Final results of the MIN-001-1203 study with 2OHOA in oncology presented at ASCO 2017 annual meeting in Chicago

54 patients with advanced solid tumours have participated in the Phase I/IIa clinical study with 2OHOA, half of them with malignant glioma. Primary objective has been achieved, with the definition or the MTD, the confirmation of an excellent safety profile, even at doses well above the expected therapeutic range and the identification of the recommended Phase 2 dose (RP2D). A favourable PK profile, with no food-effect interactions and supporting oral dosing of 2OHOA was also determined. Very encouraging clinical activity has been observed in at least 8 patients with recurrent solid tumours, five of them with malignant glioma. Preliminary biomarkers analysis confirm biological activity of 2OHOA in patients and several potential plasmatic biomarkers have already been identified for future development and validation.

Palma de Mallorca, June 5st 2017– Lipopharma, a pioneering clinical stage biopharmaceutical company developing a new generation of products modulating metabolism of membrane lipids based on the groundbreaking MLT platform, announced today that the final results of the of MIN-001-1203 clinical study with 2OHOA in patients with advanced solid tumours, including malignant glioma, have been presented at a poster session within the *Developmental Therapeutics and Translational Research* track at the 2017 **ASCO** meeting in Chicago. 5 leading clinical investigational sites in Spain and in the UK have participated in this study

2OHOA, administered as an **oral suspension** two (**BID**) or three (**TID**) times daily, has been generally well tolerated in monotherapy up to 12 g/day, while patients have had difficulties to handle the large volume of liquid intake required for 16g/day (8 g BID), experiencing frequent gastrointestinal effects. Overall **54 patients have received 2OHOA** at different doses. One Dose Limiting Toxicity (DLT) was reported at the dose of 12g/day and 3 DLT at 16g/day. 12G/day (4g TID) was confirmed as the maximum Tolerated Dose (MTD) since there were no DLTs reported in the second part of the study conducted with this dose (expansion phase)

No **drug-related serious adverse events** or other relevant toxicity effects associated to the investigational product have been reported in any of the 54 patients treated, other than the tolerability issues experienced at the highest dose levels (gastrointestinal effects). Study drug related AE (≥10%) at any grade were **diarrhoea** (53 [26%]), **vomiting** (29[14%]), **nausea** (26 [13%]). No G3/G4 whether regardless of study drug relationship or suspected as being study drug related occurred over 10% of patients.

Pharmacokinetic (PK) profile was determined. 2OHOA was quantifiable in all dose levels and maximum concentration (Cmax) was reached at 1 hour after administration in the fasted state. When administered under fed conditions, 2OHOA had bioavailability comparable to that found in the fasted state, although food caused a non-clinically significant delay in the time needed to reach the CMax. Therefore, 2OHOA could be taken without regard to food. The half-life was between 1.4 and 4.6 hours up to 8g/day, increasing to more than 7h at the higher doses. Systemic exposure of 2OHOA increased in proportion to dose following single and repeat BID administration. After repeat BID dosing, systemic exposure of 2OHOA, increased between 1- and 1.7-fold from first dose on Day 1 to last dose on Day 21. PK data supports the planned twice-a-day oral administration of 2OHOA

Very encouraging anti-cancer activity of 2OHOA as single agent has been confirmed in several recurrent, heavily pre-treated patients, including **5** recurrent **High Grade Glioma (rHGG)** and 3 with other advanced solid tumours (AST). One recurrent glioblastoma (**rGBM**) pt had sustained partial response for more than 2.5 years (**93% shrinkage** of target lesion) and 4 rHGG patients (3 GBM) achieved **stable disease (SD)**, by RANO, for at least 6 months. Other 3 AST patients had clinical benefit by RECIST: 1 with mesothelioma (SD for 10 months), 1 with colorectal cancer (SD for 3 months) and 1 with lung metastasis of biliary duct carcinoma (SD for 5 months)

Preliminary analysis of available **biomarkers** data confirms biological activity by 2OHOA in cancer patients. On the one hand, a reduction of **GFAP levels in plasma** from rHGG patients after 8 days of treatment was observed in more than 80% of patients analyzed. Average reduction in GFAP levels in the whole set of patients was 20% (n=15). On the other hand, initial analysis of **plasma miRNA expression** profiles in a subset of 22 patients, shows that at least 3 miRNA were differentially expressed in response to 2OHOA treatment. Target gene analysis of these miRNA is ongoing. These, and other potential plasmatic biomarkers currently being analyzed, are expected to be developed and eventually validated in future clinical studies with 2OHOA, providing valuable support for patient selection strategies and for clinical study design.

Further clinical studies with 2OHOA are currently under preparation, including a Phase IIb study to evaluate the potential clinical benefit of adding 2OHOA to the current Standard of Care in patients with newly-diagnosed glioblastoma, given that "*the preliminary antitumor activity, including a sustained PR in heavy pretreated rHGG pt, warrants further investigation in a Ph2 study*", as concluded in the poster presented by Dr. A. Azaro, Principal Investigator at Vall d'Hebron Institute of Oncology, one of the 5 sites participating in this study, and the first author of the poster presented at ASCO.

Lipopharma is also preparing a PI trial in **children** with malignant glioma and other advanced cancers is being prepared in the USA, with the collaboration of top clinical investigational institutions in New Jersey and Boston.

ADDITIONAL INFORMATION

About 2OHOA

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**), which restores the normal, healthy levels and ratios of membrane lipids. This "normalization" modulates the localization and activity of important peripheral membrane proteins, such as K-Ras, which is translocated from its active domain in the cell membrane to the cytosol. Consequently, Ras-associated proliferative signalling pathways are effectively regulated, including MAP Kinases, Pi3K/AKT/MTor, PKC/Cyclin CDK or Notch pathways, which commonly exhibit an aberrant activity in different types of cancer.

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 tumors 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 clinically-relevant anti-cancer activity was reported in at least 8 patients with advanced recurrent solid tumours, including five 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 derives in the design of 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.

About Lipopharma

Lipopharma is a pioneering clinical-stage biopharmaceutical company that focuses on the discovery, design and clinical development of a new generation of medicines that act through the innovative therapeutic strategy: Membrane-Lipid Therapy (MLT). Since 2006 Lipopharma develops industrial applications of new scientific breakthroughs and discoveries patented by leading researchers at the University of the Balearic Islands (UIB).

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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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