This is a 3-part open-label Phase I study (Figure 1).

Part A1 – Dose escalation to RDE

• The first and second single-patient cohorts received 5 mg and 10 mg M1774 once daily on a 21-day cycle.

Part A2 – Preliminary effect

Randomized, two-sequence two-period crossover design.

Patients will receive a single dose of RDE at RDE determined in Part A1, either in a fasted or fed condition, followed by a 1-week washout period.

Patients will subsequently receive M1774 at the RDE determined in Part A1.

Part A3 – Preliminary efficacy study

Patients with tumors harboring loss-of-function mutation in ARID1A, ATRX and/or DAXX, or ATR, will receive M1774 at the RDE determined in Part A1.

Mutations are detected by next-generation sequencing, either by an approved local test or a targeted gene panel.

The effect of a fixed dose of M1774 will be assessed with a mixed effects model for the randomized two-sequence two-period crossover design.

After six patients are enrolled, the data will be reviewed, and a decision made whether an additional six patients will be enrolled.

Part A3

• The effects of fixed dose of M1774 will be assessed with a mixed-effects model for the randomized two-sequence two-period crossover design.

• Occurrence of DLTs during the DLT observation period.

• Occurrence of TEAEs.

Main exclusion criteria

• Age ≥16 years.

• Eastern Cooperative Oncology Group performance status (ECOG PS) of ≥2.

• Locally advanced or metastatic disease refractory to standard therapy or for which no standard therapy is in appropriate.

• Adequate baseline hematoietical, renal and hepatic function.

• Tumors with loss of function mutations in ARID1A, ATRX and/or DAXX. TEAEs: Treatment-emergent adverse events within 30 days before dosing (no restrictions regarding SARS-CoV-2 vaccinations).

• Major surgery 4 weeks prior to study intervention.

• Anticancer treatment within 28 days of study intervention.

• Prior treatment with an ATR and/or checkpoint kinase 1 (CHK1) inhibitor.

Primary objectives

• To determine safety, tolerability and the MTD of M1774 as a single agent in participants with solid tumors.

• To determine the DCE.

• To assess the effect of food on the PK of M1774 administered as a single dose under fasting/feeding conditions in a cohort of participants.

• To further characterize safety of M1774 as a single agent.

• To assess the efficacy of M1774.

• Occurrence of TEAEs and treatment-related AEs.

• Occurrence of abnormalities (Grade ≥3) in laboratory test values.

• Occurrence of markedly abnormal vital sign measurements.

• Occurrence of clinically significant abnormal ECGs.

• Occurrence of adverse events (Grade ≥3).