4movingbiotech

Pioneering Innovation in Osteoarthritis Treatment for Patients

PRIX GALIEN USA

THE GALIEN FOUNDATION
Innovation to improve the human condition

AGENDA

- Executive Summary, PMR Insights
  - Osteoarthritis (OA), a serious untreated disease
  - 4P004, First-in-class disease modifying drug for OA (DMOAD)
- Introduction
  - 4Moving Biotech team
  - 4Moving Biotech development approach
- Osteoarthritis challenges and opportunities
  - OA disease epidemiology and burden
  - Risk factors and effects
  - Current OA drug development landscape
  - 4P004 Differentiation factors
- 4Moving Biotech asset key results
  - Preclinical key results
  - In silico clinical trial results
  - Phase 1 clinical trial
  - Next steps and key features

OSTEOARTHRITIS A SERIOUS UNTREATED DISEASE, PMR INSIGHTS

Lack of treatment options and inability in halting disease progression impacts patients' mobility and increases cardiovascular mortality due to a sedentary lifestyle

Epidemiology

- Prevalence of knee OA is expected to have a growth rate of 10-15% in the next 5 years
- Payers cite aging and increasing obesity as the main factors that will influence future prevalence growth at rate of 1-4% annually

Unmet Needs

- Current Txs are effective in dealing with the symptoms but there is an inability in stopping disease progression as no Tx targets the underlying cause, which impacts patient's mobility and pain
- The biggest unmet needs are patient quality of life, pain management and mobility limitations. Both payers and KOLs highlighted the need to stop the disease progression as an important unaddressed issue, while KOLs indicated that the limited efficacy of the current treatments was a significant unmet need

Treatment Landscape

- Initially patients start off with oral and topical NSAIDs, then move to opioids and IA injections (corticosteroids and hyaluronic acid (HA)) - If no response, then progress to knee replacement surgery although 20% of the operated patients will still need analgesics at one year.
- Treatment is focused on managing pain via NSAIDs, opioids, duloxetine (limited use) and IA injections. Patient preference dictates the use of HA IA injections as they are not reimbursed by public systems across the EU

US and Europe Primary Market Research has been performed by IQVIA

4P004, FIRST-IN-CLASS DISEASE MODIFYING DRUG, PMR INSIGHTS

4P004 disease modifying profile is its strongest attribute, delay in knee replacement surgery involves high economic value

4P004 perception

- Excitement with disease-modifying profile. Potential for use in earlier lines of Tx to prevent cartilage degradation
- KOLs across the EU see significant opportunity for the disease-modifying profile but require additional information such as long-term efficacy data at weeks 12, 26, 52, data on the delay in knee-replacement surgeries

Reimbursement Landscape

- Potential of 20-30% premium over HA injections as a disease modifying agent,
- Price potential can increase based on economic value provided according to evidence on avoidance of knee replacement surgery due to its structural effect.

US and Europe Primary Market Research has been performed by IQVIA

AGENDA

- Introduction
  - 4Moving Biotech team
  - 4Moving Biotech development approach

INTRODUCTIONS TO 4MOVING TEAM

Revital Rattenbach

Co-Founder and President

- **More than 15 years of experience** in the creation and development of life sciences start-ups
- **Past experience as CEO at AdSTEM and Pharmaseed Europe**
- **Inventor of 6 families of patents**

Celine Martin

R&D operations

- **More than 10 years of experience** in the industry
- **Preclinical studies** according to quality standards and regulation
- implementation of processes in a **GLP-like environment**

Francis Berenbaum

Co-Founder and CEO/CMO

- **Head of the Rheumatology department** at AP-HP Saint- Antoine Hospital in Paris
- **Professor of Rheumatology** at Sorbonne University
- **Director of a OA research team** at INSERM Institute
- **Former President of OARSI** and of the **French Society of Rheumatology**

Mathilde Merot

Head Clinical and Regulatory

- **More than 10 years of experience** in regulatory affairs
- **Past experience at MSD France** (clinical trials in in 20+ countries), **Inventiva** (fibrosis, lysosomal diseases and oncology), and **Poxel** (rare metabolic diseases)

Emmanuelle Lopez

CFO

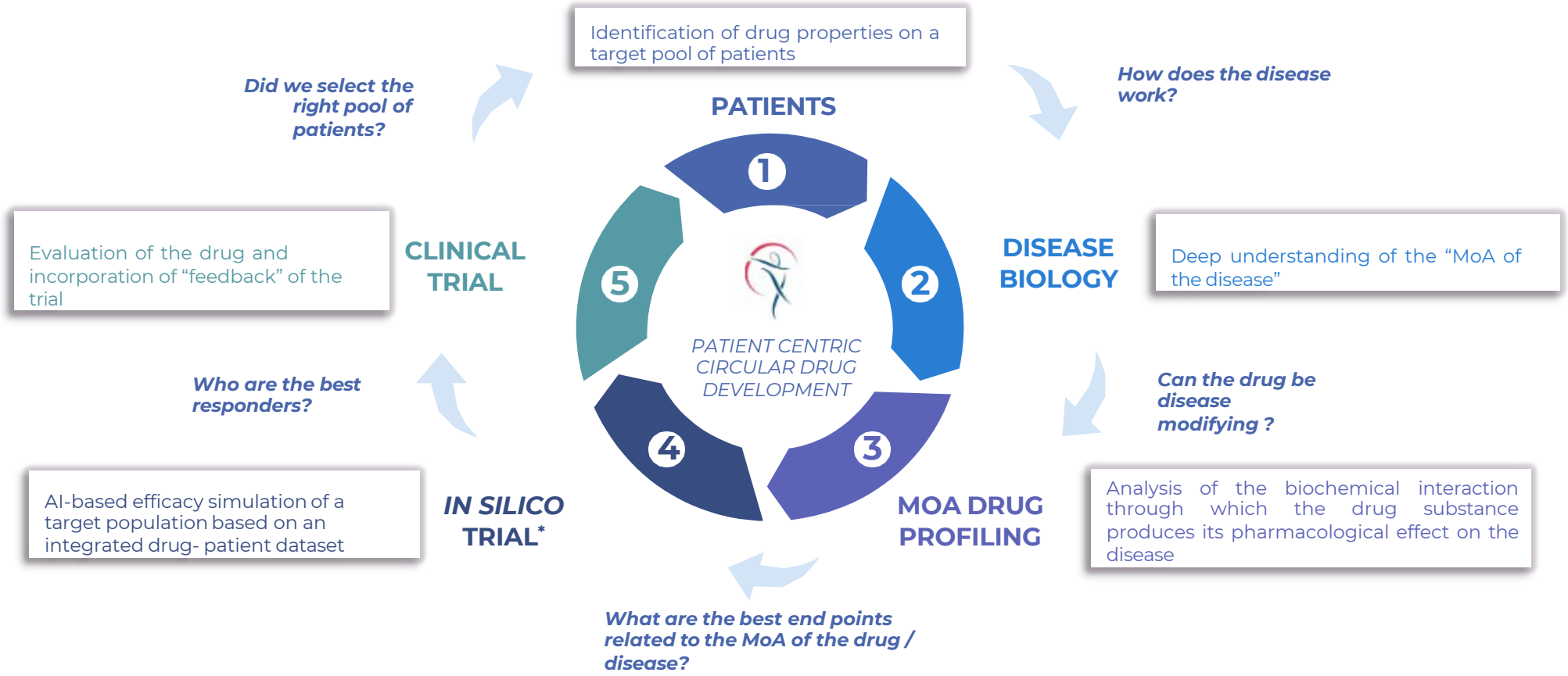
- **25 years of experience** in finance at pharmaceutical and biotech companies (incl. IPO and fundraising)
- **Past experience at DBV Technologies and IPSEN**

Frederic Marin

CDO

- **Past experience at Roche, Novartis, and Schering** in various positions in France and abroad
- Entrepreneur in med tech, API development and manufacturing, as well as drug development
- **Co-founder of Orphalan**

4MOVING BIOTECH DEVELOPMENT APPROACH



QUANTHEALTH Close **collaboration** with key partners during the process, especially QuantHealth for all ***in silico* trials**

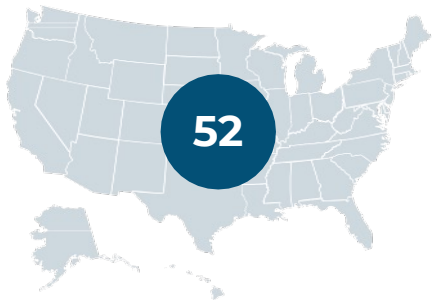
In partnership since March 2022

AGENDA

- Osteoarthritis challenges and opportunities
  - OA disease epidemiology and burden
  - Risk factors and effects
  - Current OA drug development landscape
  - 4P004 Differentiation factors

OA AFFECTS NEARLY ~100M PEOPLE IN THE US AND EUROPE

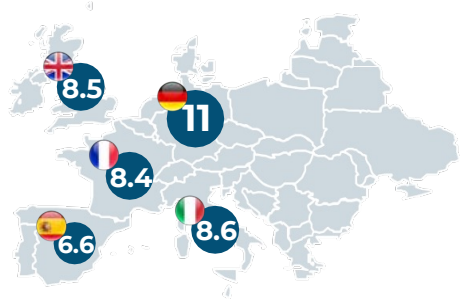
OA PATIENTS IN MILLIONS IN THE US



~52m adults are affected by OA and it is the **most frequent cause** of **disability** among adults

~16% of the population suffers from OA

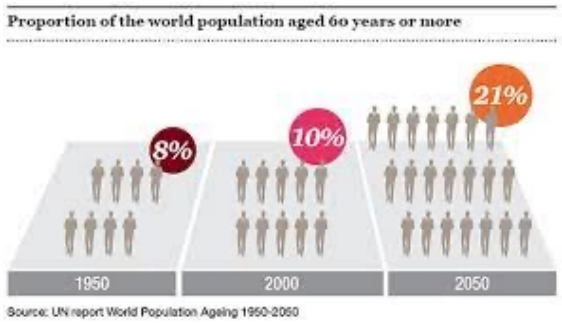
OA PATIENTS IN MILLIONS IN EUROPE



~57m people in Western Europe were affected by OA in 2019

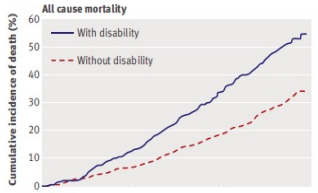
Prevalence of OA in EU4 and the UK ranges from **13 - 14%** of the overall country populations

OA IS A MAJOR NONCOMMUNICABLE DISEASES

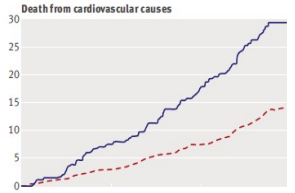


With **the ageing population and obesity** the global burden of OA has grown **by 54% since 1990** (IHME, Global Burden of disease Data 2019)

KNEE OA INCREASES MORTALITY RATE



Adjusted hazard ratio
1.48 (1.17 - 1.86)



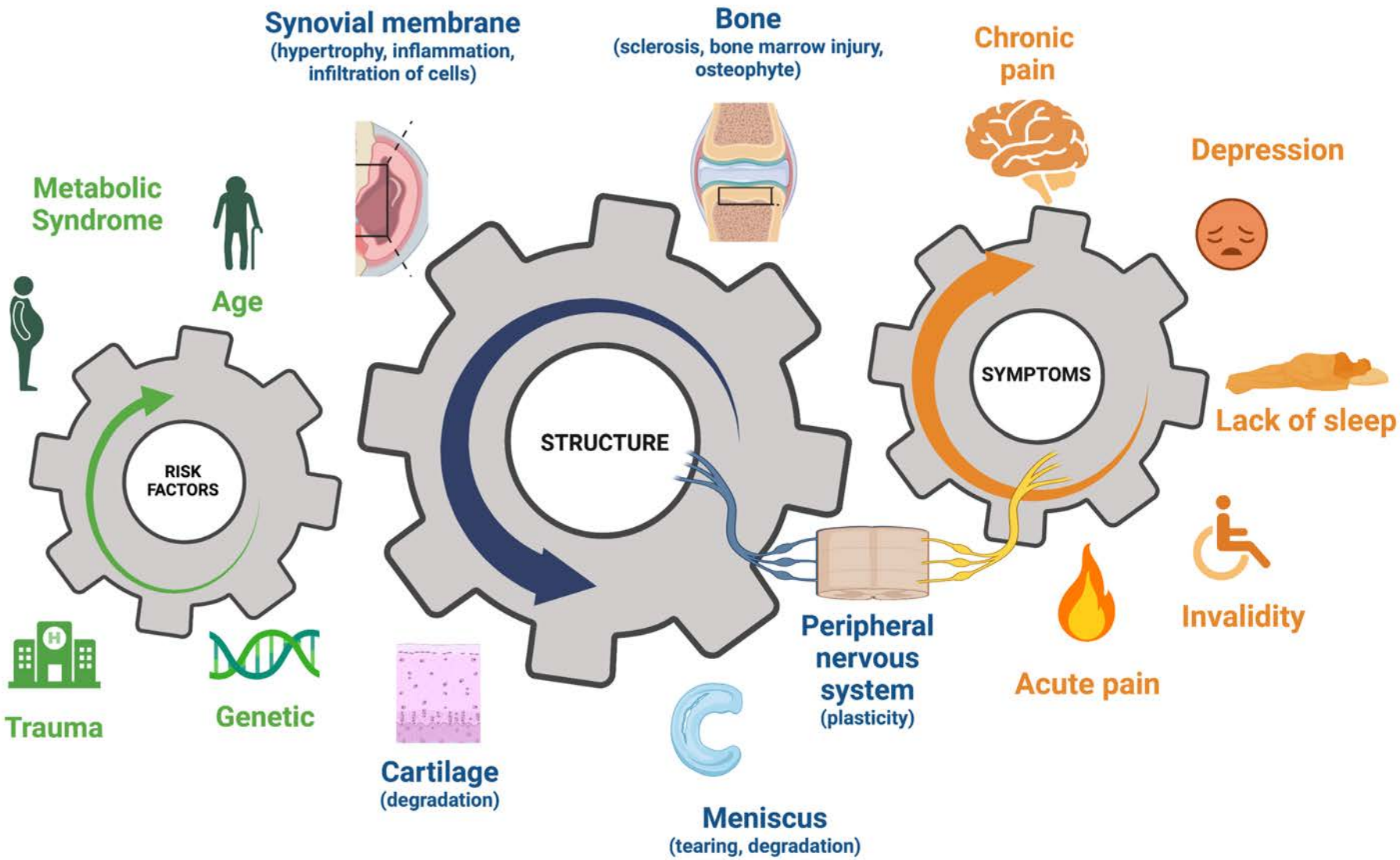
Adjusted hazard ratio
1.72 (1.22 - 2.41)

Patients experiencing chronic pain that is severe or disabling have **increase risk of premature death**, particularly from **cardiovascular death** (Nuesch, 2011, BMJ)

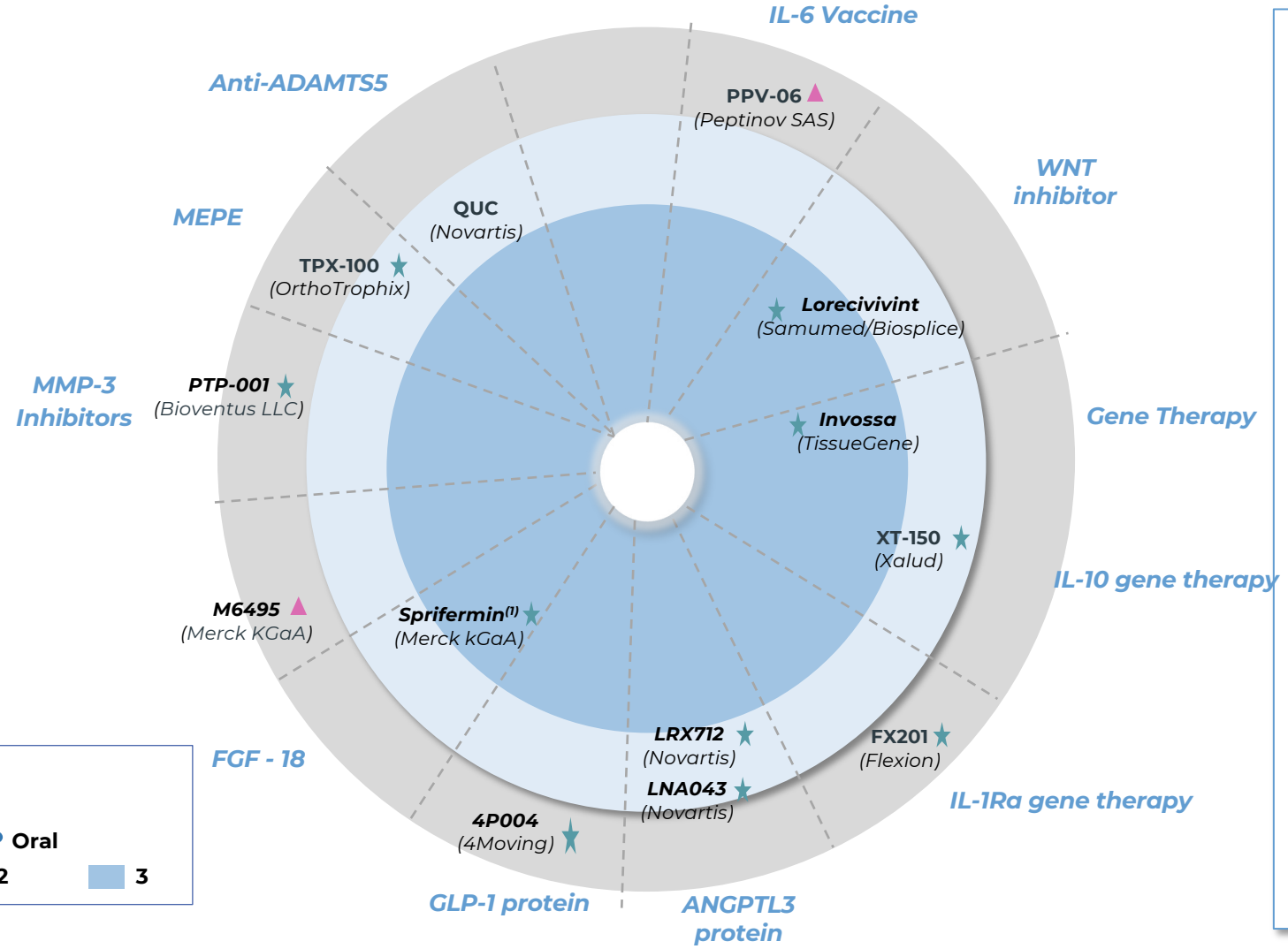
- The **prevalence of knee OA is expected to continue to increase** as a result of rising life expectancy, obesity rates, and more sensitive methods of detection
- OA has a **comprehensive treatment paradigm**, but it is **mainly for managing pain**
- In severe cases, **total knee replacement** represents the main treatment option and there is a **large unmet need for a disease modifying therapy like 4P004**

***Sources**: IQVIA; Global Burden of Disease Study 2019; EU Osteoarthritis Europe; The Economist*

KNEE OSTEOARTHRITIS RISK FACTORS AND EFFECTS



INNOVATIVE DMOAD PIPELINE



- Around **14 pipeline products** which could be potentially considered as DMOADs have been identified
- **Two assets** have reached **Phase III**
- **Highest activity** is observed in **the Phase-II stage**, with **8 assets in development**
- Pipeline drugs basically relate to the three **main OA endotypes (cartilage-driven, synovitis-driven, and bone-driven endotypes)**

Source: *IQVIA*
Note: *(1) Sprifermin & MIV-711 earlier showed structural benefit but no symptomatic benefit. However post-hoc studies in a subgroup of patients show symptomatic relief with structural improvements*

4P004 DIFFERENTIATES ITSELF FROM THE PIPELINE OF POTENTIAL INNOVATIVE DMOAD

	4P004	Lorecivivint	Sprifermin	UBX0101	LNA043	LRX712	GLPG1972	MIV-711	TPX-100	M6495	PTP-001
Symptomatic	✓	×	×	×	×	✓	×	×	×	×	×
Structure Modifying	✓	✓	✓	×	✓	✓	×	✓	✓	✓	✓
Target/MoA	GLP-1R	WNT inhibitor	FGF - 18	Senolytic	ANGPTL3 protein	ANGPTL3 + anti-IL1	ADAMTS-5 inhibitor	Cathepsin K Inh	MEPE	ADAMTS-5 inhibitor	MMP-3 inhibitor
Phase	I	III	II	II	II	II	II	II	II	I	I
Expected market approval	**2027**	?	?	stop	**2026/27**	?	stop	stop	**2026/27**	?	Q2 2030
Developed by	4Moving Biotech	Biosplice	Merck/Trial Spark	Unity Biotech	Novartis	Novartis	Galapagos	Medivir	OrthoTrophix	Novartis	Bioventus
Bone driven	✓	×	×	×	×	×	×	✓	✓	×	×
Cartilage driven	✓	✓	✓	✓	✓	✓	✓	×	×	✓	✓
Synovitis driven	✓	×	×	×	×	×	×	×	×	×	×
Safety	Well known	NCE	NCE	NCE	NCE	NCE	NCE	NCE	NCE	NCE	NCE

4P004 is the **only drug** expected to be a DMOAD with **properties on the three OA structure effects** (bone, synovitis, cartilage)

LNA043 is positioned as **the only direct competitor** of 4P004 with a market entry expected to happen before 4P004. However, it **did not demonstrate any symptomatic effect preclinically**

***Source**: IQVIA*

AGENDA

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  - Preclinical key results
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RATIONALE FOR LIRAGLUTIDE AS A TREATMENT FOR OSTEOARTHRITIS

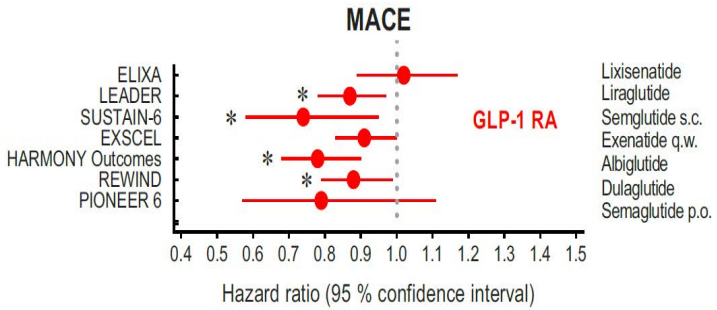
SCIENTIFIC RATIONALE OF 4P004

- 4P004 consists in the **regeneration of Liraglutide from its subcutaneous use in type II diabetes mellitus and weight management to the treatment of osteoarthritis (OA) through intra-articular (IA) administration**

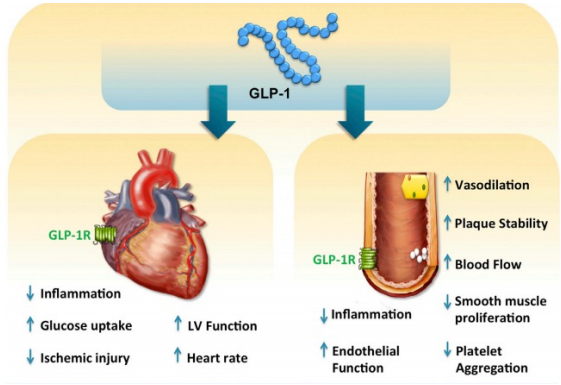
- In recent years, **numerous studies have detailed the anti-inflammatory impact of GLP-1 in numerous organs and diseases** (Nauck, 2016; Li et al., 2017, Meurot et al., 2022)

LITERATURE DATA: GLP-1 ANALOGUES HAVE ANTI-INFLAMMATORY PROPERTIES

*The **unique cardioprotective properties** of GLP-1 analogues have been demonstrated in pivotal clinical trials*



*Cardio protection of GLP-1 analogues is explained at least in part by **anti-inflammatory properties***

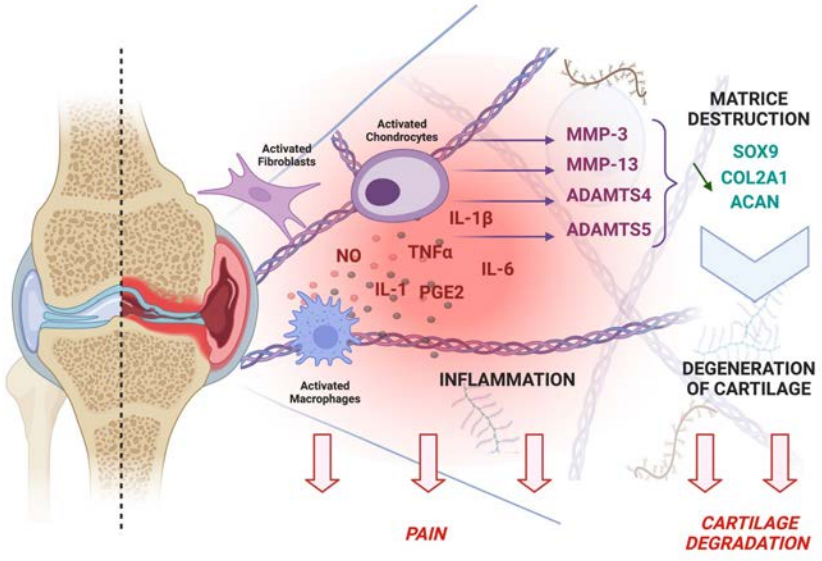


***Sources**: Company information; IQVIA; Investigator's brochure 4MB-LAS-IB (07-Jun-2022); Nauck & Meier (2019)*

LINKING OA PHYSIOPATHOLOGY TO 4P004 MOA

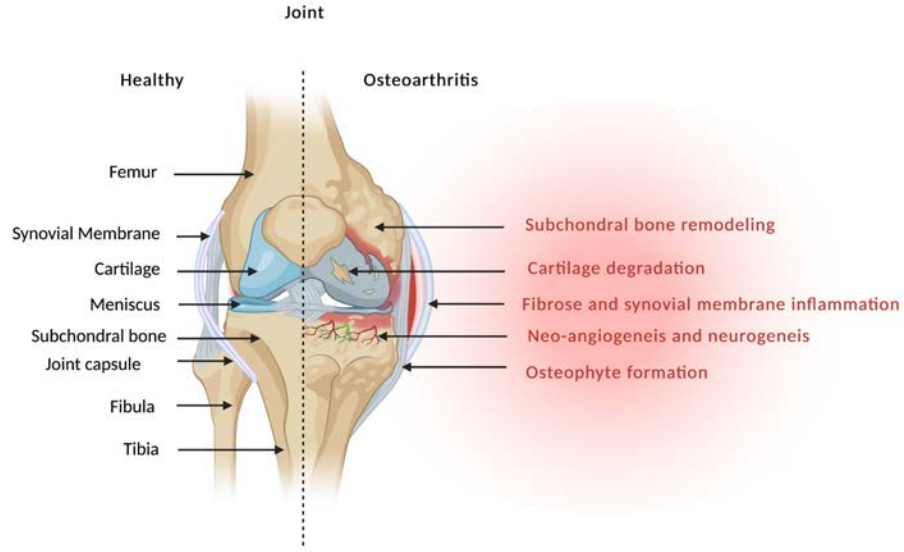
Thanks to the expression of GLP-1 in three different types of cells in the knee (chondrocytes, synovial fibroblasts and macrophages), 4P004 is **expected to address all symptomatic effects of OA**:

- ✓ Anti-inflammatory properties,
- ✓ Analgesic effects,
- ✓ Dose-response effect
- ✓ Long-lasting effect



Knee OA is characterized by **significant structural features** leading to the **degradation of the joint** through **3 main identified structures,** all of which are **expected to be addressed by 4P004**

- ✓ Synovial Membrane
- ✓ Cartilage
- ✓ Bone



4P004: STRATEGY TO ACCELERATED FDA APPROVAL

"The ultimate goal of treatments related to the inhibition of structural damage or targeting the underlying pathophysiology associated with OA is to avoid or significantly delay the complications of joint failure and the need for joint replacement, and also to reduce the deterioration of function and worsening of pain"
FDA, 2018

Preclinical data suggests that **intra-articular administration of Liraglutide** provides **both structural benefits and analgesic effects**, hence fulfilling the **FDA definition of a Disease Modifying Drug for OA**

Patient reported Outcomes

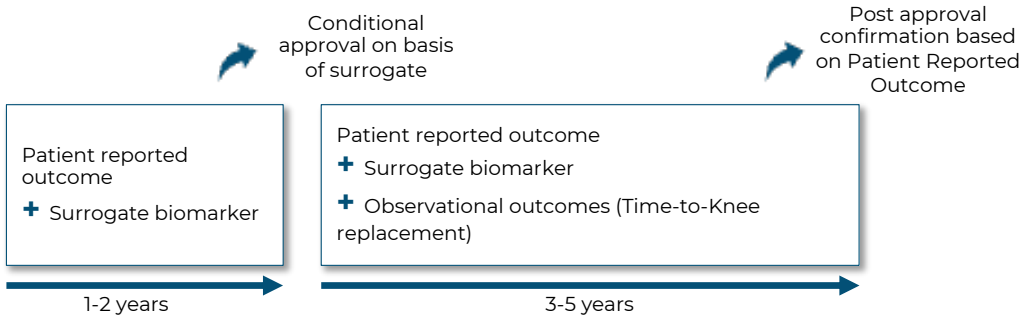
1. **ANTI-INFLAMMATORY PROPERTIES**
2. **ANALGESIC EFFECTS**
3. **DOSE RESPONSE EFFECT**
4. **LONG LASTING EFFECT**

Surrogate Biomarkers

5. **DECREASED SYNOVITIS SCORE**
6. **DECREASED CATABOLIC MEDIATORS**
7. **DECREASED MEDIAL TIBIAL CARTILAGE DEGENERATION**
8. **DECREASED OSTEOPHYTE SCORE**

Observational Outcomes

9. **SLOWING OA PROGRESSION**
10. **DELAYING TIME TO KNEE REPLACEMENT**

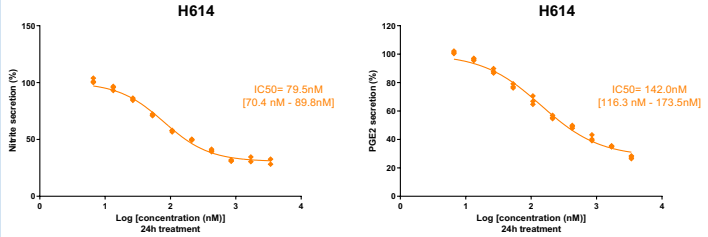


Sources: *OARSI; FDA; Kraus et al, 2019*

4P004: SYMPTOMATIC PROPERTIES ON OSTEOARTHRITIS

1 ANTI-INFLAMMATORY PROPERTIES

- *In vitro* quantification of NO and PGE2 as inflammatory markers
- Human OA patients chondrocytes or synoviocytes treated with IL1β[(1)] 1 ng/mL + ascending doses of Liraglutide (6.6nM to 3.4µM) for 24 hours
- 5 patients chondrocytes and synoviocytes have been used and results were reproductible

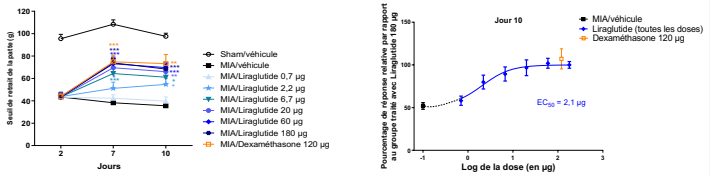


Liraglutide dose-dependently decreases anti-inflammatory markers in **human OA chondrocytes** and **synoviocytes at a nanomolar concentration**

2 ANALGESIC EFFECTS

3 DOSE RESPONSE EFFECT

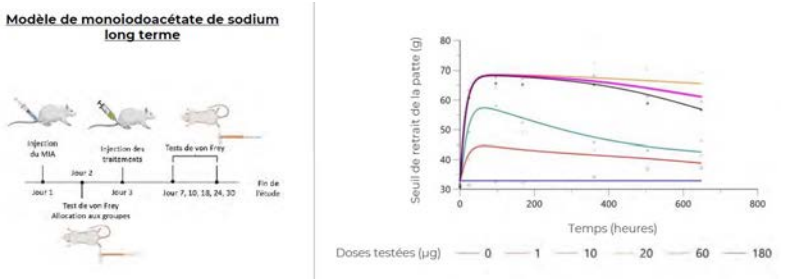
- *In vivo* single IA injection of Liraglutide
- Short term MIA[(1)] model and dose response study in comparison with dexamethasone
- EC50 was determined to be 2.1 µg on day 10 in this rat model



In the short-term MIA model, Liraglutide provided a **dose-dependent decrease** in pain

4 LONG LASTING EFFECT

- Long term MIA model and several dose response studies
- Liraglutide in a single injection reduces pain in the different doses tested with duration of analgesic effect up to 30 days in rats



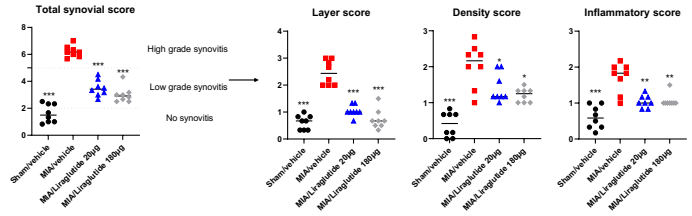
IA single Liraglutide injection **reduces pain** over the **long-term**

Source: *Company information*
Notes: *(1) IL1β: model inducer; (2) IC50: measure of the potency of the drug*

4P004: STRUCTURE MODIFYING DRUG FOR OSTEOARTHRITIS

5 DECREASE SYNOVITIS SCORE

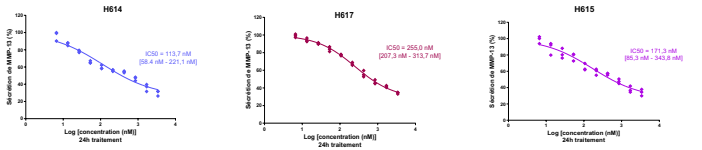
- *In vivo* MIA rat model
- One single intra-articular injection of Liraglutide
- Synovial membranes histological score was assessed at day 4 according to *Krenn et al.*



Liraglutide **decreased synovitis score** including a decrease in the **thickness of the synovial membrane**, the **inflammatory infiltrates** as well as the **density of resident cells**

6 DECREASE CATABOLIC MEDIATORS

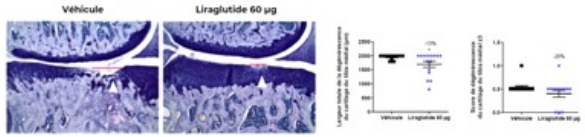
- *In vitro quantification of MMP-13 as a catabolic marker*
- *Human OA chondrocytes treated with IL1β 1 ng/mL + ascending doses of Liraglutide (6.6nM to 3.4µM) for 24 hours*



Liraglutide **dose-dependently reduced a catabolic marker** in human primary **OA chondrocytes** suggesting a protective role in articular cartilage in OA patients

7 DECREASED MEDIAL TIBIAL CARTILAGE DEGENERATION WIDTH

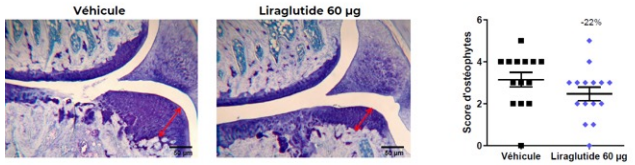
- *An OA rat surgical model (DMM, Destabilisation of Medial Meniscus) has been performed in an independent laboratory to assess structural degeneration scores after Liraglutide treatment*
- *15 rats per group (statistics : Mann Whitney, t-test)*
- *Rats treated with 60 µg Liraglutide had significantly reduced total cartilage degeneration widths as compared to vehicle-treated disease controls (as a result of decreased proteoglycan loss in zone 3 of the tibial cartilage)*



Liraglutide reduced several measures and histological scores, thereby inducing **beneficial structural effects on articular cartilage**

8 DECREASED OSTEOPHYTE SCORE

- An OA rat surgical model (DMM, Destabilisation of Medial Meniscus) has been performed in an independent laboratory to assess structural degeneration scores after Liraglutide treatment
- 15 rats per group (statistics : Mann Whitney, t-test)
- A slight (non-significant) benefit on osteophyte scores and measures

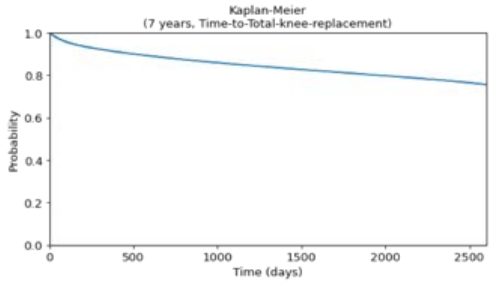


Liraglutide reduced osteophyte score, thereby **inducing beneficial structural changes on subchondral bone**

4P004: CLINICAL *IN SILICO* SIMULATION - OBSERVATIONAL OUTCOME

9 SLOWING OA PROGRESSION

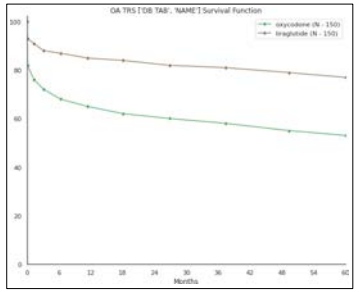
- **Patients retrospective study on OA progression**: data from 11.4 million OA patients and ***in silico* simulation** compared to Oxycodone treatment (severe pain patients)



Specific records were aggregated into 3 categories of progression:
- Progression category 1: pain
- Progression category 2: functional disorder
- Progression category 3: total knee replacement

The first occurrence of records from the above categories is considered as a progression event

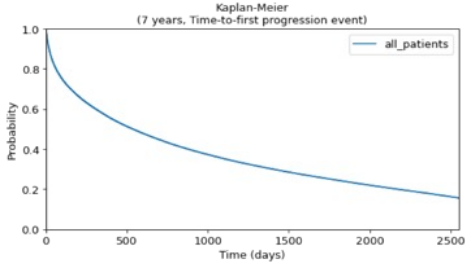
In silico simulation using Liraglutide compared to Oxycodone



Progression free period			
	Probability (60 months)	Median (months)	Hazard ratio
Liraglutide	**34%**	16.56	0.61
Oxycodone	14%	1.55	
Pvalue	≤0.0001	≤0.0001	

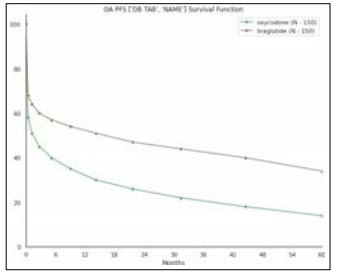
10 DELAYING TIME TO KNEE REPLACEMENT

- **Patients retrospective study on OA progression**: data from 11.4 million OA patients and ***in silico* simulation** compared to Oxycodone treatment (severe pain patients)



Time-to-event analysis demonstrates the kinetics of joint replacement probability over a period of 7 years
- At 2 years from diagnosis, the probability for knee joint replacement is 12%
- At 7 years from diagnosis, the probability for knee joint replacement is 24%

In silico simulation using Liraglutide compared to Oxycodone



Total knee replacement free period			
	Probability (60 months)	Median (months)	Hazard ratio
Liraglutide	**77%**	99.71	0.63
Oxycodone	53%	63.75	
Pvalue	≤0.0001	≤0.0001	

Longer median time to disease progression (c.16.6 vs. c.1.6 months)

Higher probability of no disease progression at 60 months with 4P004 vs. Oxycodone

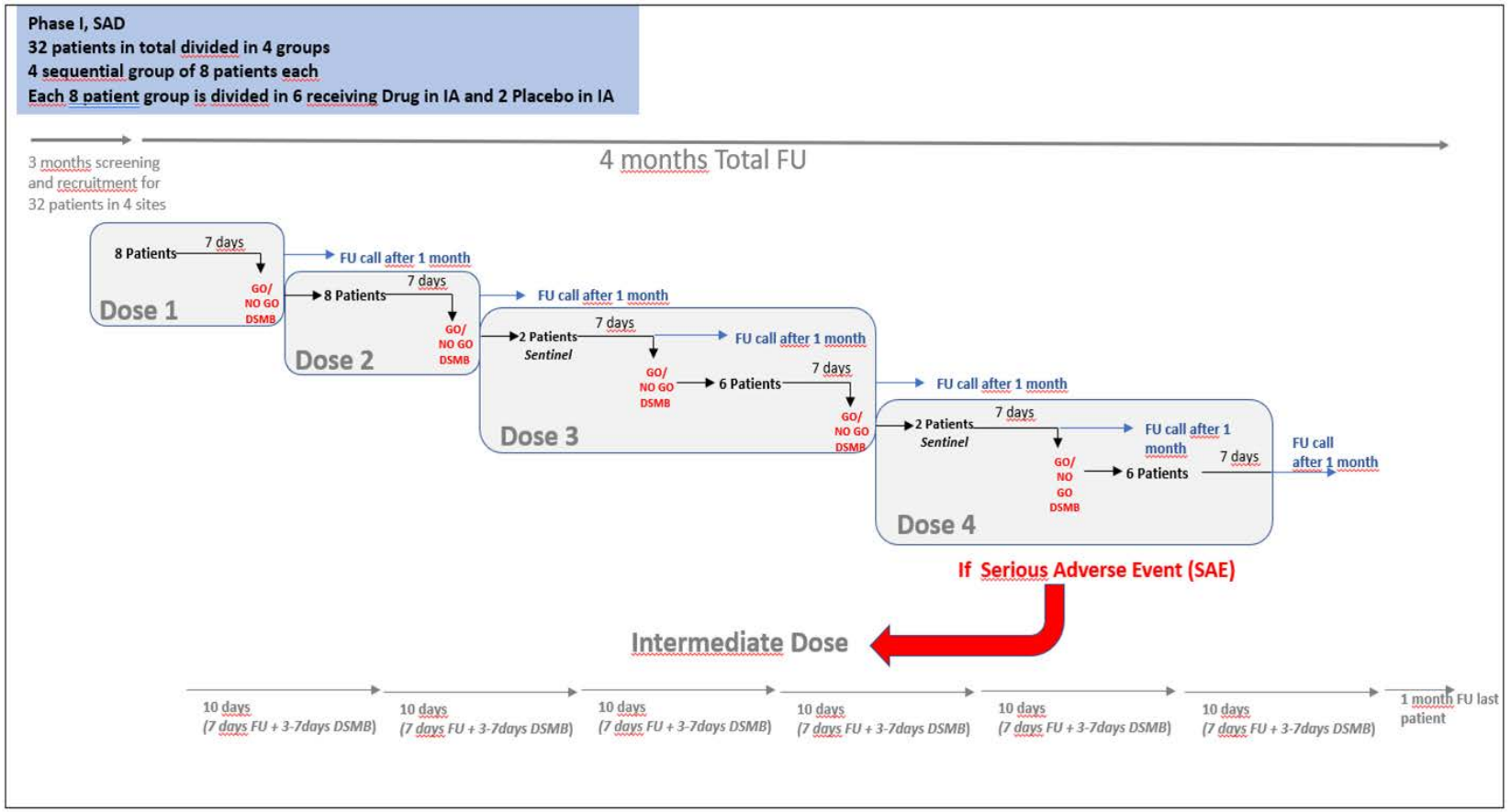
Longer median time to total knee replacement (c.100 months vs. c.64 months)

Higher probability of no total knee replacement at 60 months with 4P004 vs. Oxycodone

Sources: *Company information; QuantHealth*

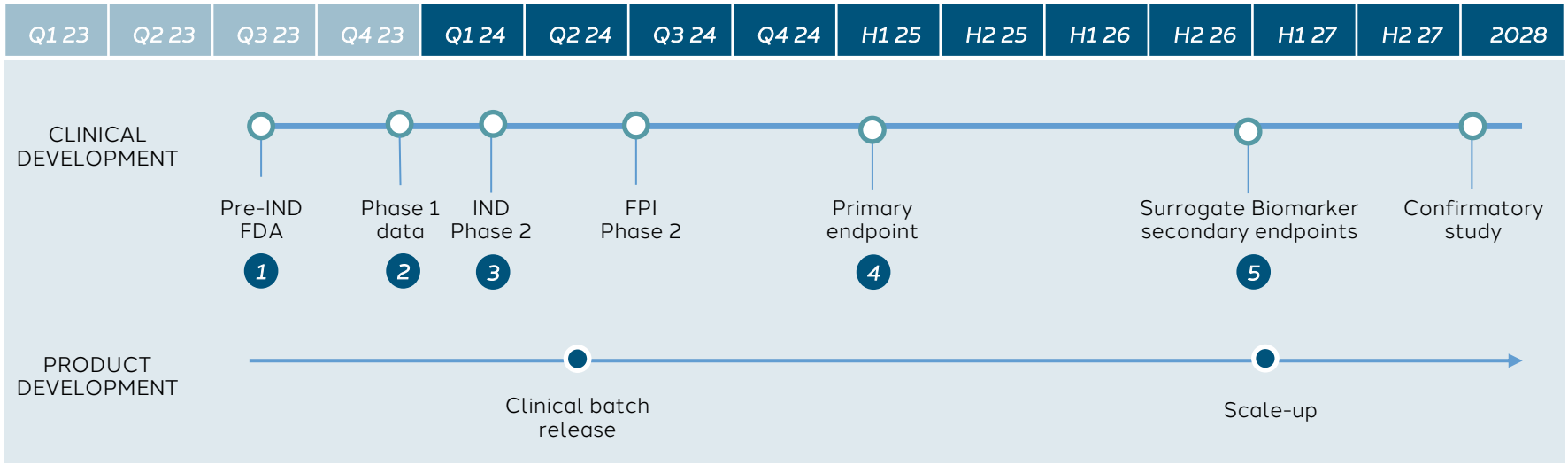
ONGOING PHASE 1

- Safety, Tolerability and Pharmacokinetics of Intra-articular (IA) Single Ascending Dose of 4P-004 in Patient With Kellgren and Lawrence Grade 2 to 4 Osteoarthritic (OA) Knee (LASARE)
- Multicenter, randomized, double-blind, placebo-controlled study to assess the safety and tolerability of single ascending dose of IA 4P-004 at 0.3, 1.0, 3.0 and 6.0 mg in participants (increasing from cohort 1 to 4)



4P004 DEVELOPMENT PATH

4P004 (Regenerated Liraglutide)



1. Pre-IND meeting including non-clinical, CMC and in silico trials approach
2. Phase 1 data expected to be released Q4 2023
3. Phase 2 expected to be on more than 600 patients over 2 years (US and Europe) using PK/PD modelling for dosing / dosing regimen
4. Patient outcome (pain and function)
5. MRI – surrogate biomarkers

4MOVING BIOTECH – KEY FEATURES

1 No effective treatment to address disease progression

- Current OA treatments target pain reduction and improvement in function
- There is no non-surgical intervention that can prevent, halt or even delay disease progression. DMOADs are highly anticipated by both physicians & patients

2 Limited efficacy of current treatments

- There is significant need to develop efficacious treatment alternatives for OA patients that do not undergo joint replacement; especially younger (<55yo) symptomatic patients and those who are not considered radiographically advanced enough

3 Safety concerns limits long term use

- NSAIDs are associated with gastrointestinal (ulcer formation), renal and CV risk
- IA corticosteroids increase blood glucose levels and impact patients with co-morbidities such as diabetes
- High risk of addiction with long-term opioid use

4 Economic burden

- Due to unavailability of any disease modifying treatment leads to high disease burden associated with high number of knee replacement surgeries and indirectly from loss of working days due to disability which impacts GDP of a nation

Opportunity for 4P004

Long lasting analgesia effect; not available in current SoC

Disease modifying properties on cartilage, bone or synovial inflammation of joints

Higher probability of no disease progression and no total knee replacement at 60 months

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