Clinical Update of the SHELTER Study:
A Phase I/II Trial of HDAC Inhibitor Resminostat in Patients with Sorafenib-Resistant Hepatocellular Carcinoma (HCC)

Background
- Resminostat is a novel oral pan-HDAC inhibitor in clinical development for a variety of cancer indications.
- IC50 values in cellular cancer models are in the low micro-molar range.
- There is excellent anti-tumor activity in in vivo cancer models.
- Additive or synergistic activity in combination with established chemotherapeutic agents was proven in cancer models.
- Resminostat has a direct effect on the regulation of genes relevant to cancer therapy, e.g. thymidylate synthase (TYMS).
- A phase I study in cancer patients revealed a favourable safety profile. A remarkable portion of patients could be stabilized under resminostat treatment.
- The SHELTER study evaluates safety, tolerability and efficacy in patients with HCC exhibiting progressive disease under sorafenib first-line therapy.

Methods
- Sorafenib-refractory patients with advanced HCC, stages BCLC B or C are included.
- Multi-center open-label trial, two-arm parallel group design.
- Arm A: once-daily oral administration of resminostat in combination with twice-daily sorafenib at the maximum tolerated dose (MTD). Precedent dose escalation phase for the determination of the MTD: 200 mg | 400 mg | 600 mg resminostat plus 400 mg | 800 mg sorafenib.
- Arm B: once-daily oral administration of 600 mg resminostat.
- In both arms, resminostat is given for 5 consecutive days, followed by 9 days rest (*5+9 scheme). This results in treatment cycles of 14 days.
- Sorafenib in arm A is given continuously throughout the treatment.
- The main study period is 12 weeks. Patients benefitting from the treatment can stay on treatment for an unlimited period.

Radial imaging is performed after 6 and 12 weeks treatment. Dynamic contrast-enhanced magnetic resonance tomodiagram (DCE-MRT) is used for imaging. Analysis is performed according to AASL/EAES criteria for the differentiation of vital and total lesion size.
- Primary endpoint: progression-free survival rate (PFSR) at 12 weeks.
- Secondary endpoints: PFS, PFSR at 6 weeks, safety, tolerability, tumor response, time to progression, overall survival, assessment of pharmacokinetics and biomarkers.
- Study sites: 8 sites in Germany. Further sites in Italy are currently under treatment.

Initial Pharmacokinetics Data
- The systemic resminostat exposure was in good correlation with the dose administered.
- The AUC (0-6 h) values increase dose-dependently, with values of 10.5 h*mg/l (for 600 mg resminostat mono) and 9.0 h*mg/l (for 600 mg resminostat plus 400 mg sorafenib combo).
- No PK interference of resminostat with sorafenib was detected.
- The initial data on the clinical activity of resminostat are promising with regard to a new second line treatment option in HCC.

Initial Safety Data
- The majority of adverse events included gastrointestinal effects (abdominal pain, nausea, vomiting, diarrhea), rash, vertigo and fever (*), all of those were of mild to moderate intensity.
- Further events included ascites, transient troponin I elevation, aminotransferase elevation, QT prolongation in association with T wave abnormality, insulin, anemia, detachment of retina, thrombosis and bleeding (*). These events occurred only once in single patients and were at least partly attributable to the underlying disease.
- Regardless of the received dose, 6 out of those 7 patients staged after 12 weeks (6 cycles) had SD. Together with the 4 patients with PD at cycle 3, this yields an interim PFSR at 12 weeks of 54%.
- Case study: 64-year-old male patient, primary HCC diagnosis in 2008. Sorafenib treatment from Feb, 2009 to Nov, 2009. PD in Nov, 2009. Start in SHELTER study in Dec, 2009 with 400 mg resminostat plus 400 mg sorafenib. Treatment duration with resminostat/sorafenib combination was 18 cycles (36 weeks). Patient was progression-free until cycle 18. One target lesion displayed a decrease by 40% in vital lesion size.

Conclusions
- The preliminary clinical data show the favourable PK and safety profile of resminostat.
- The initial data on the clinical activity of resminostat are promising with regard to a new second line treatment option in HCC, potentially overcoming resistance to sorafenib.