Esperite (ESP) with The Cell Factory has confirmed a long-term effect of extracellular vesicle drug candidate CF-MEV-132 for the treatment of Bronchopulmonary Dysplasia.

CF-MEV-132 drug candidate belongs to the CF-MEV family of anti-inflammatory EV drugs produced by The Cell Factory

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The Cell Factory and the University of Padova, Italy have confirmed the long-term therapeutic effect of the CF-MEV-132 drug candidate for the treatment of bronchopulmonary dysplasia (BPD). The results demonstrate a full regeneration of the lungs affected by the BPD by CF-MEV-132 drug and the effect is stable until adulthood. This is an important milestone in the ongoing process of clinical translation of the CF-MEV-132 extracellular vesicle product. The company is expecting to receive the clinical authorization (CTA) in the 2nd half of the year thus it can start the clinical tests by the end of 2019. The scientific results will be presented during the annual meeting of Gruppo Italiano Staminali Mesenchimali in Genova, Italy on April 4-5, 2019.

The long-term effect of CF-MEV-132 has been demonstrated using a rat model of hyperoxia-induced BPD developed by the University of Padova and Pediatric Clinic and Institute of Pediatric Research, Città della Speranza, Padova, Italy. The model perfectly reflects the clinical mechanism of the diseases and can be used to obtain reliable preclinical data about drug safety and efficacy. EVs were injected intratracheally into experimental animals to demonstrate efficacy with the non-invasive method of drug administration. The animals were investigated at 6 weeks of age (adult animals) which corresponds to the human development time until adulthood. The lung tissue stereological analysis revealed a significant increase in the total surface area and volume of alveolar air spaces in the animals treated with EVs when comparing to the con-

trol animals. These results demonstrated that an immediate therapeutic effect of the EVs which was observed in the recent study can be maintained until adulthood. No adverse effects or toxicity were observed after administration of CF-MEV-132 neither short-time nor in the long-term study. This study demonstrates that EVs can cure the BPD and restore the original lung function. This therapy will allow children's proper growth and development in the future.

Bronchopulmonary dysplasia (BPD) is a severe disease of the respiratory system which occurs in app. 30% of preterm born children (below 30 weeks of gestation). Incidents of BPD are correlated with the low gestational age at birth, and over 90% of extremely immature babies are affected by the disease. The lungs of the babies affected with BPD are not properly developed and the patients require oxygen therapy and intensive care immediately after birth. BPD has severe long-term consequences for the patients, and the disease is responsible for the major cause of death in the first month of life in developed countries. Current treatment of BPD is focused on mechanic ventilation and oxygen therapy immediately after birth and supplementation of surfactant. Mechanic ventilation and oxygen treatment lead to hyperoxia and severe inflammation damaging lungs. In consequence, inflammation prevents the development of the lungs, and cause a significant reduction in lung surface, lower number of alveoli and impaired lung vascularization. Effectively lungs cannot provide a sufficient amount of air to the organism what results in impaired development and metabolic functions of the entire organism.

CF-MEV-132 drug candidate belongs to the CF-MEV family of anti-inflammatory EV drugs produced by The Cell Factory. CF-MEV drugs share the mode of action targeting both innate and acquired immune systems. All CF-MEV drugs are manufactured using The Cell Factory proprietary EVs technology platform. The efficacy of CF-MEV-132 drug candidate was investigated by The Call Factory in collaboration with The Human Anatomy Section, Department of Neurosciences, The Neonatal Intensive Care Unit, and the Stem Cell and Regenerative Medicine Laboratory of the Department of Women's and Children's Health, Department of Cardiac, Thoracic and Vascular Sciences of the University of Padova and Pediatric Clinic and Institute of Pediatric Research, Città della Speranza, Padova, Italy. The experimental results of the pre-clinical

study on CF-MEV-132 drug candidate were recently published by Porzionato et al. in Am J Physiol Lung Cell Mol Physiol. 2018 Oct 4 (reference: 1).

CF-MEV-132 drug candidate (extracellular vesicles derived from mesenchymal stem cells) has been developed to inhibit lung inflammation and improve the regeneration process in preterm babies with BPD. CF-MEV-132 treatment will be supplementary to the life-saving therapies, i.e., oxygen treatment, ventilation, and surfactant treatment. CF-MEV-132 belongs to the CF-MEV family of anti-inflammatory EV drugs produced by The Cell Factory. CF-MEV drugs share the mode of action targeting both innate and acquired immune systems. All CF-MEV drugs are manufactured using The Cell Factory proprietary EVs technology platform. The efficacy of CF-MEV-132 drug candidate was investigated by The Call Factory in collaboration with The Human Anatomy Section, Department of Neurosciences, The Neonatal Intensive Care Unit, and the Stem Cell and Regenerative Medicine Laboratory of the Department of Women's and Children's Health, Department of Cardiac, Thoracic and Vascular Sciences of the University of Padova and Pediatric Clinic and Institute of Pediatric Research, Città della Speranza, Padova, Italy. The experimental results of the pre-clinical study on CF-MEV-132 drug candidate were recently published by Porzionato et al. in Am J Physiol Lung Cell Mol Physiol. 2018 Oct 4 (reference: 1). The study was performed using a rat model of hyperoxia-induced BPD. EVs were injected intratracheally to demonstrate efficacy with the non-invasive method of drug administration. This approach could significantly reduce the risk of future therapy of newborn preterm children with BPD. Histomorphometric analysis of the lungs showed significant reduction of organ injury in the animals treated with CF-MEV-132 compared with sham-treated controls, i.e., increased the total number of alveoli and decreased mean alveolar volume. In addition, EVs treatment prevented an increase in medial thickness of small pulmonary vessels, a sign of pulmonary hypertension associated with BPD development. No adverse effects were observed after administration of CF-MEV-132. This study reveals that EVs can reduce hyperoxia-induced lung damage and can be safely delivered via the intratracheal route into patients.

Mode of action of The Cell Factory's EVs drug candidates is focused on immunomodulation and suppression of the innate and acquired immune systems. EVs have multi-target anti-inflammatory activity and therefore can be more effective when comparing to the classical biologic drugs targeting single molecular pathways. On the other hand, EVs are more stable and save in vivo when comparing to allogenic stem cell therapeutics. In collaboration with our academic and clinical partners, we have demonstrated that CF-MEVs drug candidates suppress B cell proliferation, differentiation and antibody production. CF-MEVs induce apoptosis of activated conventional T cell and induce regulatory T cells increasing the Treg/Teff ratio. Other experiments have demonstrated that co-culture of EVs (CF-MEVs drug candidates) with PBMCs resulted in significant reduction of degranulating NK cells (CD56+ CD107a+). Exposure of K562-stimulated PBMCs to EVs induced a significant reduction of CD56+ IFN-γ+ cells compared to co-culture with parental MSCs. (references: 2,3,4,5). The additional assay has been developed to investigate the EVs activity on the innate immune system. EVs were co-cultured with INFgamma/LPS-induced macrophages, and this resulted in a shift of the macrophage polarization from M1 (pro-inflammatory) to M2 (anti-inflammatory).

In vitro data have been confirmed in several in vivo models. For example, EVs were injected intraperitoneally into a mouse model of DSS-induced ulcerative colitis. EVs treatment showed improved disease activity index and less severe reduction in colon length. RT-PCR of colon tissue demonstrated a significant reduction of IL-1β and COX2 in EVs treated animals. Subsequent in vivo study showed an enhanced anti-inflammatory effect of 2nd generation EVs-Annexin. (references: 6,7).

Technology. The Cell Factory has developed a proprietary technology of large-scale production of ultra-pure EVs according to GMP guidelines, using fully defined, serum-free, xeno-free defined media with no use of animal-derived components and human platelet lysates at any stage of the production process. Production is performed in a closed and scalable stirring bioreactor including downstream processing based on the integrated sequential filtration system. The Cell Factory set up new standards in drag production where EVs are continuously secreting by expanded MSCs allowing multiple harvests during one production cycle. This approach significantly reduces the contam-

ination risk, production time, staff, GMP labs use and the cost of goods. Effectively a production of a single EVs dose is now up to 10 times cheaper when comparing to the allogenic MSCs dose equivalent, and these costs will be further reduced in the future. Closed and semi-automated production system, fully defined culture media and ISO/GLP based quality assurance system facilitates a technology transfer what is expected in collaboration with the international partners. The EVs will become a viable alternative to many allogenic stem cell therapies soon and will be able to target niche indications beyond the scope of current cell therapies, i.e., immediate anti-inflammatory interventions in neurology.

EVs including exosomes are nanometer size, natural biological particles secreted by different types of cells in vivo and in vitro. They contain proteins, growth factors, mRNA and other molecules responsible for the therapeutic effect of MSCs. Besides, EVs have several advantages over allogenic MSCs, e.g., up to 10-times lower production costs, no risk of uncontrolled proliferation and differentiation, lower risk of the immune response, penetration through the blood-brain-barrier and easy and safe delivery into different tissues and organs in vivo. High stability allows for easy transport and storage of the “ready-to-use” EVs products.

The Cell Factory is looking for investors and research collaboration opportunities to continue the development of the EVs drug candiates and manufacturing technology.

The Cell Factory's product portfolio:

CF-MEV-107: Crohn's disease

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 regular activity and may lead to complications such an increased risk of cancer and life-threating systemic inflammation. In Europe, the current treatment of Crohn's disease is focused on anti-TNF-alpha therapy whereas anti-integrin biologics are an alternative available in the US. Perianal fistulas often do not respond to these systemic treatments. Several clinical trials are ongoing to target perianal fistulas using allogeneic mesenchymal stem cells (MSCs) with very positive results.

Epidemiology and market size (CF-MEV-107). IBD affects 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 challenging treatments for perianal fistulas, and 75% require surgery (according to CDC) what estimates the potential market size of the CF-MEV-107.

CF-MEV-132: Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) is a severe disease of the respiratory system which occurs in preterm born children (below 30 weeks of gestation). The baby's lungs affected with BPD are not adequately developed and the patients require oxygen therapy and intensive care immediately after birth. BPD has severe long-term consequences for the patients, and the disease is responsible for the primary cause of death in the first month of life in developed countries.

The current treatment of BPD is focused on mechanic ventilation and oxygen therapy immediately after birth and supplementation of surfactant. Mechanic ventilation and oxygen treatment lead to hyperoxia and severe inflammation damaging lungs. In consequence, inflammation prevents the development of the lungs, a significant reduction in lung surface, lower number of alveoli and impaired lung vascularization. Effectively lungs cannot provide a sufficient amount of air to the organism what results in impaired development and metabolic functions.

Our approach is focused on using the CF-MEV-132 drug candidate (extracellular vesicles derived from mesenchymal stem cells) to inhibit lung inflammation and improve the regeneration process in preterm babies with BPD. CF-MEV-132 treatment will be supplementary to the life -saving therapies, i.e., oxygen treatment, ventilation, and surfactant treatment.

Epidemiology and market size (CF-MEV-132). Bronchopulmonary dysplasia occurs in app. 30% of preterm born children (below 30 weeks of gestation). Incidents of BPD are correlated with the low gestational age at birth, and over 90% of extremely immature babies are affected by the disease. The costs related to BPD are significant and spread over the lifetime of patients affected by the disease. It is estimated that the average hospitalization time of a premature infant with BPD is on average 94 days and the annual cost per patient ranges from 400.000 USD to over 700.000 USD (reference: 9).

CF-MEV-117: Acute and chronic drug-resistant epilepsy

The Cell Factory is developing MSC-EVs drug candidate (CF-MEV-117) for 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 size (CF-MEV-117). 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: Stroke

Stroke is one of the most devastating and still incurable diseases. Brain damage following stroke is correlated with the inflammation which plays a key role in the brain’s response to a stroke incident. New generation EVs drugs are containing an additional genetic cargo (miRNAs) or have bound surface molecules (i.e., Annexin V) to enhance their anti-inflammatory and neuroprotective properties.

The stability of these nanometer-sized EVs will allow the drug candidate CF-MEV-126 to be used outside the hospital immediately after a stroke incident which reduces the brain damage and improves the recovery process. Another advantage of the EVs, when

comparing to MSCs and other cell therapies, is their penetration through the blood-brain barrier what is crucial for any effective treatment targeting the central nervous system.

Epidemiology and market size (CF-MEV-126). Diseases of the central nervous system are among the most devastating for patients and their relatives. Neurological disorders are generating a significant additional cost related to hospitalization, rehabilitation, often eliminate the patients and their relatives from a job market.
Stroke is the second leading cause of disability in Europe, and 10-35% of these patients die within 28-30 days. Current stroke therapy is very limited and focused on general care and rehabilitation. In the EU 27 countries, the annual cost of stroke is estimated to be at €27 billion (WHO). The number of stroke events in Europe is projected to rise from 1.1 million in 2000 to 1.5 million per year by 2025 due to the aging population.

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About ESPERITE

ESPERITE is a diversified biotech global group leader in regenerative and precision medicine. Established in 2000, the holding group is headquartered in the Netherlands, listed at Euronext Amsterdam and Paris and operational in over 30 countries.

ESPERITE transforms the power of state-of-the-art technologies and scientific advancements into high quality products that bring the future of medicine to customers today at an affordable price.

THE CELL FACTORY is a biotech company, a subsidy of the Esperite group, developing highest quality therapeutic tools for affordable regenerative medicine. The Cell Factory is focused on development, clinical translation and commercialization of the advanced extracellular vesicles (EVs) biologic drugs and autologous stem cell therapies. The Cell Factory goal is to become a leader in development and production of extracellular vesicles drugs in treatment of different indications i.e. inflammatory diseases, graft versus host disease (GvHD) after solid organ and cell transplantations, arthritis, multiple sclerosis, cystic fibrosis, stroke, traumatic brain and spinal cord injury, newborn encephalopathy, and type 1 diabetes among others.

To learn more about the *ESPERITE* Group, or to book an interview with CEO Frédéric Amar: +31 575 548 998 - ir@esperite.com or visit the websites at www.esperite.com and www.cell-factory.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).