Risk Assessment for Drug-Drug Interactions in Early Development

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Biomarkers of CYP3A Activity:

What Have We Learned and are We Ready to Utilize Biomarkers to Replace Clinical DDI Studies?

CASE STUDY 1

Introduction & Rationale

- A clinical study is often required to put perspective on in vitro results that indicate a drug is a perpetrator of CYP3A DDI (or other enzyme/transporter -inhibitor or inducer)
  - Midazolam is a common probe substrate for the clinical DDI study to assess CYP3A perpetrator potential
- A biomarker assay to assess CYP3A modulation could provide some assessment prior to a formal DDI
  - Potential resource savings by delaying study
  - Potential to replace formal DDI once validated?
- Urinary 6β-OH-cortisol, 6β-OH-cortisone, and plasma 4β-OH-cholesterol are considered to be predictive markers of CYP3A activity; however, the signal for inhibition using these markers is much less robust than the signal for induction
- A recently published paper by Shin *et al.* suggests that the CYP3A-mediated inhibition with midazolam clearance could be predicted using a combination of urinary DHEA levels, 7β-hydroxy-DHEA:DHEA ratios, 6β-hydroxycortisone: cortisone ratios, and CYP3A5 genotype

Combined Evaluation of MAD & DDI with Midazolam

- Assess the effect of Compound A on PK of midazolam and 1-OH midazolam.
- Assess the effect of Compound A on 7β-OH-DHEA:DHEA & 6β-OH-cortisone: cortisone urine excretion ratios

MAD Evaluation

Compound A 2.5 mg QD 14 days

Compound A 10 mg QD 14 days

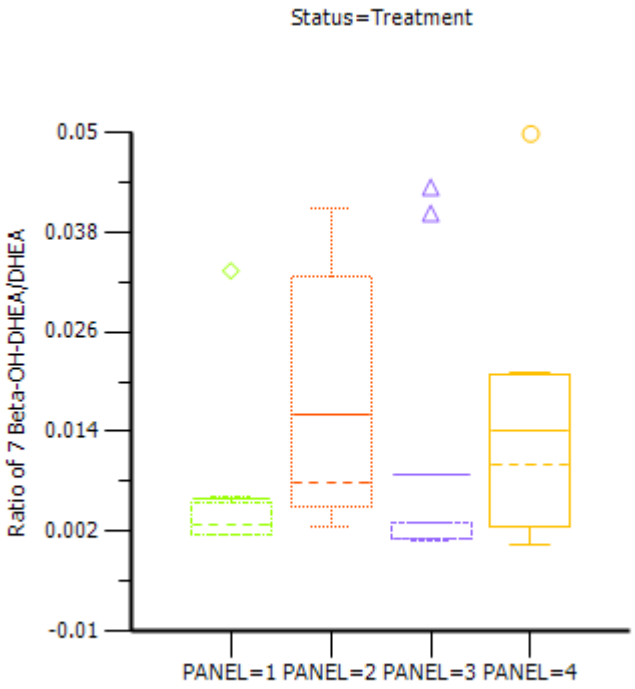
Compound A 40 mg QD 14 Days

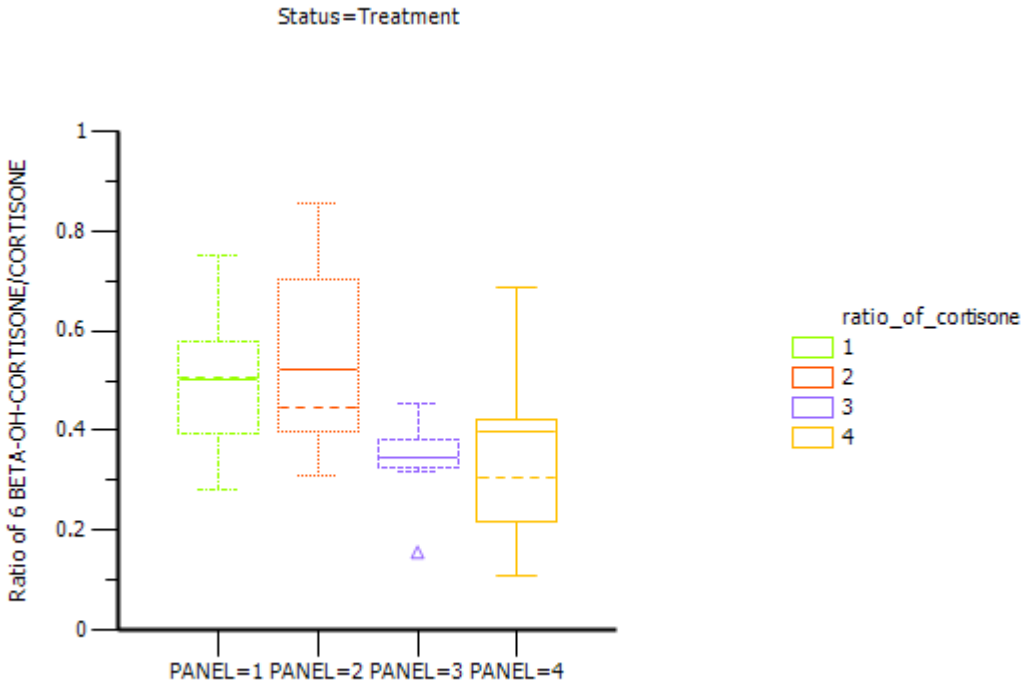
Compound A 100 mg QD 14 Days

DDI Evaluation

Day -1 Midazolam only → Day 1-12 40 mg Compound A (or Placebo) → Day 13 Midazolam+ 40 mg Compound A (or Placebo)

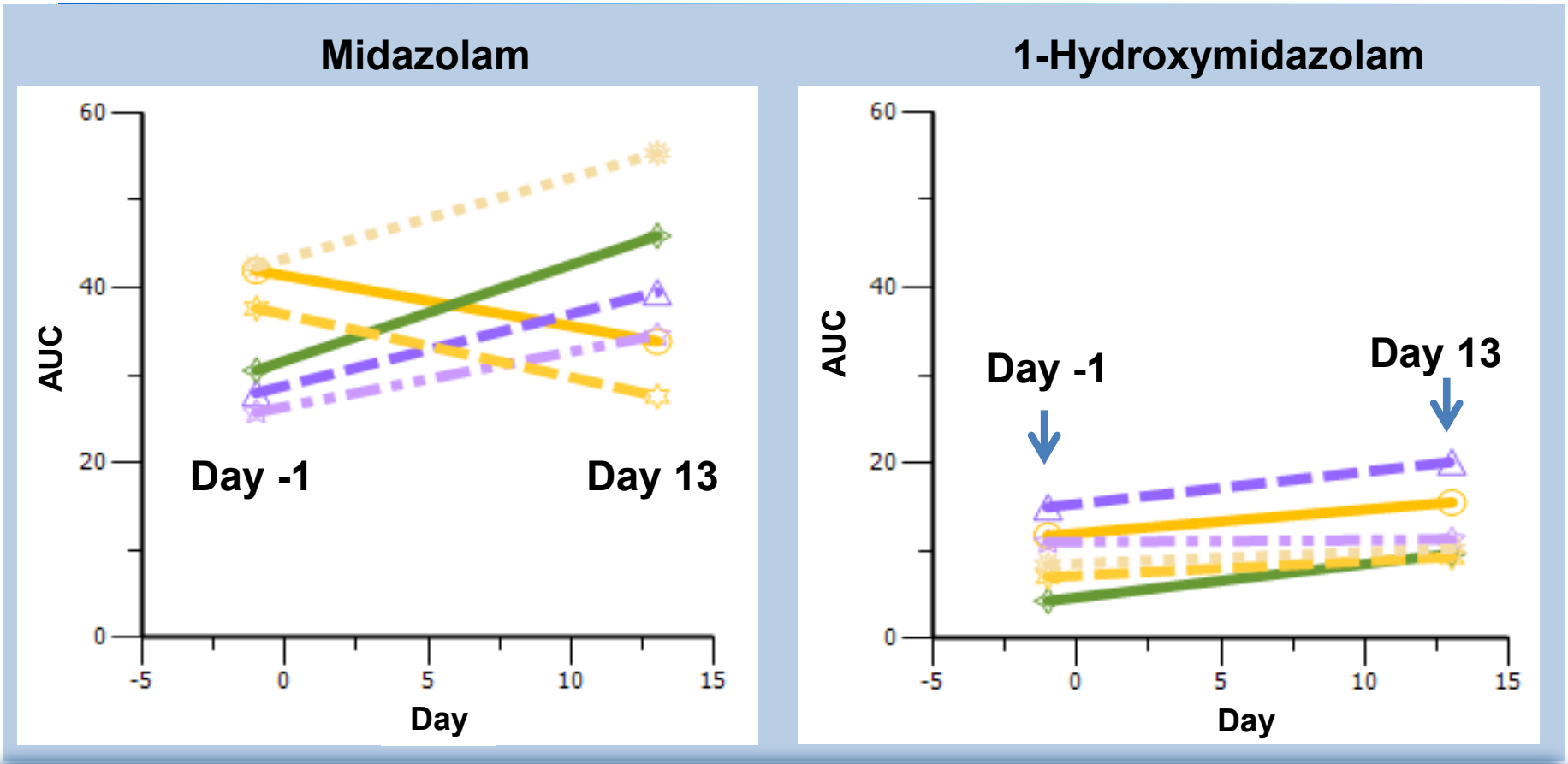
Ratios of 7 Beta-OH-DHEA/DHEA and 6β-OH-Cortisone/Cortisone Following MAD at Different Doses of Compound A





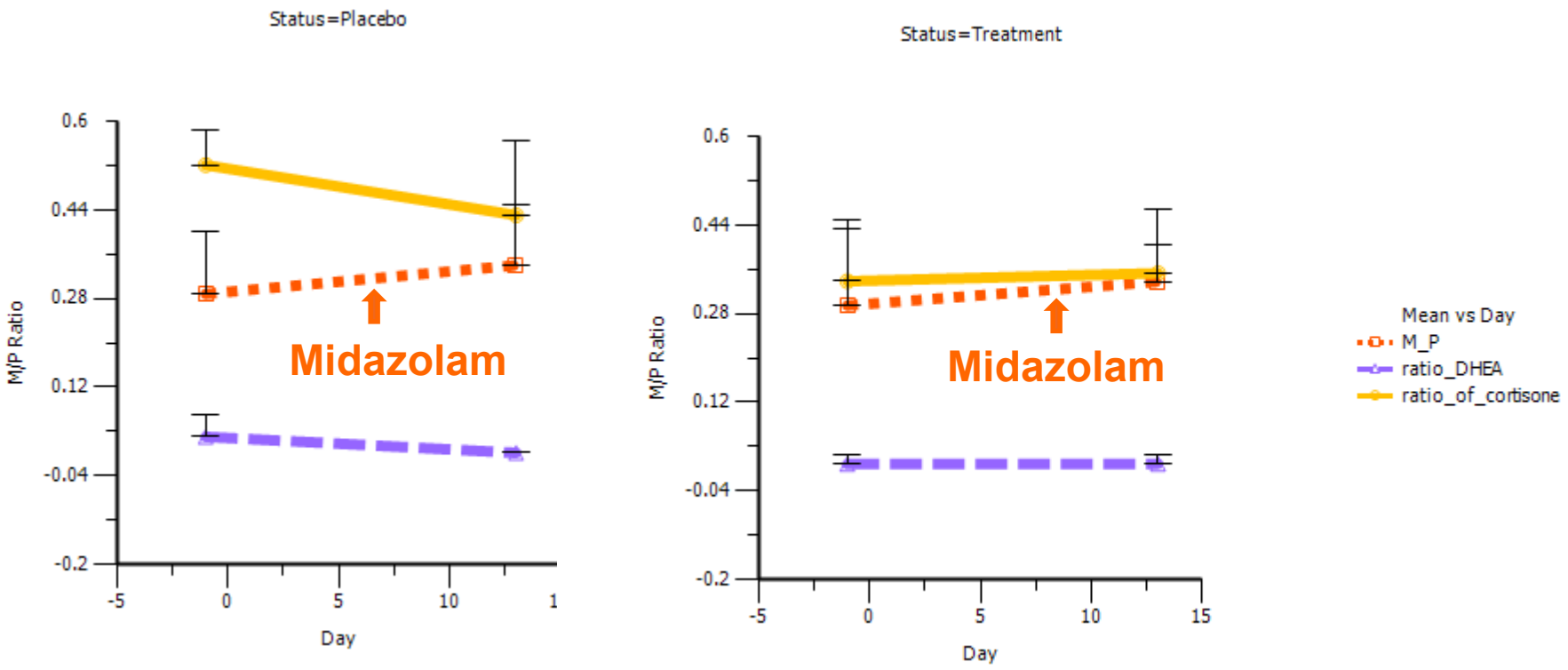
Ratios of 7 Beta-OH-DHEA/DHEA and 6β-OH-Cortisone/Cortisone were not dose dependent and there was substantial inter-subject variability.

The Change in AUCs of Midazolam and 1-OH-midazolam Before and After Dosing with 40 mg of Compound A



Preliminary data from both midazolam and 1-hydroxymidazolam suggest that Compound A has minimal effect on CYP3A activity and the disposition of 1-OH-midazolam

The Correlation of Mean Ratios of 1'-OH-Midazolam/Midazolam, 7β-OH-DHEA/DHEA and 6β-OH-Cortisone/Cortisone are Directionally Similar



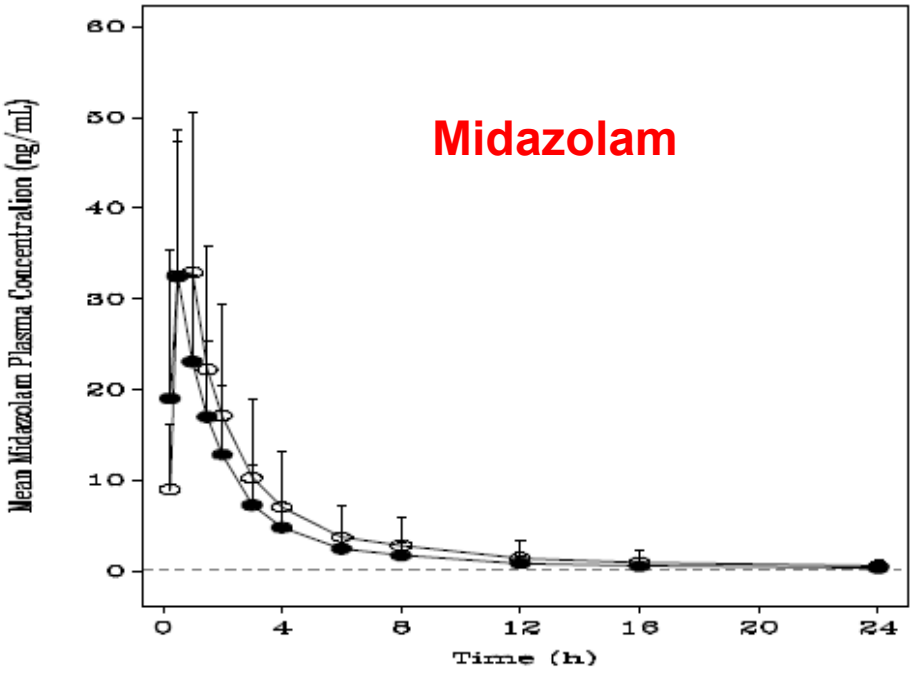
Mean Ratios of 1'-OH-Midazolam/Midazolam, 7β-OH-DHEA/DHEA and 6β-OH-Cortisone/Cortisone were consistent in terms of demonstrating lack of an effect of Compound A on CYP3A4 Activity.

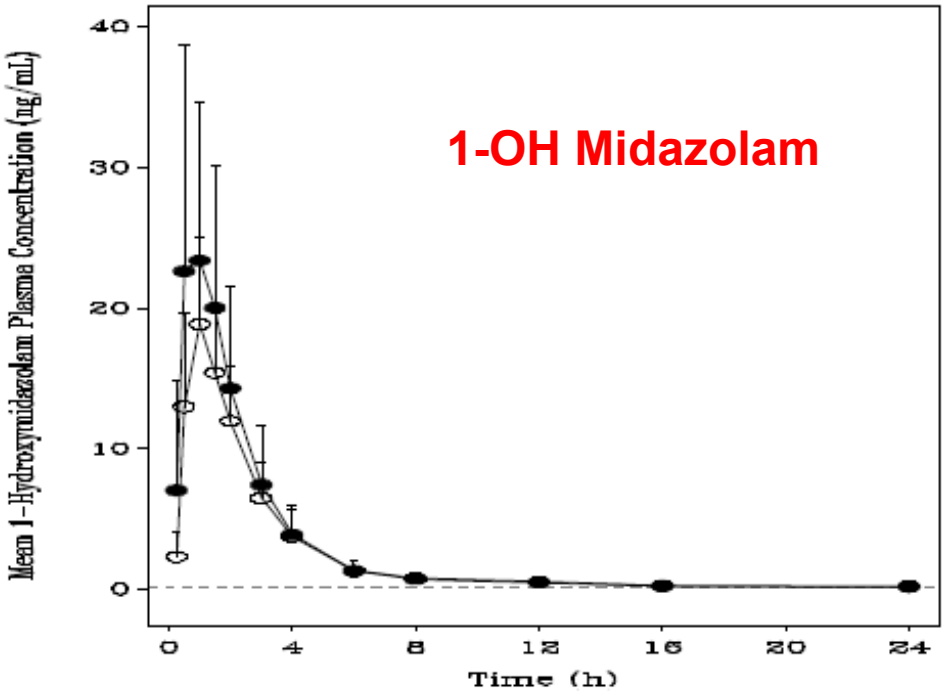
CASE STUDY 2

Introduction & Rationale

- In Vitro Data Suggested Compound B has a Dual Potential for Induction and Inhibition for CYP3A4
  - At therapeutic concentrations inhibition was observed with an IC50 of 6.4 µM using midazolam as a probe
  - Induction was also noted with a 4-fold increase in mRNA over control at 2.5 µM
- The overall long-term effect on CYP3A4 was difficult to predict
- In order to inform the Phase 2 program in a timely manner, we proposed DDI Strategy as a tiered approach
  - Perform a standard cocktail DDI study to address inhibitory potential at the highest potential therapeutic dose of 350 mg QD
  - In parallel, monitor 4β-OH-cholesterol in the MAD to determine whether induction would occur
- Results from the 4β-OH-cholesterol evaluation in the MAD would inform the need for further induction studies

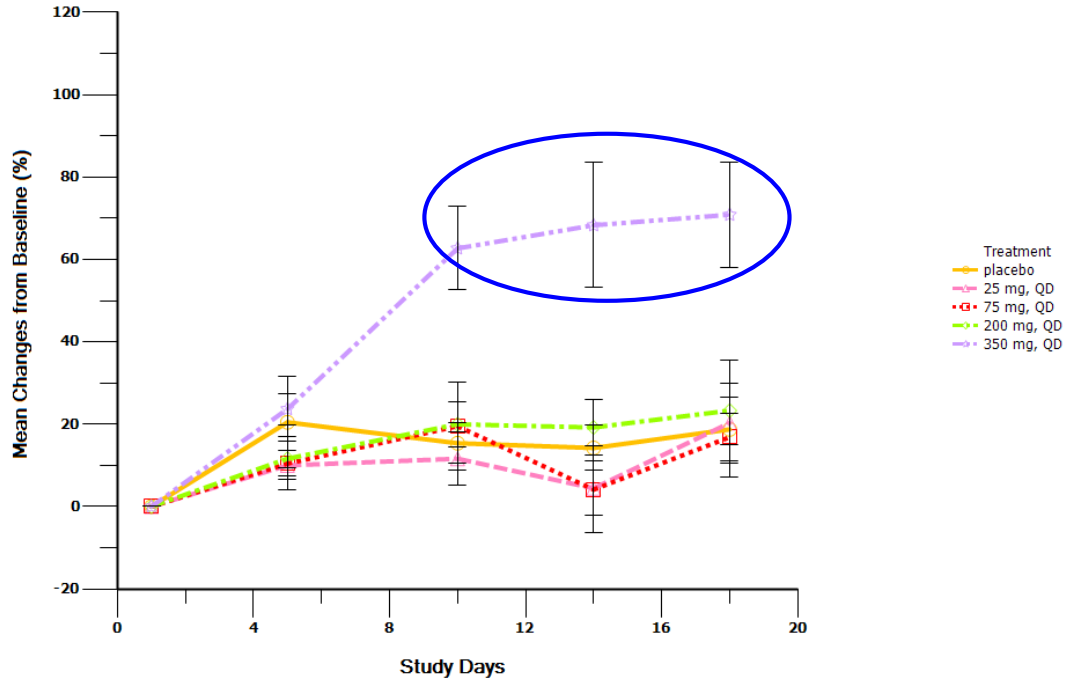
DDI Study Suggested Compound B inhibited CYP3A4 Resulting in Increased Midazolam & Decreased 1-OH Midazolam Exposure





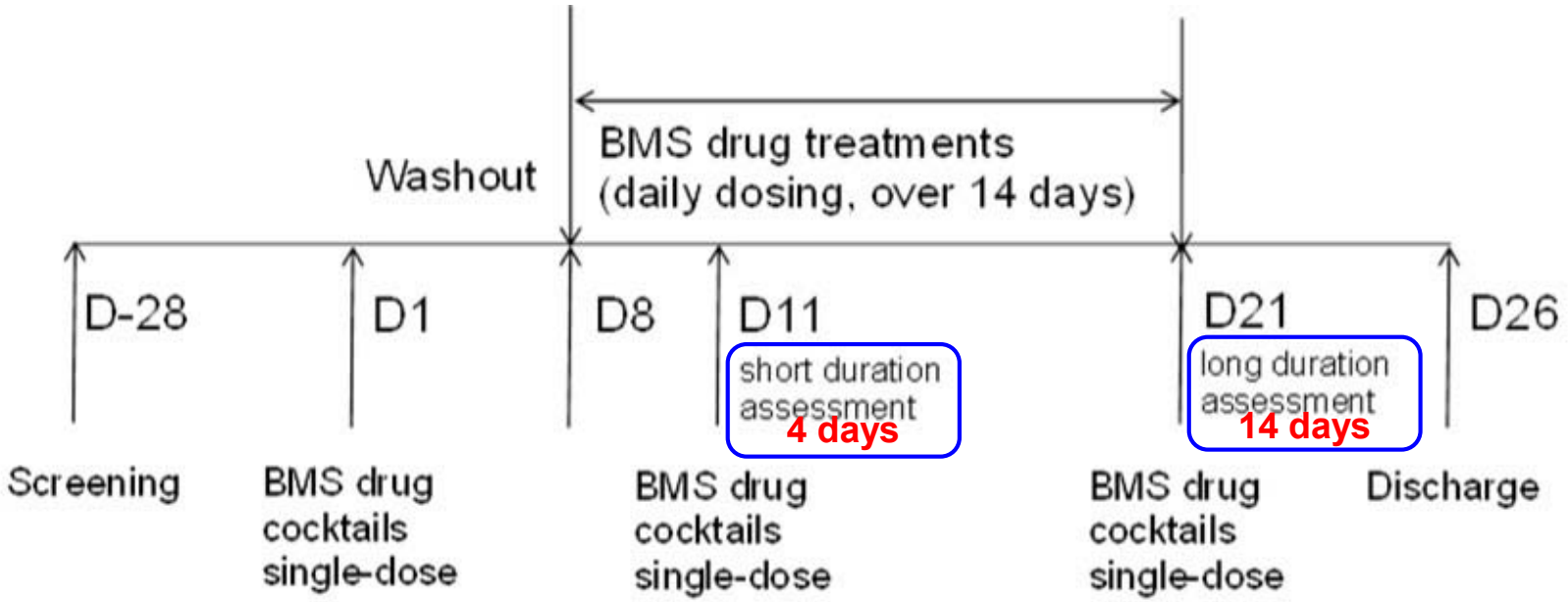
Analyte	GMR (90% CI) AUC	GMR (90% CI) Cmax	Assessment
Midazolam	1.23 (1.09, 1.39)	1.13 (1.01, 1.26)	**Weak Inhibition**
1-OH Midazolam	0.88 (0.74, 1.03)	0.76 (0.60, 0.97)	

4β-OH-cholesterol data from MAD Study Suggested Potential for Induction



- Meaningful increases (~70%) were observed only at the highest dose panel of 350 mg
- Compared to strong inducers like rifampin, data suggests that compound B may not be a strong inducer for CYP3A4
- However, the potential for weak or moderate induction remained a question

Study Design for Repeat Cocktail DDI Study: *Multiple Dose Levels and Longer Duration of Treatment*



BMS cocktail probes

- **Midazolam (3A4): 5 mg**
- **Digoxin (p-gp): 0.25 mg**
- **Montelukast (2C8): 10 mg**
- **Flurbiprofen (2C9): 50 mg**
- **Omeprazole (2C19): 40 mg**

BMS drug treatment cohorts

- **Cohort 1:Compound B, 200 mg, QD**
- **Cohort 2: Compound B, 350 mg, QD**

Compound B Caused Time-dependent Alterations in the PK of Midazolam

Dose (mg)	Duration	GMR (90 CI) Cmax	GMR (90 CI) AUC(INF)	Interpretation
200	4 days	1.06 (0.87, 1.30)	1.10 (0.93, 1.31)	Weak inhibition
200	14 days	0.85 (0.68, 1.06)	0.73 (0.59, 0.91)	Weak induction
350	4 days	1.21 (1.08, 1.35)	1.21 (1.13, 1.30)	Weak inhibition
350	**14 days**	**0.92 (0.81, 1.05)**	**0.69 (0.60, 0.80)**	**Weak induction**

Conclusion: The long-term effect of administration of Compound B was weak induction of CYP3A4. Therefore, no dosage adjustments for sensitive substrates of CYP3A4 are warranted.

Conclusions from Case Studies

- In general, biomarkers are a useful tool to detect potential DDI signals
- From these 2 case studies, biomarkers were predictive of the direction of the DDI
- With agents that have the potential for dual inhibition and induction it remains difficult to predict the net effect of long-term administration
- Clinical studies with probe studies are still needed to confirm the extent of the DDI

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