2OHOA is an orally bioavailable synthetic derivative of oleic acid that crosses the Blood-Brain Barrier and activates sphingomyelin synthase 1 (SMS1), a key enzyme that catalyses the reversible conversion of PC, PE or PS into SM and DAG, leading to an increased SM/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 PI3K/Akt/mTOR. In addition, the modulation of Cer/SM and PC/SM ratios have been reported to boost the immune system against the tumour.

The activation of SMS1 accumulates sphingomyelin-2OHOA in the cell membrane, translocating K-Ras to non-active cytosolic domains in human glioma U118 cells (top left). As a consequence K/Ras mislocalizes from its active domain in the plasma membrane inhibiting its nanoclustering and Ras-dependent proliferation pathways (like Ras/MAPK, PI3K/AKT/mTOR or PKC/Cyclin CDK), causing cell cycle arrest followed by selective death of cancer cells (top right).

2OHOA activates immune system in cancer patients. Gene ontology functions determined by the expression of miRNAs analysis performed in patient samples (Clinical Study MIN-001-1203) demonstrated an activation of the antitumoral immune response in cancer patients (negative lor values indicate a blocking activity of miRNA inhibitory effects).

2OHOA has greater efficacy than temozolomide (TMZ) and no tumour relapse was observed after treatment termination.

2OHOA (HOA) efficacy in mice xenograft models of human lung cancer (A549) and pancreatic cancer (BXPC3), all with low SMS1 levels.
MIN-001-1203: “A phase I/IIa open-label dose escalation study of 2-OHOA in subjects with advanced solid tumors including malignant glioma”

**Study design / results**

**Part A. Dose escalating study.** 32 patients (pts) in 7 cohorts. 21-day cycles.

**Part B. Exploratory study.** 22 pts in 2 cohorts. 21-day cycles. Cohort #30: 12 glioma pts. Cohort #40: 10 biopsiable Advanced Solid-Tumours (AST) pts for biomarker evaluation.

**Objectives**

Dose-escalation, multicentre phase 1 clinical trial of 2-OHOA in advanced solid tumours including recurrent malignant glioma

- **Primary objective:** To determine safety, tolerability and recommended phase 2 dose of 2-OHOA
- **Secondary objectives:** To determine pharmacokinetics (PK) and pharmacodynamics (PD) profile and preliminary anti-tumoral activity
- **Exploratory objectives:**
  - To evaluate the effect of 2-OHOA on glial fibrillary acidic protein (GFAP) in glioma pts
  - To study miRNA as a potential response biomarker

**Main results**

![Dose Escalation (Part A)]

**Part A highlights (completed):**
- 7 cohorts completed. 32 pts (28 ≥1 cycle) treated
- No relevant safety issues (only GI effects (diarrhoea, nausea,..) in some pts at the higher doses)
- MTD established as 12g/day (4g TID)

**Part B highlights (completed):**
- 22 pts treated with 12g/day.
- No DLTs. No safety/tolerability issues
- MTD confirmed as 12g/day (4g TID)

**Anti-tumour activity**

Encouraging signs of efficacy in heavily pre-treated recurrent AST, specially in glioblastoma (rGBM) pts:
- **Clinical benefit by RANO/RECIST in 13 pts (8 with malignant glioma)**
- **50% (4/8) of rGBM pts treated for ≥2 cycles had objective clinical benefit for at least 6 months (m.)**

**Pharmacokinetic profile**

2-OHOA was quantifiable in all dose levels and Cmax was reached 1 hour post-dose (fasted).

**Food effect** was not relevant. Fed and fasted bioavailability of 2-OHOA were comparable, although food caused a non-clinically significant delay in Tmax from 1 hour to 2-4 hours.

**Systemic exposure** of 2-OHOA increased in proportion to dose following repeated BID administration. After repeated BID dosing, systemic exposure of 2-OHOA, increased between 1- and 2-fold from first dose on Day 1 to last dose on Day 21. **Median half-life**, calculated based on accumulation ratio, was 11h (min. 3h, max. 19h)

**Pharmacodynamics**

GFAP. A reduction of GFAP levels in plasma from rHGG patients after 8 days of treatment observed in more than 80% of patients analyzed. Average reduction in GFAP levels in the whole set of patients was 20% (n=15)

miRNA. At least 3 miRNA found to be differentially expressed in response to 2-OHOA treatment (n=22).

Further biomarker testing (DHFR, SM, SMS1, SMS2, genomic evaluation,...) ongoing in samples obtained from MIN-001-1203 study