Lipopharma announces IND approval by the FDA to proceed with a PhI paediatric trial assessing 2OHOA in children with advanced brain and other solid tumours.

Following the positive conclusion of a PI/IIa trial in Europe with 2OHOA in adult patients with advanced solid tumours, including malignant glioma, this paediatric trial will investigate the safety profile and preliminary anticancer activity of this novel cell-membrane modulator in children with malignant glioma and other advanced solid tumours.

Palma de Mallorca (Spain) and Acton (MA, USA). May 29th 2018– Lipopharma, a pioneering clinical stage biopharmaceutical company developing a new generation of products modulating metabolism of membrane lipids based on the groundbreaking MLT platform, announces that the FDA has approved an IND for a paediatric trial entitled "***a phase I study of 2-hydroxyoleic acid (2OHOA) in pediatric patients with malignant glioma and other advanced solid tumors***"

This will be the first clinical study with 2OHOA in children with advanced malignant cancer and will be conducted in collaboration with two leading US paediatric clinical research institutions: Hackensack University Medical Center, in New Jersey and Dana-Farber Cancer Institute in Boston. The main objectives of this study are to determine the safety and tolerability of 2OHOA in paediatric population (under 18 years), to characterize the pharmacokinetic profiles in this population and to assess the preliminary anti-tumour efficacy of the product. The trial follows a standard 3+3 design in the dose escalation phase, where 9 to 18 patients will be recruited in three cohorts, and that will be followed by an expansion cohort with 10 additional patients.

High-grade gliomas (HGG) are relatively rare forms of paediatric brain tumours, constituting only 8–12% of primary central nervous system (CNS) tumours in children. The management of these tumours involves surgical resection to the extent feasible, as well as adjuvant radiation and chemotherapy. Even with these interventions, the prognosis for patients with these tumours is poor, with most patients succumbing to their disease within 12–18 months. The incidence rate of primary malignant and non-malignant brain and CNS tumours in the US in paediatric and adolescent population (0-19 years) is 5.42 cases per 100,000 for a total count of around 23,000 incident tumours per year, of which over 2.500 cases correspond to HGG.

Lipopharma is committed to advance the clinical development of this promising product and is excited about the prospect of providing a potential therapeutic alternative for children and adult patients with brain and other aggressive cancers.

The approval by the FDA of the Investigational New Drug (IND) application for this paediatric trial in the US is a significant regulatory milestone for 2OHOA, (re)validating the extensive preclinical and clinical development that Lipopharma is carrying out with this innovative product.

A PIIb trial in adult patients with newly-diagnosed glioblastoma (CLINGLIO) with 2OHOA added to the current chemoradiation standard of care for this type of tumours is also planned to open within this year in leading Hospitals in Europe and Israel, following the award of an important H2020 grant by the European Commission to an international consortium lead by Lipopharma.

ADDITIONAL INFORMATION

About LP561A1 (2OHOA)

LP561A1 (2-hydroxyoleic acid, 2OHOA) is an orally bioavailable synthetic derivative of oleic acid that activates **sphingomyelin synthase 1 (SMS1)**, an enzyme catalysing the reversible conversion of phosphatidylcholine (**PC**), phosphatidylethanolamine (**PE**) or ceramide (**Cer**) into sphingomyelin (**SM**) and diacylglycerol (**DAG**), leading to an increased sphingomyelin (SM)/phosphatydil choline (PC) ratio and the formation of new lipid species as 2-OHOA-PC in the cancer cell membrane. This impairs Ras nanoclustering and translocates K-Ras from the cell plasma membrane to cytosolic cell membranes (e.g. Golgi membranes) and consequently inhibits Ras-associated proliferative signalling pathways, including MAPKs, Notch, PKC or P13K/Akt/mTOR pathways (Barceló-Coblijn et al. 2011; Terés et al. 2012). Interestingly, this novel mechanism of action has been recently reproduced by independent research groups (Cho et al. 2016; Van der Hoeven et al. 2017). In addition, the modulation of the ratios Cer/SM and PC/SM have recently been reported to boost the immune system against the tumour (Kachler et al. 2017)

In several pre-clinical studies in cellular and animal models, 2OHOA has demonstrated very high efficacy with no apparent toxicity in different types of cancer with low basal levels of SMS1. Available data, both from internal studies and from external literature references, suggest that a significant percentage (30% to 50%) of patients with aggressive cancer malignancies (such as brain, pancreas, lung, colon, prostate cancer or leukaemia) have important alterations in the SMS system.

2OHOA obtained the **Orphan Drug** designation in Europe by the EMA for the treatment of glioma in October 2011. Comprehensive safety and tolerability data has been generated in a PI/IIa clinical study (MIN-001-1203) where 54 adult patients with advanced solid tumours including malignant glioma have been treated with different doses of 2OHOA. The results of this study confirmed an excellent safety and tolerability profile of the product, while encouraging overall **clinical activity** was reported in **13 heavily pre-treated patients** with advanced recurrent solid tumours, including **eight patients with recurrent high grade glioma**.

About MLT

Membrane-Lipid Therapy (MLT) is an innovative scientific platform based on an expanding area of knowledge in today's cell biology that enables us to design novel molecules that regulate the activity of key membrane-associated signal transduction proteins, through the modulation of the structure and organization of the membrane lipid micro-domains involved in cell signalling. This innovative approach is a paradigm-shift in drug discovery and pharmacology that can lead to the development of transformative new medicines with an exceptional safety/efficacy combination in serious pathologies with critical medical needs unmet, such as Oncology, Neurodegenerative diseases, Metabolic disorders or Inflammation. Results available of the first clinical trials with MLT-based molecules, such as MIN-001-1203 study with 2OHOA in oncology, represent a major step forward towards the clinical validation of this novel therapeutic strategy.

Disclaimer

Except for historical information, this press release may contain forward-looking statements, which reflect the companies' current expectations regarding future events. These forward looking statements involve risk and uncertainties, which may cause but are not limited to, changing market conditions, the successful and timely completion of clinical studies, the establishment of corporate alliances, the impact of competitive products and pricing, new product development, uncertainties related to the regulatory approval process and other financial, technical or market risks. All forward-looking statements are qualified in their entirety by this cautionary statement and Lipopharma Therapeutics SL does not undertake any obligation to revise or update this press release to reflect events or circumstances after the date hereof.

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