



**Esperite NV (ESP) with The Cell Factory has signed the agreement with the PHARM CRO to start preparation for the first-in-man clinical trials in treatment of Crohn's disease.**

Amsterdam, The Netherlands –17<sup>th</sup> May 2018

Esperite's The Cell Factory has signed today the agreement with PHARM, the Italian CRO company which is preparing for the first-in-man clinical trials using CF-MEV-107 EVs. A drug for treatment of Crohn's disease targeting those who are affected by drug-resistant of perianal fistulae. The CF-MEV-107 drug was developed in collaboration between The Cell Factory and the Padua University Hospital in Italy. The CF-MEV-107 drug will be manufactured by The Cell Factory, a biotech company based in Belgium. The Cell Factory owns the IP for the treatment of inflammatory diseases which was granted in Europe and China. The clinical trials will be performed in Italy at Padua University Hospital in collaboration with the Women's and Children's Health Department of the University of Padua.

Allogenic "off-the-shelf" cell therapies using mesenchymal stromal cells (MSCs) have shown significant efficacy in the treatment of multiple inflammatory diseases including Crohn's diseases. However, development of new cell therapy products is limited due to high production costs and difficult largescale manufacturing of the GMP products. In addition, low stability of the living cells and variable activity in different patients could influence the therapeutic effect. Extracellular vesicles (EVs) secreted by the MSCs can reproduce multiple activities of the cells of origin. It has been demonstrated by several independent studies that EVs are responsible for the therapeutic effect of the allogenic not-matched MSCs in vivo. MSC-EVs can be considered as the exact active substance in MSCs therapies, and therefore the EVs can replace the allogenic "off-the-shelf" MSCs products in multiple therapeutic indications.

In the preclinical tests, the CF-MEV-107 drug candidate has shown significant activity in suppression of B cell proliferation, differentiation and antibody production, inducing apoptosis of activated Tconv, inducing proliferation of Treg and increasing the Treg/Teff ratio (in vitro assay), thus shifting the immune system towards an anti-inflammatory response. In vivo (DSS-induced colitis model), CF-MEV-107 drug candidate has confirmed its safety and induced clinical improvement, while suppressing the expression of pro-inflammatory cytokines in intestinal mucosa. However, the histological improvement was not evident, reflecting the limitations of the currently available animal models for Crohn's diseases and species-related differences in the immune regulatory pathways. Therefore, further progress in the development of the CF-MEV-107 drug candidate can be achieved during the clinical tests.

Clinical study of the drug CF-MEV-107 EVs will be prospective and uncontrolled. The primary objective of the study will assess the safety of the topical administration in patients affected by fistulizing Crohn's disease refractory to conventional therapies. The study will test the effect of dose escalation aiming to evaluate the efficacy of the topical administration of the CF-MEV-107 drug in achieving the resolution of perianal fistulas in patients with Crohn's disease after failure of standard therapies.

Inflammatory bowel disease (IBD) encompasses a spectrum of diseases affecting the gastrointestinal tract. The most common are Crohn's disease and ulcerative colitis. IBD is a chronic and often recurring inflammation of the intestines with unknown cause and limited treatment options. In the most severe cases of Crohn's disease, the patients suffer from perianal fistulas that significantly affect normal activity and may lead to complications such as an increased risk of cancer and life-threatening systemic inflammation. Inflammatory bowel disease (IBD) affects approximately 0.5% of the western countries population, and this number is rapidly increasing. There are over 0.5 million people in the US and over 1 million in Europe with Crohn's disease, with over 10 new cases per 100,000 people every year. The annual cost of therapy exceeds 5 billion USD in the US only (CDC). Up to 50% of Crohn's disease patients are affected with difficult to treat perianal fistulas, and 75% require surgery (CDC). In Europe current treatment of Crohn's disease is focused on anti-TNF-alpha therapy whereas anti-integrin biologics are an alternative available in the US. Unfortunately, perianal fistulas often do not respond to these systemic treatments and the surgical intervention becomes the only choice for those patients. The target of the CF-MEV-107 drug is to close the fistulas following the ambulatory injection of the drug, and to avoid the surgical treatment and hospitalization.

The production process of the CF-MEV-107 drug was developed according to GMP guidelines. The Cell Factory's proprietary EVs production platform is leading the EVs field by manufacturing the ultra-pure vesicles. Its proprietary production process of MSCs and MSC-derived EVs uses defined raw materials (ancillary products) during the entire production process. MSCs and EVs are manufactured without animal-derived components, and human-derived undefined components, i.e., serum, undefined serum replacements, plasma, platelet lysates, gelatine, etc. This technology eliminates the risk of product contamination with pathogens, unknown active substances, and external EVs. The production process significantly improves the EVs purity, quality and batch-to-batch reproducibility. Our company controls the entire production process, starting from procurement of the source material (via bio-bank), donor selection, international transport of the biological products (controlled cold-chain), tissue processing, storage (cryopreservation in liquid nitrogen), cell (extraction and expansion), EV bioproduction and purification, final product preparation and release. The production process is designed and validated according to GLP/GMP standards and follows the international guidelines dedicated for production and clinical use of biological medicinal products. Stem cells expansion is performed in the most efficient culture systems using 3D microcarrier beads and scalable stirring bioreactor systems. In addition, the closed system can be fully automated and the entire production process (including downstream concentration and filling) can be performed in a lower sterility grade lab environment. The Cell Factory's proprietary closed cell culture system, and multi-harvest EVs batch production provide new standards in biologic drugs production, resulting in significant cost reductions without

compromising product quality. Ultimately, EVs can be produced at least 10-times more efficiently and cheaper when comparing to allogenic MSCs equivalent. Furthermore, the Cell Factory's production system has developed a new method for EVs quantification available for the scientific and biotech community. Currently, quantification methods do not allow precise enumeration of EVs and quantification is presently one of the most significant challenges in the EVs field. Lack of standardized analytical instruments and methods for the EVs quantification have a considerable impact on the quality and reproducibility of scientific data and clinical translation of the EVs drug candidates. The Cell Factory has developed and validated a new method for EVs quantification using a combination of 3 techniques: nanoparticle tracking (NTA), multiparametric immunophenotyping (FACS) and immunomagnetic cell sorting adopted to EVs particles (MACS). Our method can precisely quantify EVs based on different markers combination, e.g., tetraspanin proteins (CD9, CD63, CD81). This method is not limited, however, tetraspanins, and other markers can be used for detection and quantification of EVs. The method will be published in a peer-review journal soon and we hope it will help accelerate progress in the EVs field by improving the quality of EVs drug products for clinical use.

#### **The Cell Factory is currently developing the EVs biologic drugs for:**

- CF-MEV-107 for Crohn's disease (drug-resistant perianal fistulae)

The Cell Factory is leading a translational project on EVs first in man use in the treatment of Crohn's disease perianal fistulas. Inflammatory bowel disease (IBD) encompasses a spectrum of conditions affecting the gastrointestinal tract. The most common are Crohn's disease and ulcerative colitis. IBD is a chronic and often recurring inflammation of the intestines with unknown cause and limited treatment options. In the most severe cases of Crohn's disease, the patients suffer from perianal fistulas that significantly affect normal activity and may lead to complications such as an increased risk of cancer and life-threatening systemic inflammation.

Epidemiology and market estimation: IBD affects approximately 0.5% of the western countries population, and this number is rapidly increasing. There are over 0.5 million people in the US and over 1 million in Europe with Crohn's disease, with over 10 new cases per 100.000 people every year. The annual cost of therapy exceeds 5 billion USD in the US only (CDC). Up to 50% of Crohn's disease patients are affected significantly to treat perianal fistulas, and 75% require surgery (according to CDC) what estimates the potential market size of the CF-MEV-107.

- CF-MEV-117 for Epilepsy (acute and chronic drug-resistant epilepsy)

The Cell Factory is developing the MSC-EVs drug candidate for the treatment of untreatable-yet acute and chronic drug-resistant epilepsy. Epilepsy carries significant detrimental effects on the quality of life and can lead to secondary brain damage. The disease can have different etiology, including stroke, brain trauma, and neuro-inflammation.

Epidemiology and market estimation: Epilepsy is one of the most common brain diseases affecting about 1 in 100 children under 17-year old according to CDC. The severity of the seizures is variable, and the antiepileptic drugs are effective only in about 2/3 of the patients.

CDC estimated annual costs related to epilepsy exceeds 15 billion USD in the United States alone.

- CF-MEV-126 for stroke (brain stroke and acute injuries of the central nervous system)

Brain stroke is the most devastating neurological disease with no effective therapy available yet. The brain damage could be significantly reduced if anti-inflammatory and neuroprotective treatment is applied immediately after stroke or injury. Esperite is looking for partners to support the development of extracellular vesicle therapeutics.

Epidemiology and market estimation: According to WHO, 1 in 6 people will have a stroke during lifetime and 6 million people die because of a stroke every year. Those who survive, very often suffer from severe physical and cognitive impairments due to brain damage following a stroke. CDC estimates the brain stroke-related costs around 34 billion USD every year only in the United States.

### **About the partners:**

**Azienda Ospedaliera di Padova (AOP)** carried out over 50% of clinical trials of the Veneto region, developing significant expertise in the field. In 2012, 321 studies (of which 40% with commercial sponsors) were approved by the AOP Ethics Committee for Clinical Trial, with an increment of 20% compared to the previous year. AOP has significant expertise in the project coordination, being Coordinator of 2 International projects, and Partner in many other projects (more than 40 International Projects, with 10 projects ongoing). The Unit "Progetti e Ricerca Clinica" (UPRC) is the AOP structure dedicated to research projects management. AOP has more than 110.000 admissions to emergency health care unit per year, 60.000 hospital admissions per year, and 45.000 surgical operations per year.

**Università di Padova (UNIPD)**, will be the scientific coordinator in the project with the Department of Woman's and Child's Health in collaboration with the Division of General Surgery. This project will be aimed at providing scientific, and technical expertise on preclinical models of human, mouse neoplasia, genomics, viral vector development and production assessment of adoptive immunotherapy approaches based on their state-of-art competences in imaging technologies. UNIPD offers its students 32 departments, 37 doctoral degree courses and 44 research and service centers across the spectrum of sciences, medicines, social sciences and humanities, with about 2,300 professors and researchers employed. UNIPD participated in 196 European Research projects within the 7th Framework Programme and in about 40 projects from other EU funds, accounting for more than 70 Million Euro. It currently manages 70 Horizon 2020 actions for a total budget of 20 Million Euro.

The department of Woman's and Child's Health of the University of Padua is a 269-bed tertiary pediatric academic care center, serving the entire North East region of Italy, devoted to providing excellence in patient's care, teaching, and research, also including a ten-store research building. It is one of the eleven fully recognized Italian Children's Hospitals.

**PHARM**, PHArmaceutical Research Management SRL, is the CRO Company in Italy ([www.pharmsrl.com](http://www.pharmsrl.com)) providing complex services for preparation and management of the clinical trial with advanced medicinal products. PHARM is a SME with the mission of stimulating and facilitating pharmaceutical companies to invest in new therapeutic areas (i.e. paediatrics, rare disorders and advanced therapies). PHARM acts as an interface between public and private sector offering experience and support in all management, organizational, strategic, regulatory, biostatistics, methodological aspects of drug research development, in compliance with applicable regulations and GXPs. PHARM is registered as Contract Research Organization within AIFA register.

**ESPERITE Group** (Euronext: ESP), listed at Euronext Amsterdam and Paris, is a leading international company in regenerative and predictive medicine established in 2000.

**The Cell Factory** is a company of ESPERITE Group, focused on innovative drug products development, clinical translation and commercialization using autologous mesenchymal stromal cells (MSCs) and allogenic MSC-derived extracellular vesicles (MSC-EVs). TCF-Biotech goal is a development of the highest quality therapeutic tools for affordable treatment of unmet medical needs.

To learn more about ESPERITE Group, or to book an interview with CEO Frederic Amar: +31 575 548 998 - [ir@esperite.com](mailto:ir@esperite.com) or visit the website at [www.esperite.com](http://www.esperite.com).

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*This press release contains inside information as referred to in article 7 paragraph 1 of Regulation (EU) 596/2014 (Market Abuse Regulation).*