DEVELOPMENT & CLINICAL OR PRECLINICAL EVIDENCES ***(500 words)***
History of the development of the solution/product

4Moving Biotech, a spin-off of 4P-Pharma, is emerging as a leading player in the field of biopharmaceuticals, particularly in the treatment of osteoarthritis with its groundbreaking development, 4P004.

4P004 is an innovative regenerative biopharmaceutical developed by 4P-Pharma in collaboration with SATT Lutech and the team led by Professor Berenbaum at Saint Antoine Hospital.

Our product, 4P004 is a new proprietary formulation of Liraglutide (marketed as Victoza®/Saxenda®) for intra-articular (IA) administration **targeting the OA root causes themselves** (i.e. inflammation, pain symptoms and cartilage destruction). In addition, 4P004 active pharmaceutical ingredient based on a decade of pharmacovigilance data from diabetic patient experience with Liraglutide has a very solid safety profile.

The **breakthrough innovative feature** of 4P-004 is its **DMOAD properties**. In 2018, the FDA recognized OA as a serious disease with a huge unmet medical need and edited a guideline for the development of DMOADs[i], which should include the following requirements:

- Improvement of articulation function;
- Decrease of pain;
- Inhibition of structural damage or targeting underlying OA pathophysiology, to avoid or significantly delay the complication of joint failure and the need for joint replacement.

4P004 is claimed to be a DMOAD as it fulfils these endpoints. It showed **a triple effect on OA disease**[ii/iii] in preclinical studies performed so far:

1. **Anti-inflammatory (short/mid-term effect):** Under OA inflammatory conditions, chondrocytes, macrophages and synoviocytes secrete cytokines and degradative enzymes involved in joint cartilage destruction. We showed *in vitro* and *in vivo* that 4P004 blocks the overexpression of several cytokines as well as degradative enzymes in all joint cells leading to the inhibition of the inflammatory process involved in OA, associated with an amelioration of joint function.
2. **Anti-pain (short/long-term effect):** OA induced pain is correlated to inflammation in the joint. We showed in 4 different preclinical OA models in rodents that 4P004 has analgesic effects associated with inflammation markers decrease. We have also shown in clinically diagnosed OA dogs, a sustained amelioration of mobility and activity observed by dog owners as well as by the veterinarian for at least 10 weeks (observation period) after treatment with 4P004.
3. **Cartilage protection/regeneration (mid/long-term):** OA key feature is a chronic and irreversible joint cartilage degeneration. It is therefore mandatory to avoid cartilage destruction and/or promote cartilage regeneration in order to stop or

delay OA progression. We showed in OA surgical model in rodents, a significant increase of medial joint repair and, interestingly, an increase in the number and density of chondrocytes nests (clusters of proliferating chondrocytes), revealing not only a decrease in cartilage degeneration, but a more intense cartilage regeneration. In clinical practice, Liraglutide may thus have a direct effect on cartilage cells, therefore showing a great novelty compared to existing solutions.

Following those successful preclinical studies, which were recognized with the European Commission's Seal of Excellence and the EUROSTAR collaborative program, the development of 4P004 has reached regulatory and clinical stages and has been isolated within a dedicated entity, 4Moving Biotech. In addition to rigorous preclinical evaluations, 4Moving Biotech has adopted a pioneering approach by conducting extensive in silico clinical trials. Leveraging advanced computational modeling and a retrospective analysis involving 11.4 million osteoarthritis patients, we have successfully stratified the population to identify the best responders population for our phase 2 clinical trial.

Integration of in silico trials with traditional clinical evaluations is a powerful combination that accelerates the evaluation of treatment efficacy and forecasts patient outcomes in a cost-effective and time-efficient manner[iv]. Through the comprehensive analysis of vast amounts of data, these virtual trials provide valuable insights into the effectiveness of 4P004, supporting its development and potential accelerated regulatory approval. Currently, a phase 1 clinical trial is underway in osteoarthritis patients in Belgium, and a phase 2 trial is planned.

References

[i] Food and Drug Administration (FDA), Guidance Document. Osteoarthritis: Structural Endpoints for the Development of Drugs, August 2018. Docket no. 2018-18214. Issued by: Center for Drug Evaluation and Research; Center for Devices and Radiological Health; Center for Biologics Evaluation and Research. Available online at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/osteoarthritis-structural-endpoints-development-drugs (consulted on September 24th 2019).

[ii] Meurot C, Martin C, Sudre L, Breton J, Bougault C, Rattenbach R, Bismuth K, Jacques C, Berenbaum F. Liraglutide, a glucagon-like peptide 1 receptor agonist, exerts analgesic, anti-inflammatory and anti-degradative actions in osteoarthritis. Sci Rep. 2022 Jan 28;12(1):1567. doi: 10.1038/s41598-022-05323-7. PMID: 35091584; PMCID: PMC8799666.

[iii] Meurot C, Jacques C, Martin C, Sudre L, Breton J, Rattenbach R, Bismuth K, Berenbaum F. Targeting the GLP-1/GLP-1R axis to treat osteoarthritis: A new opportunity? J Orthop Translat. 2022 Feb 25;32:121-129. doi: 10.1016/j.jot.2022.02.001. PMID: 35280931; PMCID: PMC8888891.

[iv] Food and Drug Administration (FDA), Webcast lecture: "How Simulation Can Transform Regulatory Pathways" Tina Morrison, PhD, Deputy DirectorDivision of Applied Mechanics FDA's Center for Devices and Radiological Health (CDRH). Available online at: https://www.fda.gov/science-research/about-science-research-fda/how-simulation-can-transform-regulatory-pathways