Category

Best Startup

Product/Solution Name

4P004-DMOAD

Date of Approval

N/A

Indications

Osteoarthritis

Therapeutic Categories

Disease modifying drug for osteoarthritis

Attached Files:

- 4MovingBiotechGalien USA awardJune2023.pdf

Background information and need for solution/product

Osteoarthritis (OA) is the most common degenerative joint condition and the leading cause of disability worldwide . In 2017, it affected over 40 million Europeans and 303 million people globally . “Sharp, burning, predominant, omnipresent, daily activities, less confident, feel old, no foreseeable end” This is how patients describe OA pain.
The prevalence of OA is rising sharply due to an ageing population and rising obesity rates. Characterized by chronic joint pain and functional disability, OA imposes a huge burden on patients and healthcare systems (costs per patient per year: ca. €15k). The cost of OA in the US is estimated at $200bn annually with OA being the 3rd most common hospital admission/discharge diagnosis, ahead of cardiovascular diseases . This financial burden primarily stems from over 900,000 hospitalizations, mainly for joint replacement surgery. OA increases the risk of cardiovascular mortality by 50%, diabetes, hypertension, obesity, cancer and dementia, due to the sedentary lifestyle imposed by chronic pain and joint stiffening that makes walking difficult or impossible . So, far from being a benign disease, knee OA must be seen as a serious condition that justifies the relentless search for preventive and curative solutions.
Current treatments only provide temporary relief of symptoms (pain and inflammation), but do not stop the progression of the disease at the tissue level. Eventually, surgical joint replacement becomes inevitable and is a highly invasive procedure that exposes the patients to the risk of complications and requires post-operative recovery . In addition, 20% of patients still experience chronic pain one year after surgery.

The therapeutic concept and the medical rationale behind our product is based on the clinical observation of one of the world’s most renowned rheumatologists, Prof. Francis Berenbaum (leading researcher and clinician, former president of OA Research Society International (OARSI))) on his OA patients at the Sorbonne St-Antoine University Hospital in Paris, France. He was one of the first clinicians to correlate OA with low-grade inflammation induced by metabolic disorders such as

diabetes , his intuition later confirmed by other investigators . He proposed that drugs targeting metabolic-induced low grade inflammation could become a Disease-Modifying OsteoArthritis Drug (DMOAD).

Our innovation is based on this major paradigm shift that GLP-1 analogues used in the management of Type-2 Diabetes Mellitus and obesity could be the next game-changing therapeutic solutions for OA. Researchers and clinicians have recognized that the GLP-1 analogue liraglutide, the active pharmaceutical principle in 4P004, indeed has tremendous potential as a broad-spectrum treatment for various age-related diseases, and is currently in clinical trials for the treatment of neurodegenerative and cardiovascular diseases .

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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 breakthrough 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 the Sorbonne Saint Antoine University Hospital.
Our product, 4P004 is a new proprietary formulation of liraglutide (marketed as Victoza®/Saxenda®) for intra-articular (IA) administration that targets the root causes of OA (i.e. inflammation, pain symptoms and cartilage destruction). In addition, based on a decade of pharmacovigilance data from diabetic patients with liraglutide, 4P004 has a very solid safety profile.
The breakthrough innovation of 4P-004 is its DMOAD properties. In 2018, the FDA recognized OA as a serious disease with a huge unmet medical need and issued a guideline for the development of DMOADs , which should include the following requirements:
 Improve joint of function;
 Reduce pain;
 Inhibit of structural damage or target the underlying the pathophysiology of OA to prevent or significantly delay the complication of joint failure and the need for joint replacement.

A recent cohort study comparing diabetic patient suffering from knee OA and treated w/o a GLP-1 analogue has shown a strong association between GLP-1 analogues exposure and level of knee pain, cartilage loss velocity on MRI and a decreased incidence of knee surgery, an association only partly mediated by weight reduction .

In our preclinical studies, 4P004 is claimed to be a DMOAD as it meets these endpoints. It has demonstrated a triple effect on OA disease / in preclinical studies to date:

1. Anti-inflammatory (short-/mid-term effect): Under inflammatory conditions of OA, chondrocytes, macrophages and synoviocytes secrete cytokines and degradative enzymes involved in joint cartilage destruction. We have shown in vitro and in vivo that 4P004 blocks the overexpression of multiple cytokines as well as degradative enzymes in all joint cells resulting in inhibition of the inflammatory process involved in OA, associated with improvement in joint function.

2. Anti-pain (short-/long-term effect): OA-related pain is correlated with inflammation in the joint. We have shown in 4 different preclinical rodent models of OA that 4P004 has analgesic effects associated with a decrease in inflammatory markers. We have also shown in clinically diagnosed OA dogs, a sustained improvement of mobility and activity observed by both dog owners and veterinarians for at least 10 weeks (observation period) following treatment with 4P004.
3. Cartilage protection/regeneration (mid/long-term): is the hallmark of OA is chronic and irreversible joint cartilage degeneration. Therefore, it is mandatory to prevent cartilage destruction and/or promote cartilage regeneration in order to stop or delay OA progression. In the rodent OA surgical model, we have shown a significant increase in medial joint repair and, interestingly, an increase in the number and density of chondrocyte nests (clusters of proliferating chondrocytes), indicating not only a decrease in cartilage degeneration, but a more intense cartilage regeneration. In clinical practice, liraglutide may therefore have a direct effect on cartilage cells, which is a major novelty compared to existing solutions.

Following these 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 taken a pioneering approach by conducting extensive in silico clinical trials. Leveraging advanced computational modeling and a retrospective analysis of 11.4 million OA patients, we have successfully stratified the population to identify the best responders population for our phase 2 clinical trial.

The integration of in silico trials with traditional clinical assessments is a powerful combination that accelerates the evaluation of treatment efficacy and predicts patient outcomes in a cost-effective and time-efficient manner . By comprehensively analyzing large amounts of data, these virtual trials will provide valuable insights into the efficacy of 4P004, supporting its development and potentially accelerating regulatory approval. A Phase 1 clinical trial is currently underway in Belgium in patients with knee OA, and a Phase 2 trial is planned.

Attached Files:

- zhu et al GLP1ARD2023.pdf
- Meurot2022J Ortho tranlation.pdf
- meurot2022Scientific reports.pdf

Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

4Moving Biotech's solution, 4P004, represents a significant innovation in the field of OA treatment. Unlike current approaches that focus on symptom management, 4P004 offers a unique quadruple action as an analgesic, anti-inflammatory, anti-catabolic, and pro-anabolic agent. This multifaceted mechanism of action sets it apart from conventional therapies and holds great promise for addressing the underlying causes of OA.

By targeting the pain, inflammation, and the degenerative processes involved in OA, 4P004 has the potential to not only alleviate symptoms but also slow down the progression of the disease. This innovative approach opens new avenues for the treatment of OA and offers hope to patients who currently have no effective options to modify the course of their disease.

In addition, the development of 4P004 is being supported by in silico trials, which represent a pioneering and forward-thinking approach to research. These trials use computer models and simulations to analyze the effects of the treatment on a large-scale population. By retrospectively studying data from 11.4 million OA patients, 4Moving Biotech was able to stratify the population and more effectively select patients for the Phase 2 clinical trial.

The in silico clinical trials have yielded promising results, demonstrating a significant reduction in the progression of OA and a longer delay in the need for joint replacement surgery. In fact, the trials have shown a longer median time to disease progression (approximately 16.6 months) compared to the current standard of care (approximately 1.6 months). Additionally, there is a longer median time to total knee replacement (approximately 100 months) compared to the conventional approach (approximately 64 months). These remarkable figures highlight the potential of 4P004 in effectively slowing down the progression of OA and postponing the need for invasive surgical interventions.

The implications of 4Moving Biotech's innovative approach extend beyond the immediate impact on the treatment of OA . The integration of in silico trials into the drug development process represents a paradigm shift in research methodology. By leveraging large-scale data analysis and computational modeling, researchers can gain valuable insights into the efficacy and safety of potential treatments in a cost-effective and time-efficient manner.

In terms of improving the human condition, the innovative nature of 4P004 and the in silico trial approach offers hope to millions of OA patients worldwide. By providing a treatment that goes beyond symptom management to address the underlying causes of the disease, 4Moving Biotech aims to not only improve the quality of life for people with OA but also to impact all major diseases associated with sedentary lifestyle.

Moreover, the long-term implications of successful OA treatments extend beyond the individual patient. By reducing the need for joint replacement surgery and alleviating the economic burden associated with the disease, 4P004 has the potential to improve healthcare systems and contribute to the overall well-being of society.

In conclusion, 4Moving Biotech's innovative solution, 4P004, combined with the pioneering approach of in silico trials, represents a significant advancement in the treatment of OA. The multifaceted action of 4P004 and the promising results of the in silico trials provide a solid foundation for further research and development. This innovation has broad implications for future drug development, personalized medicine, and improving the human condition by addressing the underlying causes of OA and improving patient survival and quality of life.

Please provide appropriate references (ie Pubmed links)

1. C. J. L. Murray et al., ‘Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010’, Lancet Lond. Engl., vol. 380, no. 9859, pp. 2197–2223, Dec. 2012, doi: 10.1016/S0140-6736(12)61689-4.
2. T. Vos et al., ‘Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010’, Lancet Lond. Engl., vol. 380, no. 9859, pp. 2163–2196, Dec. 2012, doi: 10.1016/S0140-6736(12)61729-2.
3. P. G. Conaghan, M. Kloppenburg, G. Schett, J. W. J. Bijlsma, and EULAR osteoarthritis ad hoc committee, ‘Osteoarthritis research priorities: a report from a EULAR ad hoc expert committee’, Ann.

Rheum. Dis., vol. 73, no. 8, pp. 1442–1445, Aug. 2014, doi: 10.1136/annrheumdis-2013-204660.
4. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 'Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017', Lancet Lond. Engl., vol. 392, no. 10159, pp. 1789–1858, 10 2018, doi: 10.1016/S0140-6736(18)32279-7.
5. Wallis JA, Taylor NF, Bunzli S, et al. Experience of living with knee osteoarthritis: a systematic review of qualitative studies. BMJ Open 2019
6. S. R. Kingsbury, H. J. Gross, G. Isherwood, and P. G. Conaghan, 'Osteoarthritis in Europe: impact on health status, work productivity and use of pharmacotherapies in five European countries', Rheumatology, vol. 53, no. 5, pp. 937–947, May 2014, doi: 10.1093/rheumatology/ket463.
7. 'The economic weight of osteoarthritis in Europe', Medicographia, Oct. 31, 2013. https://www.medicographia.com/2013/10/the-economic-weight-of-osteoarthritis-in-europe/ (accessed Aug. 16, 2018).
8. 'Osteoarthritis: A Serious Disease, Submitted to the U.S. Food and Drug Administration December 1, 2016'. Accessed: Aug. 28, 2018. [Online]. Available: https://www.oarsi.org/sites/default/files/docs/2016/oarsi_white_paper_oa_serious_disease_121416_1.pdf
9. Grange L. et col.: Osteoarthritis in France the cost of ambulatory care in 2010; Le Pen C et al., Joint Bone Spine. 2005 Dec ; 72 (6) : 567-70; Bertin et al., Journal of MusculoSkeletal Pain. 2014; Sandell LI. Nat Rev Rhumatol. 2012. 8 : 77-89: Oxford Economics, Economic cost of OA, 2010; Zhao et al., Clinical, humanistic, and economic burden of osteoarthritis among noninstitutionalized adults in the United States. Osteoarthritis Cartilage. 2019 Jul 9. pii: S1063-4584(19)31126-4.
10. Agency for Healthcare Research and Quality (AHRQ), Healthcare Cost and Utilization Project (HCUP), National Inpatient Sample (NIS), 2017
11. Nüesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Jüni P. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. BMJ. 2011 Mar 8;342:d1165. doi: 10.1136/bmj.d1165. PMID: 21385807; PMCID: PMC3050438.
12. Bannuru et al., OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis, Osteoarthritis and Cartilage, 2019, ISSN 1063-4584, https://doi.org/10.1016/j.joca.2019.06.011; https://www.nhs.uk/conditions/knee-replacement/recovery/ consulted September 24th 2019; Taheriazam et al., Total hip arthroplasty and cardiovascular complications: a review. Ther Clin Risk Manag. 2018; 14: 685–690.
13. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open. 2012 Feb 22;2(1):e000435. doi: 10.1136/bmjopen-2011-000435. PMID: 22357571; PMCID: PMC3289991.
14. OARSI (Osteoarthritis Research Society International) – non-profit scientific organization;
15. Berenbaum F. Ann Rheum Dis. 2011 Aug;70(8):1354-6
16. Louati et al., 2015. RMD Open.
17. https://clinicaltrials.gov/ct2/show/NCT02953665; Watson et al., Neural correlates of liraglutide effects in persons at risk for Alzheimer's disease, Behavioural Brain Research, Vol. 356 (2019), 271-278; Femminella et al., Evaluating the effects of the novel GLP-1 analogue liraglutide in Alzheimer's disease: study protocol for a randomised controlled trial (ELAD study), Trials, Vol.20:191 (2019); Zhang et al., Incretin-based agents in type 2 diabetic patients at cardiovascular risk: compare the effect of GLP-1 agonists and DPP-4 inhibitors on cardiovascular and pancreatic outcomes. Cardiovascular Diabetology, vol. 16:31 (2017).
18. 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).
19. Zhu H, Zhou L, Wang Q, et al. Glucagon-like peptide-1 receptor agonists as a disease-modifying therapy for knee osteoarthritis mediated by weight loss: findings from the Shanghai Osteoarthritis Cohort. Ann Rheum Dis. 2023; ID 223845.
20. 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.
21. 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.
22. 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

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