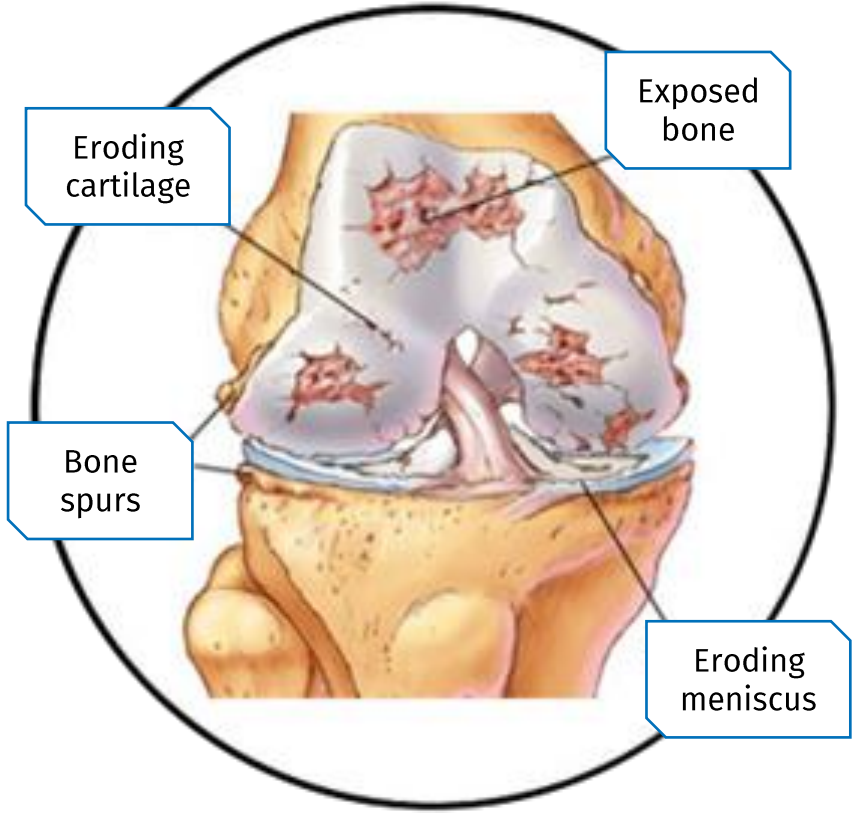
Patients suffering from chronic pain associated with knee osteoarthritis worldwide[1]

$12.1 billion

Forecasted global pharmaceutical sales in 2026 associated with pain OA. Market growing at CAGR of 9.8% from 2022 to 2026[2].

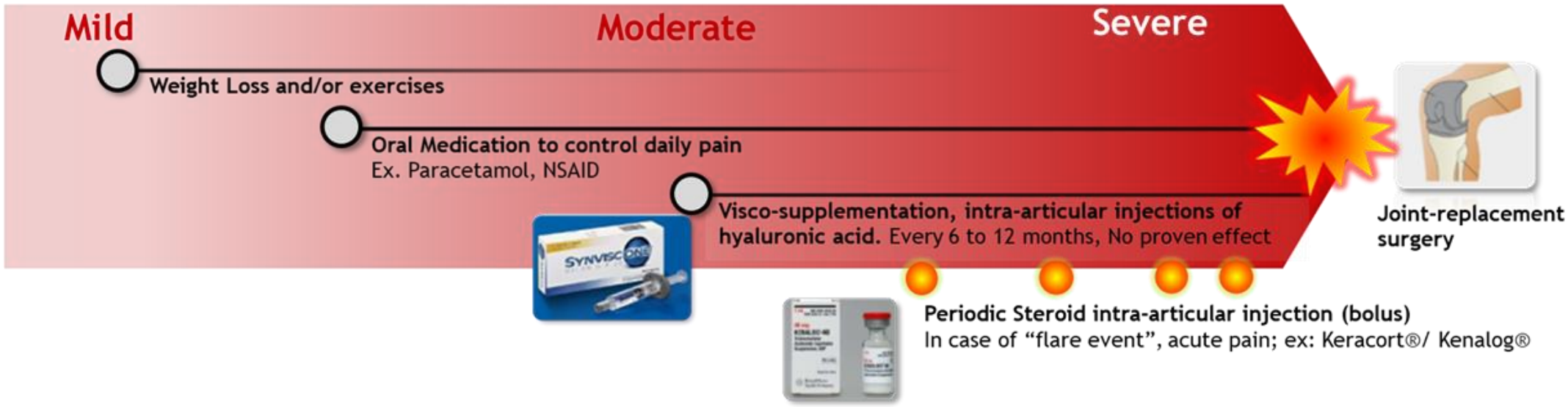
No cure

Leading to mobility loss for patient and/or knee replacement surgery. It is a major economical burden in aging societies.



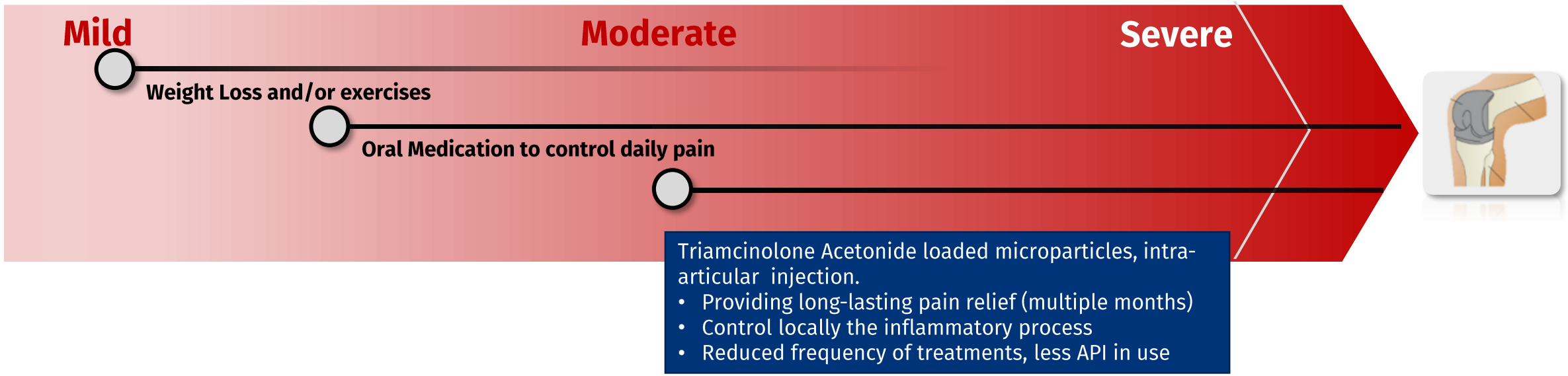
1 https://oaaction.unc.edu/oa-module/oa-prevalence-and-burden
2 https://www.globenewswire.com/en/news-release/2022/05/17/2444646/28124/en/Global-Osteoarthritis-IA-Injections-NSAIDs-Analgesics-Markets-2022-2026

Current approach for management of OA pain



- Initial therapy involves classic oral medications – acetaminophen, stronger COX inhibitors (Ibuprofen), selective COX-2 inhibitors (Celecoxib) or other pain medications.
- With pain discomfort increasing, physicians tends towards intra-articular injections of Hyaluronic acid and/or Triamcinolone acetonide (TAA).
- Based on 2019 Guidelines from American College of Rheumatology / Arthritis Foundation (ACR /AF) injections of corticosteroids (TAA) remain the only strongly recommended injectable approach (with HA injections being conditionally recommended against)
- It is known that even though recommended, IA injections of bolus corticosteroids have short lived and limited effect

Providing Value in an Extended-Release Formulation

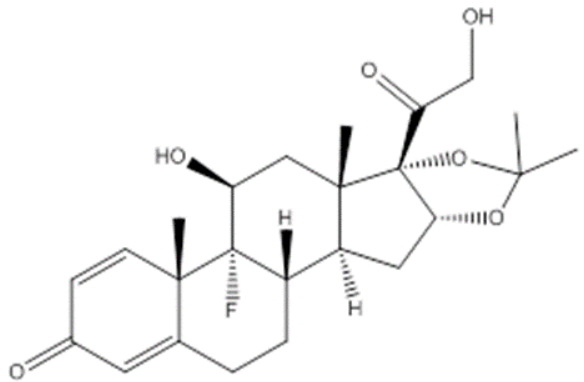


Concept

- DSM's approach envisions a treatment with **microparticles formulation administered by standard intra-articulate injection procedure.**
- Microparticles comprise an **approved API for this indication, corticosteroid Triamcinolone Acetonide (TAA), and DSM's proprietary TheraPEA™ polyester amide technology aiming at up to 6 months of therapeutic effect.**
- Results in a sustainable product with patient and physician benefits, improving OA healthcare economics.

TAA-loaded Microparticles

A microparticle design for an effective product



Triamcinolone acetonide (TAA)

- Molecular mass 434.50g.mol^{-1}
- Water solubility 21mg/L (28°C)
- Melting Point 293°C

Source: DrugBank

Product requirements (TPP)

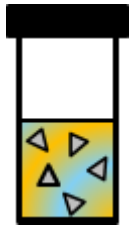
- Targeted pain relieve ≥6 months
- Product resident upon biodegradation in the knee joint
- Does not induce cartilage degradation nor inflammation
- Multi-month release of therapeutic dose. No excessive burst.

Corresponding microparticle design

- Dosage of 40mg of TAA per injection
- Loading of ≥ 20wt% of TAA
- Particle size:
- D10 > 10µm (limited phagocytosis);
- D90 < 80µm (good injectability)
- *In-vitro* release (projected) ≥3months
- Initial release burst to ≤20%
- *In vitro* stability by HPLC

Oil-in-water Emulsification

A tunable process



Continuous phase (Aqueous)

Formulation solution

Formulation with excipients (facilitate shelf life, syringe-ability) achieved in wet phase

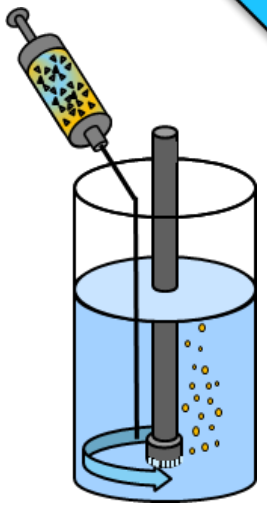
Dispersed phase (PEA + drug)

EMULSIFICATION

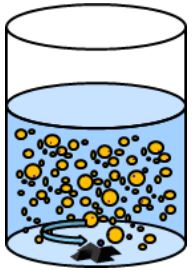
Microparticles in continuous phase

FORMULATION & CONCENTRATION

Waste



Size and loading controlled



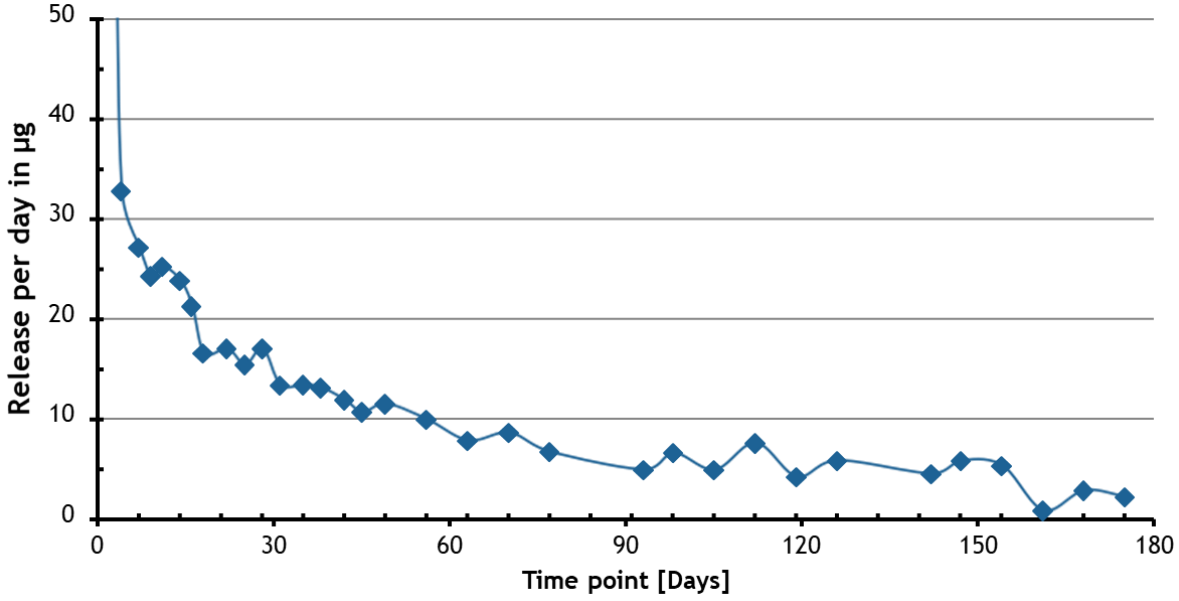
Freeze-Drying

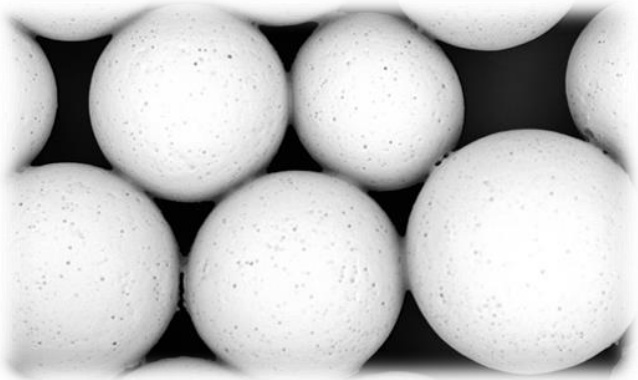
Solid particles

Removal of residual solvent by lyophilization: integrity of particles maintained

Early Feasibility – In Vitro Pharmacokinetics

TAA Loaded PEA Microparticles in a 20% w/w Formulation





Experimental Design

- In vitro release carried out in PBS buffer, 37ºC
- TAA concentration determined by HPLC, indicative of its stability upon release.
- Reproducible experiment; ≤1% of standard deviation per time point

Confirmed Compatibility of PEA/TAA

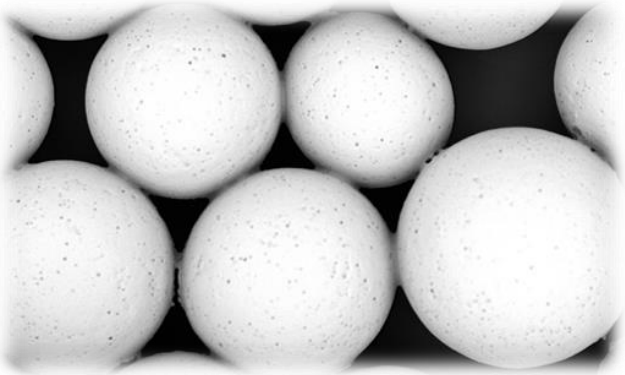
- Sustained release data support the feasibility for extended pain relief effect – up to six months

"Prolonged inhibition of inflammation in osteoarthritis by triamcinolone acetonide released from a polyester amide microsphere platform" - Journal of Controlled Release 253 (2017) 64–72

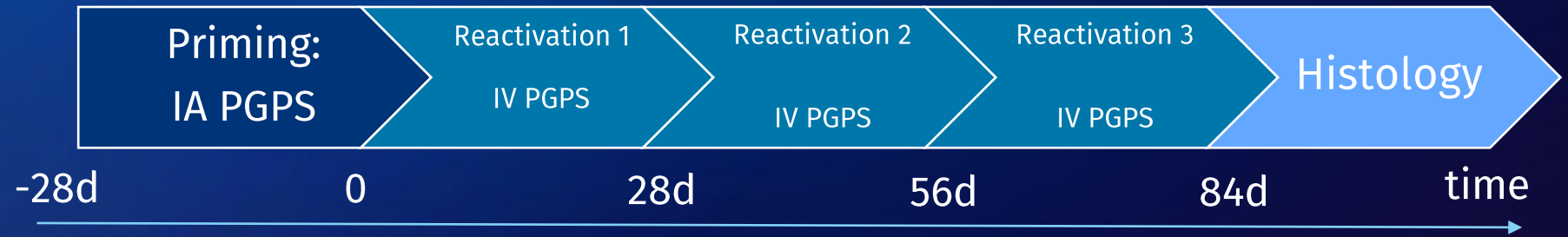
An Acute Arthritis Rat Model used for In Vivo Verification

- The safety of the TAA dose, excipient and microparticles formulation were extensively studied in collaboration with the Utrecht University, Faculty of Veterinary Medicine*

- The efficacy of the TAA loaded TheraPEA microparticles was studied in an acute arthritis rat model**
  - Unilateral synovial inflammation of the knee was induced by intra-articular injection of streptococcal cell wall peptidoglycan polysaccharide (PGPS)
  - Flare-ups were induced by intravenous PGPS injections every 4 weeks for a total duration of 84 days.



Experimental Set-up



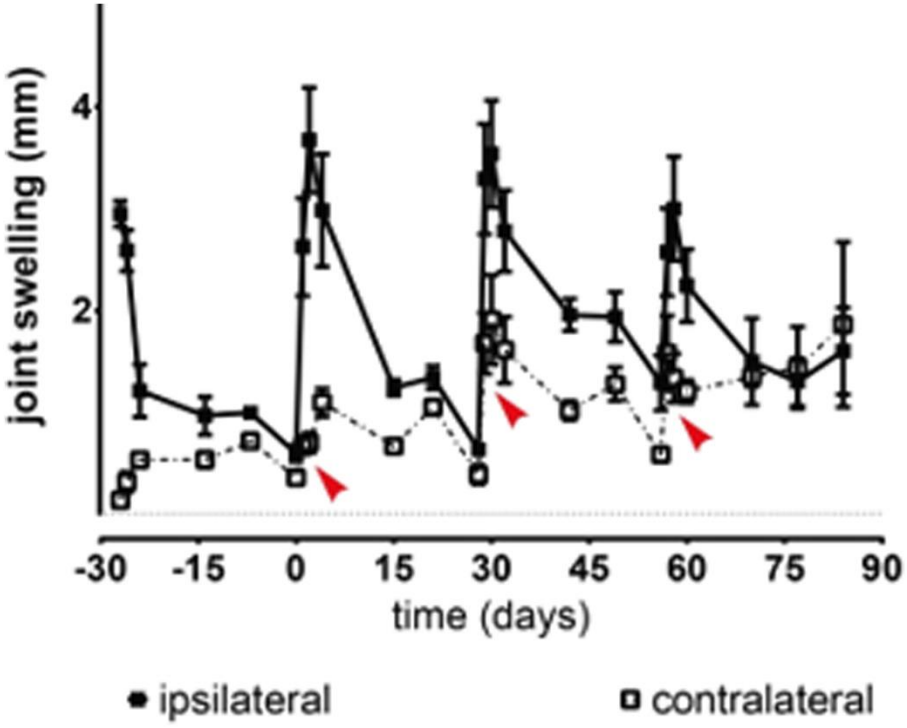
*The Spine Journal 00 (2018) 1–15
**Journal of Controlled Release 253 (2017) 64–72

Experimental Model and Readouts

- Localized synovitis was induced in the left knee of adult Sprague-Dawley rats

- Rats were divided in 3 groups, n=6:
  1) Control group
  2) Injection of TheraPEA/TAA
  3) Injection of PLGA/TAA delivery system (benchmark)

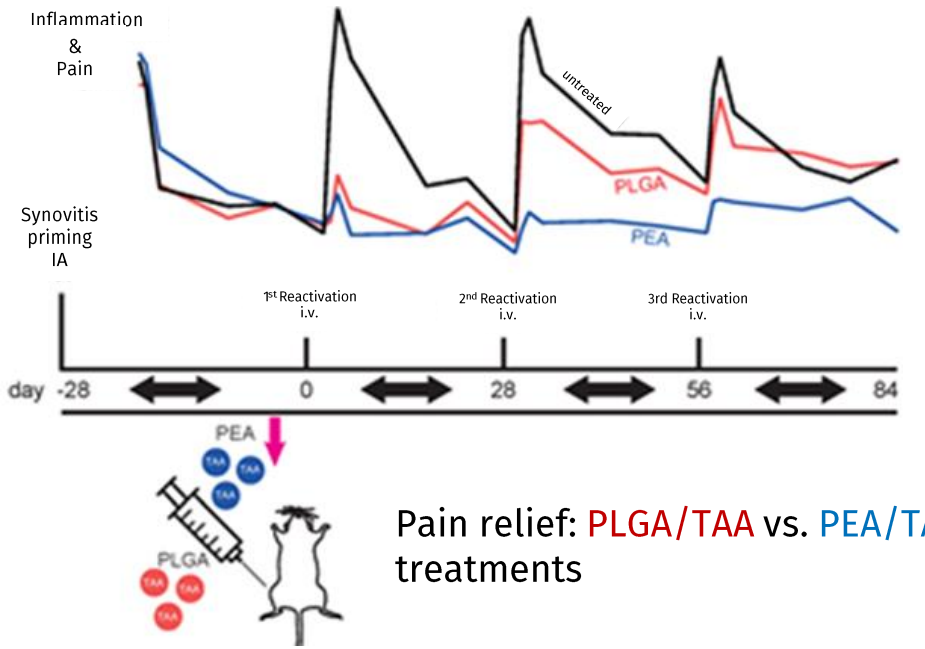
- Readouts assessed joint thickness and signs of pain-like behavior (lameness, mechanical hypersensitivity, dynamic weight bearing)



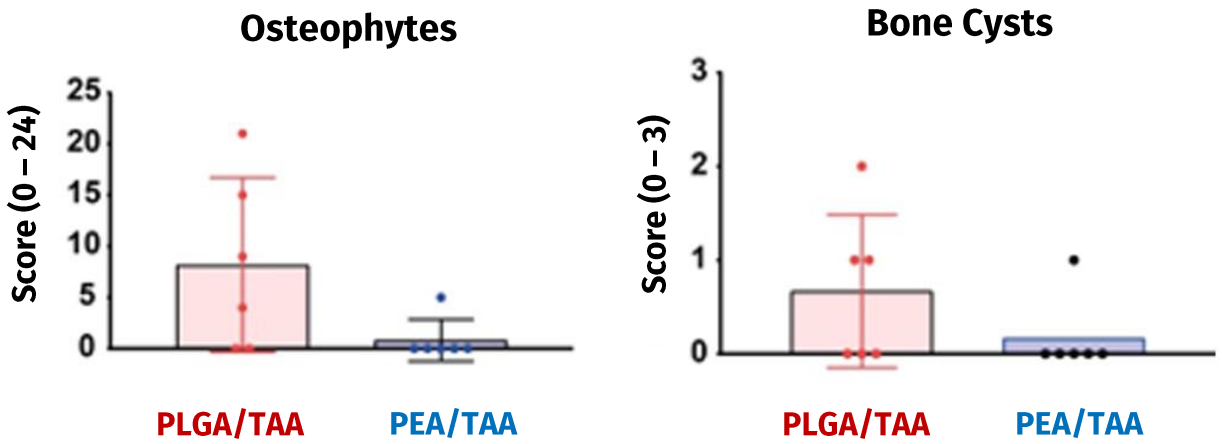
Model validation: Treated vs. Untreated knee in the control group

Pharmaceuticals, 2019 Feb., 11: 70

Results and discussion



Pain relief: PLGA/TAA vs. PEA/TAA treatments



Pathology: PLGA/TAA vs PEA/TAA treatment

*significance $p<0.005$

TheraPEA™ PEA/TAA formulation suppresses the swelling and related inflammation for all three reactivations which indicates **a better retention of TAA and efficient maintenance of the API** within the therapeutic window

Pharmaceuticals, 2019 Feb., 11: 70

Prospective Safety and Clinical Efficacy Study

First-in-Patients Veterinarian Clinical Study

Aim of the study

- TAA loaded TheraPEA™ microparticles
- Prospective safety and clinical efficacy in a small cohort of client-owned dogs with end stage osteoarthritis
- Led by an academic team of the Utrecht University

Inclusion criteria

- Body weight > 15 kg
- Moderate to severe clinical and radiographic OA
- Lameness score: 2-4/4

Exclusion criteria

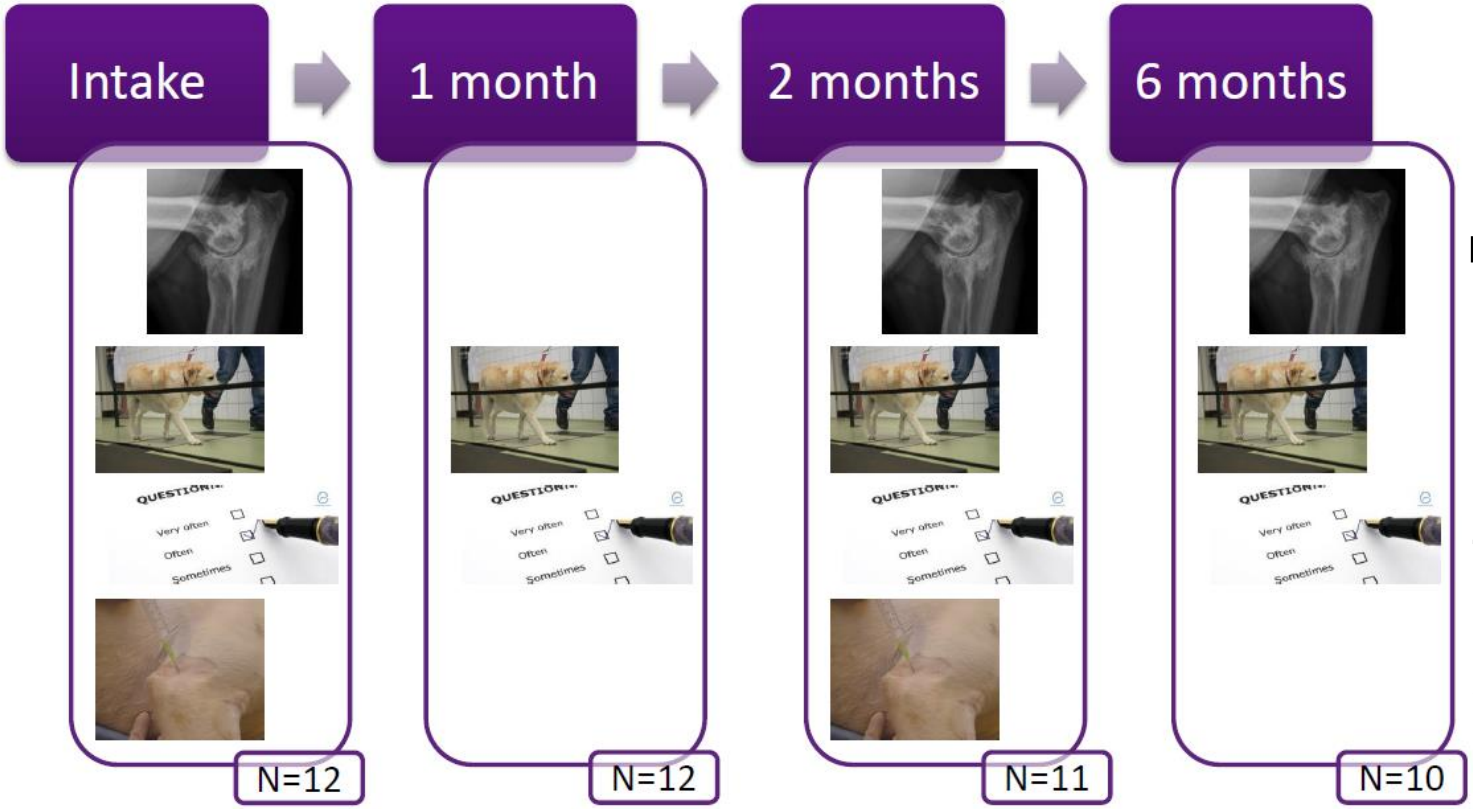
- Other orthopedic or neurologic disease
- Instability of the joint
- Joint surgery <3 months ago
- Septic arthritis
- Fractures or tumors in the ipsilateral limb

Introducing Charly

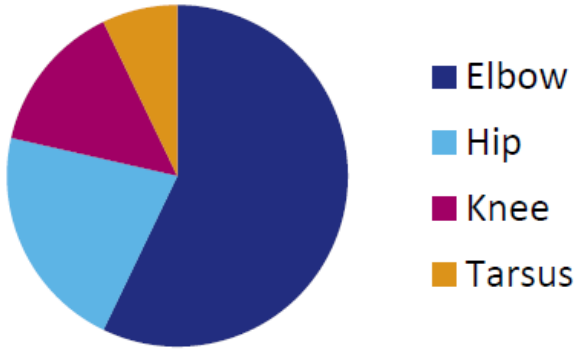
- A Rottweiler & Labrador Retriever mix
- 5 years old with severe OA in both elbows
- Pain most pronounced right front limb lameness, persistent after:
  - Arthroscopy
  - Conservative therapy (oral NSAIDs)

Pharmaceuticals, 2021 March, 13(3): 372

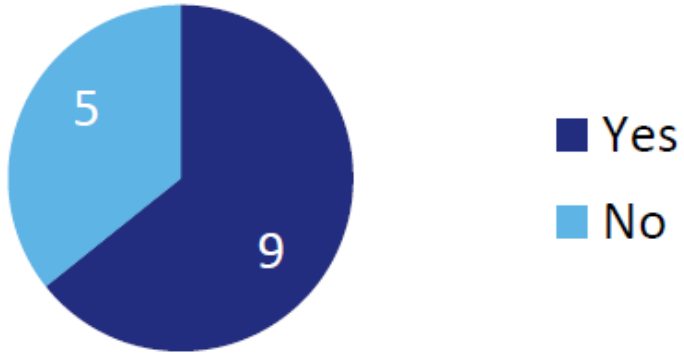
Explanation of Study Design



Injected joints



Previous surgery

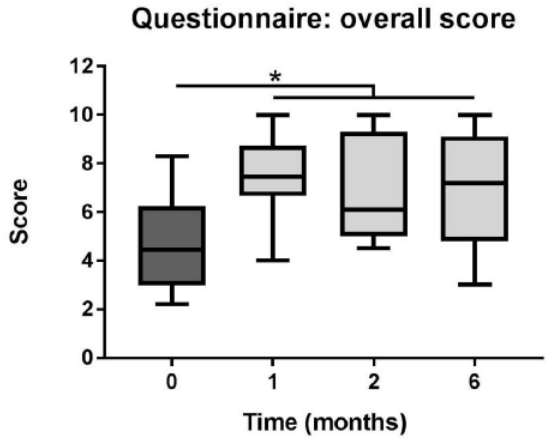


- **Patient's Age:** 7 years (1-11)
- **Body weight:** 30 kg (21-36 kg)
- 2 dogs received IA injections in 2 joints simultaneously

Study Results Show Clear Improvement in Patient Dogs

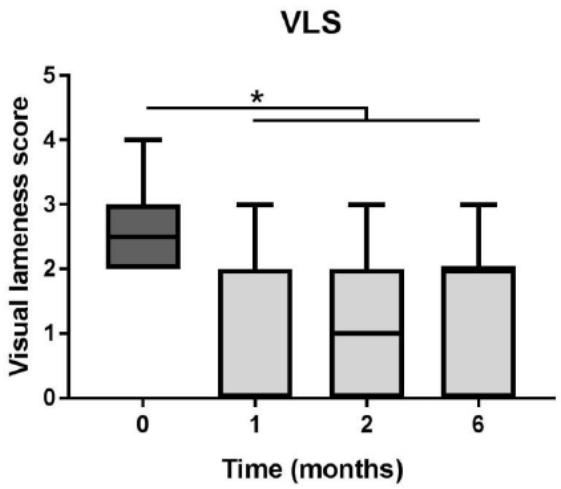
- Clear improvement in 10/12 dogs
  - Concurrent orthopedic conditions in 5/12 dogs
- Transient polyuria and polydipsia in 5/12 dogs
- Increased appetite in 3/12 dogs

Quality of Life – based on owner's feedback



*significance
one month p=0.0008
two months p=0.023
six months p=0.018

Visual Lameness – based on score (veterinarian)



*significance
one month p=0.031
two months p=0.011
six months p=0.016

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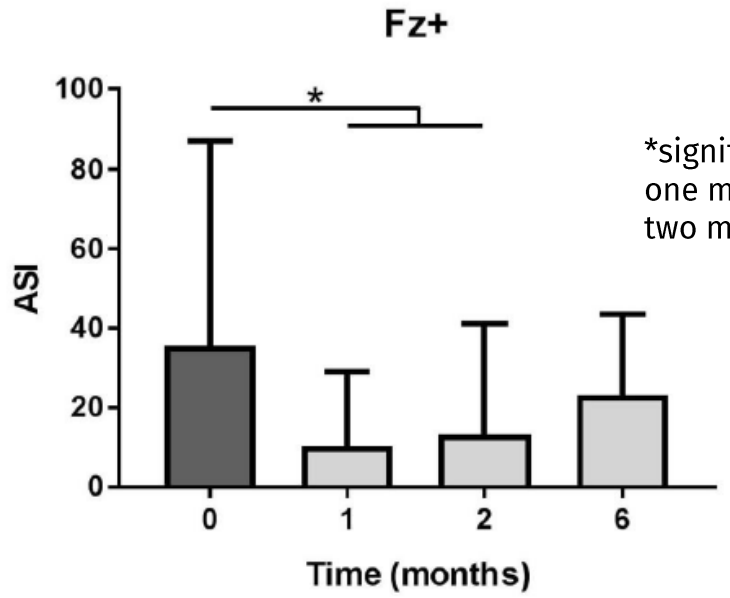
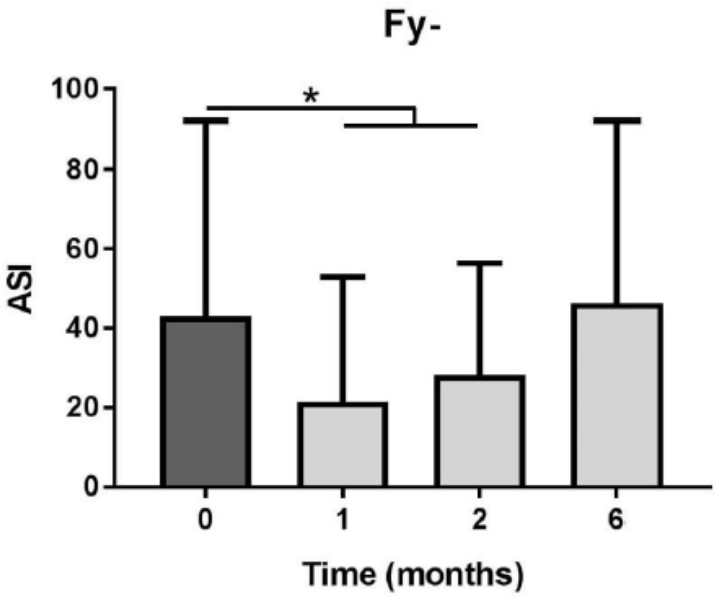
A Clear Positive Therapy Effect is Noted in the Study

Force-plate analysis to assess asymmetry and vertical force



*significance
one month p=0.04
two months p=0.027



*significance
one month p=0.041

1. Vertical force (**FZ+**) and propulsive force (**FY-**) asymmetry, clear therapy effect at 4 and 8 weeks*

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* N=12 for t=0 and 1 month, n=11 for t=2 months, n=7 for t=6 months

Veterinary Study Verifies Promising Management for Severe Osteoarthritis

- Safe administration noted in 12/12 patients
  - Transient systemic effects (similar to Moderin® IA tx)

- Preliminary results seem favorable:
  - Decrease in clinical signs

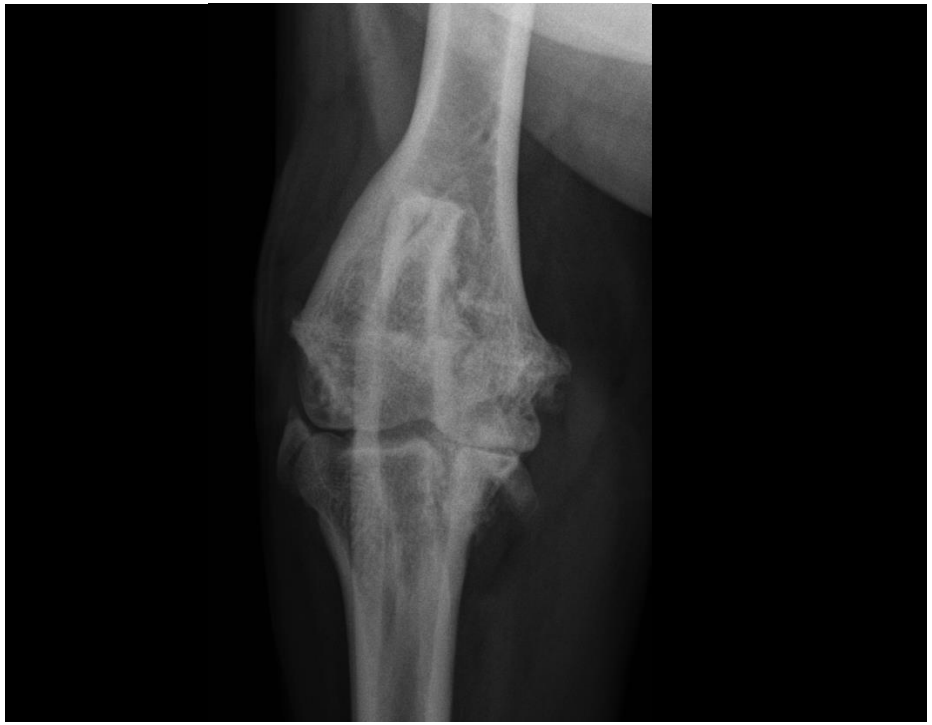
- 10/12 at 1- and 2-months follow-up
- 5/10 at 6 months follow-up
  - Concurrent orthopedic problems

- Follow-up study: prospective, comparative study

Promising results for dogs with severe OA!

A Case Study of Patient Dog, Charly

Pre-study:
Patient Charly presents with severe OA in both elbows, avoiding the use of his right-front limb



Radiography of joint showing OA

Post-study:
Patient Charly is pulling the line and enjoying the long missing run

Conclusions

- TheraPEA™ - biodegradable polymer platform addressing challenges in Drug Delivery
- Unique biodegradation properties and versatile processability – features bridging the gap between a material platform and drug delivery solution
- Developed injectable, extended-release TAA formulation for managing the OA pain
- In-vivo verification in acute OA model
- Prospective safety and clinical efficacy veterinary study – promising results in patient-dogs with severe OA

Why partner with DSM Biomedical?

TheraPEA™ biodegradable polyester amide

Differentiated technology to enable innovative sustained and controlled release therapies for the patient

Bridging the gap between biomaterials technology and drug delivery solution

Solving our world's healthcare needs through sustainable science, together with our partners

A partner you can depend on

Extensive in-house expertise, including analytical competencies and melt and solution-based processing techniques, to accelerate formulation development efforts in our dedicated high potency laboratory.

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- Medical Center of Utrecht University (NL)
- DSM Biomedical Team

Let DSM Take You FURTHER

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