Impact of food and high gastric pH on the bioavailability of the WEE1 inhibitor Debio 0123 assessed in a Phase 1 dose escalation study

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ABSTRACT CT064

BACKGROUND

Debio 0123, an oral brain-penetrant, highly selective WEE1 inhibitor, is currently in clinical development, both as monotherapy and in combination, for the treatment of solid tumors with solid tumors. Food and gastric acid-reducing agents (e.g. proton pump inhibitors, PPIs) may modify the solubility, bioavailability, safety and efficacy of oral cancer drugs. Preclinical studies in patients common and food restrictions can impact patient compliance and wellbeing. In order to adequately inform drug dosing in clinical trials, effects of food and high gastric pH on Debio 0123 bioavailability were studied over three cycles in patients participating in arm B of a dose escalation Phase 1 study in combination with carboplatin (CTD NCT03586833).

The Phase 1 study was composed of 2 arms with different cycles. While Arm A was the first-in-patient study of Debio-0123, in arm B, Debio 0123 was given once daily on D1 and 3–8 of each 21-day cycle in combination with carboplatin. Standard administration was in feed conditions and PPIs were prohibited within 72h before and after dosing. In arm B, dose limiting toxicities were evaluated in cycle 1. The effect of food and high gastric pH was assessed in cycles 2 and 3, respectively.

RESULTS

Out of the 17 patients included in the arm B, 8 coming from 3 dose level cohorts had at least one pairwise comparison. Results are presented in Figure 3 and Table 1. ❖ Food effect was assessed in 7 study participants. Change in Debio 0123 plasma exposure between cycle 2 (fed) and 1 (fasted) was low, within expected bioanalytical assay variability. ❖ High gastric pH influence was assessed in 5 study participants. Debio 0123 plasma exposure was consistently reduced by about 40% on cycle 3 (with PPI) versus cycle 1 (without PPI).

CONCLUSIONS AND PERSPECTIVES

• Food did not affect pharmacokinetics of Debio 0123 in patients with solid tumors. These results allow to administer Debio 0123 regardless of food intake. For patient convenience and well-being, administration with a light meal is being implemented in ongoing and new Debio 0123 clinical trials.

• Debio 0123 oral bioavailability is pH-dependent. Gastric acid-reducing agents such as proton pump inhibitors remain prohibited concomitantly with Debio 0123.

METHODS

Each patient in arm B of the dose escalation study received Debio 0123 and carboplatin AUC mg·h/L. The study consisted of a single cycle of 23 days, followed by several cycles of Debio-0123 as illustrated in Figure 1. Dose levels studied in the 17 patients included in the arm B were 300, 400, 520 and 720 mg. On Day 10 of cycle 2, the subject was offered a high fat meal 30 min before Debio-0123 administration. High fat meal intake resulted in a total of 800-1000 kcal (including 5 to 8 g of fat). Several waves of diet variation were proposed. Most of the patients accepted to eat at least 80% of the proposed meal.

On cycle 3, lansoprazole, a proton pump inhibitor, was administered at a dose of 30 mg in the mornings and evenings of DT 7, 8, 9 and 10. High gastric pH was reached before Day 10 and environment was kept by pre-administering lansoprazole on B as well.

The same PK samples were collected post-D10 dose in cycle 1, 2 and 3. Samples on D10, followed by 3 samples on D7, 12, 14, 16, 18 and predose on D1 in the next cycle. Tox levels before each dose of the three cycles were collected to assess potential accumulation between cycles. Figure 2 illustrates dose-normalized mean trough levels on Day 8 and of 8 patients included in at least one comparison. Box plots clearly show an absence of Debio-0123 accumulation between cycles, allowing for inter-cycle comparisons. PK parameters (area under the curve from D0 until predose in the next cycle (AUC0-∞, maximum concentration (Cmax)) were determined post-D10 dose and compared. Each patient was his/her own control.

Individual PK profiles and PK parameters were determined using Phoenix WinNonlin version 8.3.

The intra-individual difference in exposure (AUC0-∞, Cmax) between cycle 2 and 1 for food effect or cycle 3 and 1 for high gastric pH effect was calculated after having assessed the absence of any inter-study events.

The following inter-study events precluding use of at least one cycle were: vomiting events within 2h of dose administration on D10 of any cycle, reduced dose on D8, 9 or 10, absence of main PK samples collection (e.g. due to COVID isolation), use of a concomitant medication with impact on absorption, distribution, metabolism or elimination, patient out of study for any reason before cycle 2 or 3 or refusal of food/ PPI intake from the patient.

Data from 5 cohorts, 4 dose levels (n=17) resulted in 7 and 5 pairwise comparisons for food and for high gastric pH effect respectively.

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