**Introduction**

2-Hydroxyoleic acid (2-OHQA) is an orally administered synthetic analogue of oleic acid that crosses the Blood Brain Barrier and activates sphingomyelin synthase 1 (SMS1), a key enzyme for the synthesis of different lipid classes in the cell membrane. SMS activity results in a significant rise in the levels of sphingomyelins (SM), and reduced levels of phosphatidyl ethanolamine (PE) and phosphatidylcholine (PC), achieving a normalization of PLSM ratio to the levels found in non-cancer cell membranes. Modification of membrane lipids in cancer cells translocates Ras from the membrane to cytosolic leading to inactivating the MAPK pathway, PI3K/Akt and Cyclin/DK2/1-downregulation (Fig1).

**Study Background**

MIN 001-1203 (NCT01792310), Ph I open label study which originally included a dose escalation (DE) and expansion cohorts (EC) conducted in AST and HGG. In the completed EC part of the study, the 2-OHQA RP2D was established.

**Pharmacokinetics**

Pharmacokinetic data were available for seven dose cohorts (500mg, 1g, 2g, 4g, 8g, 12g and 16g of 2-OHQA daily; 32 evaluable participants in total. PK sessions presenting pharmacokinetic (PK) data were collected from all studies. Plasma (p) 2-OHQA levels were measured using a validated assay by using a LC/MS/MS method. For all treatments, 2-OHQA was quantifiable and Cmax was reached at 1 hour after administration in the fasted state. When administered under fed conditions, 2-OHQA had a bioavailability comparable to that found in the fasted state, but food caused a delay in Cmax from 1 hour to 2-4 hours. However, these are not expected to be clinically significant; therefore, 2-OHQA could be taken without regard to food. The half-life 1/2t1/2 derived from the 8 hours post dose concentrations (C) was between more than 1 hour to 5 hours up to 88g/day increasing for the 2 higher doses (> 7 hours to 10 hours). Terminal half-life was longer than 12 hours when 48 points were included in terminal elimination rate calculation (fasted state). Following single and multiple BID dose administration of 2-OHQA under fed conditions, systemic exposure of 2-OHQA increased in proportion to dose following single and repeat BID administration in the fed state, based on the results of the power analysis (Figure 3).

After repeat BID dosing, systemic exposure (Cmax and AUClast) of 2-OHQA increased between 1 and 1.7-fold from first dose on Day 1 to last day on Day 21.