Food for Thought: Effect of a High-Fat Meal on DO-2; a Novel MET-Kinase Inhibitor

Daan A.C. Lanser, Peter de Bruijn, Esther Oomen-de Hoop, Viviënne van de Walle, Florence Wastelin, Cecilia Ahlin, Desireé Kanters, Peter de Waele, Mei H. Lam, Jaap Verweij, Timothy P.S. Perera, and Ron H.J. Mathijssen

Background & rationale

- **DO-2** is a **novel selective MET-kinase inhibitor** with potential activity in solid tumors harboring **MET exon-14 skipping alterations** or **MET-amplification.**
- **DO-2 is a re-developed** and **deuterated** version ($^{1}H \rightarrow {}^{2}H$) of **JNJ-38877605** to reduce metabolite formation via AOX1.
- Preclinical data suggest an **efficacy threshold of 160 ng/mL.**
- Maintaining plasma concentrations above this threshold for **8–10 hours** (**"time over threshold"**) is considered effective while minimising wild-type MET-inhibition–related edema.
- DO-2 is currently being evaluated in patients in a **phase 1** clinical trial (NCT05752552).

Aim

- To evaluate the **effect of food on the pharmacokinetics of DO-2** and its metabolites in healthy volunteers.

Methods

- **This randomised three-period crossover** study included 12 healthy volunteers who received a single 40 mg dose of DO-2 under **fasted conditions** and **after a meal.**
- Participants were 1:1 randomised to start with either condition (fasted or fed), followed by the alternate condition.
- After each period, **24-hour pharmacokinetic sampling was performed** for DO-2 and its metabolites.
- In Part 1, a **high-fat meal** was evaluated (according to FDA guidelines); in Part 2, a low-fat **continental breakfast**.
- Non-compartmental analyses of **Time over Threshold (ToT), Area Under the Curve ($AUC_{0\text{-}24h}$)** and **maximum concentration (C_{max})** and were conducted using Phoenix WinNonlin (v8.4).
- DO-2 and its metabolites were quantified using a validated liquid chromatography–tandem mass spectrometry method.
- Study registration: EUCT 2024-518581-27-00.

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Pharmacokinetics DO-2

Time over Threshold

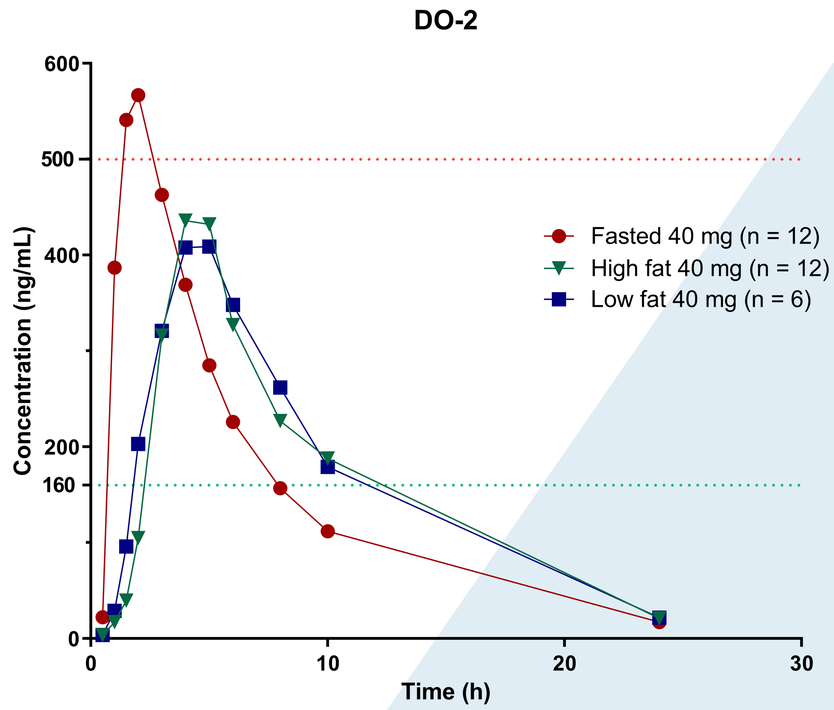
- In fasted state, a ToT of 6.9 hours [IQR: 5.5 – 9.4] was observed compared to a ToT of 10.7 hours [IQR: 5.8 – 14.7] with a high-fat meal (p = 0.005).
- In part 2: a low-fat meal showed a **comparable** ToT of 10.5 hours [IQR: 7.4 – 13.9] to a high-fat meal (p = 0.92).

Total exposure ($AUC_{0\text{-}24h}$)

- **Comparable** between fasted state and with a meal (+3.9%; 90% CI: -2.8% to +10.1%, p = 0.31).

Maximum concentration (C_{max})

- **Reduced** significantly with **16.2%** with a meal compared to fasted state (90% CI: -31.0% to 3.1%, p = 0.047).

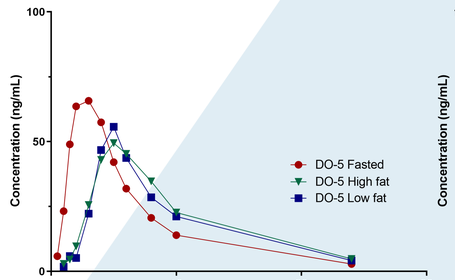


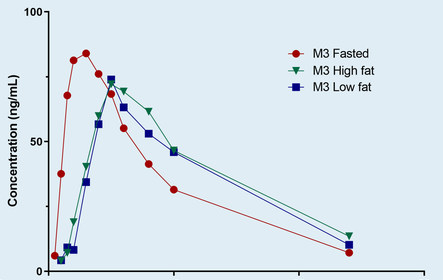
Time to reach maximum concentration (T_{max})

- In fasted state, a T_{max} of 1.5 hours [IQR: 1.4 – 2.0] was observed compared to a T_{max} of 4.5 hours [IQR: 4.0 – 5.0] with a high-fat meal (p = 0.002).
- In part 2: a low-fat meal showed a **comparable** T_{max} of 4.9 hours [IQR: 3.7 – 5.2] to high-fat meal (p = 0.25).

Metabolites DO-5 (active) & M3 (inactive)

- **Similar** pharmacokinetic effects were seen for the metabolites.





CONCLUSIONS

DO-2 pharmacokinetic profile is optimised when taken with food

The type of food (high-fat or low-fat) did not influence the effect

Discussion

- **Food** significantly **prolongs** the **ToT** and **reduces** the C_{max} for DO-2 in a clinically relevant manner.
- Probably this effect is a result of food-induced
  - **delay in gastric emptying** and;
  - **increased gastric pH**, as **DO-2 solubility is pH dependent** and therefore absorption is solubility driven.
- The total exposure of DO-2 ($AUC_{0\text{-}24h}$) is not influenced by food.
- Administration of DO-2 with food will be **further evaluated** in the ongoing patient study. For these results see poster 928P.

Timothy P.S. Perera
tperera@deuteroncology.com
DeuterOncology
Liege, Belgium

Daan A.C. Lanser
d.lanser@erasmusmc.nl
Erasmus University
Medical Centre Rotterdam,
The Netherlands