Drug-Drug Interaction Assessment of GDC-0032, a Beta-Sparing Inhibitor of Phosphoinositide 3-Kinase (PI3K), Using Midazolam, a Sensitive CYP3A4 Substrate


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BACKGROUND

GDC-0032 is an orally-bioavailable, potent, and selective inhibitor of Class IA PI3K alpha, delta and gamma isoforms, with 30-fold less inhibition of the p110 beta isoform (vs. alpha isoform).

GDC-0032 has shown promising preliminary clinical activity in PIK3CA-mutant cancers and is being explored in solid tumors and in combination with endocrine therapies in breast cancer.

In vitro, GDC-0032 was not a potent inhibitor of CYP isoforms 1A2, 2B6, 2C9, 2D6, 29D, and 3A4 (IC50 > 30 µM) but displayed weak time-dependent inhibition of CYP3A4, with IC50 and kobs values of 77 µM and 0.030 min-1, respectively. GDC-0032 induced CYP3A4, but not CYP2A6 or CYP2B6 in human hepatocytes.

Physically-Based Pharmacokinetic (PBPK) modeling platforms such as Simcyp® and GastroPlus® are commonly used by pharmacometricians and formulation scientists for mechanistic modeling and simulation of the absorption, distribution, metabolism and excretion (ADME) of drugs and drug-drug interactions in a virtual population (Chew et al., 2015; Xia et al., 2013). The drug-drug interaction potential for GDC-0032 with a CYP3A4 substrate (midazolam) was predicted using PBPK modeling.

RESULTS

1. Primary objective of the study was to evaluate the effect of GDC-0032 on the PK of midazolam.
2. Twelve patients with advanced or metastatic solid tumors were enrolled. All patients received 6 mg GDC-0032 on Day 1 (D1), followed by continuous daily dosing of GDC-0032 (9 mg) starting on D2. A second 5 mg midazolam dose was given on D16.
3. Predose, 0.5, 1, 1.5, 2, 3, 4, 8, and 24 hr post-dose plasma samples were collected on D1 and D16, maximum concentration (Cmax) and area under the concentration-time curve (AUC0-24) of midazolam were estimated from non-compartmental methods using WinNonlin (Version 5.2.1, Pharsight Corp., Mountain View, CA).
4. Midazolam plasma Cmax and AUC0-24 with GDC-0032 (D1) and after 15 days of dosing with GDC-0032 (D16) were calculated, the geometric mean ratios (GMRs) of Cmax and AUC0-24, and the corresponding 90% CIs were estimated.
5. PBPK modeling was used to predict the drug-drug interaction (DDI) potential of GDC-0032 (Simcyp® 11.0, Simcyp Limited, Sheffield, UK and GastroPlus® 8.0, Simulations Plus, Inc., Lancaster, CA).
6. Simcyp Model Specifications: The first order absorption model and the minimal PBPK distribution model were used to build the compound file for GDC-0032. DDI simulations were conducted for 10 trials with 10 subjects per trial (total n=100) using the Simcyp healthy volunteer profile.

CONCLUSIONS

• Despite in vivo results which indicated that GDC-0032 may impact the PK of concomitant medications which are metabolized by CYP3A4, continuous dosing of 9 mg GDC-0032 did not appear to impact the exposure to midazolam in patients with cancer.
• PBPK modeling predicted little to no impact of GDC-0032 on the PK of midazolam, consistent with the in vivo observation. While both Simcyp and GastroPlus models correctly predicted a lack of interaction, Simcyp provided a PK profile and parameter estimates closer to those determined in patients.

REFERENCES


ACKNOWLEDGEMENTS

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Table 1. Mean (± SD) PK Parameters of Midazolam with or without GDC-0032.

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>GDC-0032</th>
<th>Without GDC-0032</th>
<th>Predicted GastroPlus®</th>
<th>Simcyp®</th>
<th>Oberved GDC-0032</th>
<th>Predicted GastroPlus®</th>
<th>Simcyp®</th>
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<tr>
<td>Cmax(µg/L)</td>
<td>2 (± 0.238)</td>
<td>0.5 (0.28)</td>
<td>0.5 (0.28)</td>
<td>0.5 (0.28)</td>
<td>0.5 (0.28)</td>
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<tr>
<td>AUC0-24(µg*h/L)</td>
<td>0.0874 (± 0.044)</td>
<td>0.0875 (± 0.0354)</td>
<td>0.0875 (± 0.0354)</td>
<td>0.0875 (± 0.0354)</td>
<td>0.0875 (± 0.0354)</td>
<td>0.0875 (± 0.0354)</td>
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<tr>
<td>T1/2 (h)</td>
<td>0.5 (0.5-1.5)</td>
<td>0.5 (0.5-1.5)</td>
<td>0.5 (0.5-1.5)</td>
<td>0.5 (0.5-1.5)</td>
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<td>0.5 (0.5-1.5)</td>
<td>0.5 (0.5-1.5)</td>
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- Predicted PK parameter values observed in vitro.
- *T1/2 was reported as median (range).*