Preliminary data from a dose-escalation phase 1 study with HP518, an AR PROTAC degrader: Safety, tolerability, pharmacokinetics (PK), and first assessment of anti-tumor activity in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC).

Background: HP518 is an oral proteolysis targeting chimera (PROTAC) protein degrader that target androgen receptor (AR) mutations for the treatment of mCRPC. To evaluate the safety, PK, and anti-tumor activity of HP518, and select a recommended phase 2 dose (RP2D), we conducted a first-in-human, Phase 1, open-label, multicenter, non-randomized, dose escalation study in pts with mCRPC. We report results of the ongoing Phase 1 study at five Australian sites.

Methods: Pts with mCRPC with disease progression on at least 1 novel hormonal agent (NHA) and 1 line of chemotherapy received HP518 QD orally in sequential cohorts (25, 50, 100, 200, and 300, 400, 500 mg per day, Bayesian N-CRM design). Primary objectives were to assess HP518 safety and select the RP2D. Secondary objectives included evaluating the PK of HP518, PSA50 response and radiographic progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and Prostate Cancer Working Group 3 (PCWG3) criteria. Exploratory objectives were to evaluate AR expression in CTCs before and after 12 weeks of treatment and conduct genomic profiling using cfDNA.

Results: As of 08 Sep 2023, a total of 22 pts were enrolled, with current one-daily dosing of 500 mg HP518. Overall, HP518 was well tolerated, with cumulative 10 SAE (1 related/9 unrelated). No DLT was observed. There were 13 Grade $\geq$3 treatment-emergent adverse events (TEAEs) in 6 pts treated up to 500 mg; no grade $\geq$4 TEAEs. The most common TEAE in all cohorts was grade 1 or 2 vomiting and nausea which were well managed with prophylactic anti-emetics. Preliminary PK results were obtained from 18 pts dosed with 25 mg to 500 mg per day. Following multiple oral doses of HP518, median peak plasma concentrations were observed at 3-12 hours post-dose. Over the 5-fold dose range (100 to 500 mg), the increase in Cmax and AUC0-last was approximately dose proportional on day 1. Steady state was reached between day 56 and day 84. Among 16 pts who finished the DLT period, a PSA50 response was seen in 3 pts. 2 pts had confirmed partial responses per RECIST criteria, with 8 pts remaining on treatment. 2 pts received HP518 for $\geq$24 weeks including 1 pt with a durable PSA50 response for 52 weeks, who also showed PR. Notably, this patient harbored an F877L, E873_F879del AR ligand–binding domain (LBD) mutations.

Conclusions: HP518, a novel AR PROTAC degrader, demonstrates in this Phase 1a dose-escalation study, an acceptable safety/tolerability profile and a signal of efficacy in an un-selected mCRPC patient population. The presence of AR LBD mutations may predict benefit from HP518, and merits further investigation in pts with mCRPC. Clinical trial information: NCT05252364. Research Sponsor: None.