Power to the People: Estimating Sample Sizes for No Effect Drug-Drug Interaction Studies with Sensitive CYP and Transporter Substrates

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BACKGROUND

- Drug-drug interactions (DDI) potentially result in increased or decreased drug exposure, thereby impacting drug safety or efficacy, respectively. To avoid such potential interactions, drug developers are required to list all potential DDIs on the drug label.
- In line with M12 Drug Interaction Guidance[1], a clinical DDI study with a sensitive index CYP substrate is recommended if an investigational product (IP) may induce or inhibit CYP enzymes, or if the IP inhibits transporters in vitro.
- A powered study, with sample size justification, is recommended to support a no-effect label claim.
- The sample size of a given substrate is dependent upon the percent intra-subject coefficient of variation (intraCV%) of the relevant pharmacokinetic (PK) parameters and the goal of the study (i.e., to assess the magnitude of an interaction or to confirm a no-effect).
- We calculated the recommended sample size based on our previous experience with key substrates in healthy volunteer studies.

METHODS

- Drug exposure parameters data from 6 CYPs and 3 transporter substrates were reviewed.
- As maximum exposure (Cmax) is usually more variable than total exposure (AUC), we determined an adequate sample size based on Cmax.
- Cmax intraCV% was obtained from >25 DDI studies conducted at Celerion since 2020.
- For each substrate, the sample size was calculated using a power of at least 80%, an alpha error of 5%, and a ratio of 100%, using the R program. The power was defined as the probability of having a 90% confidence interval (CI) of the true geometric mean ratio (GMR) within the acceptance criteria of 80-125%, reflecting the default no-effect boundary for these study types.
- Results were compared to data from industry-sponsored, Phase 1 DDI studies listed on www.clinicaltrials.gov (CTG) and administering probes as standalone (probe cocktails and multi-part studies excluded). Only substrates with ≥5 studies listed were included in the CTG analysis.

RESULTS

Table 1: Sample Size Calculation for Key Index Substrates

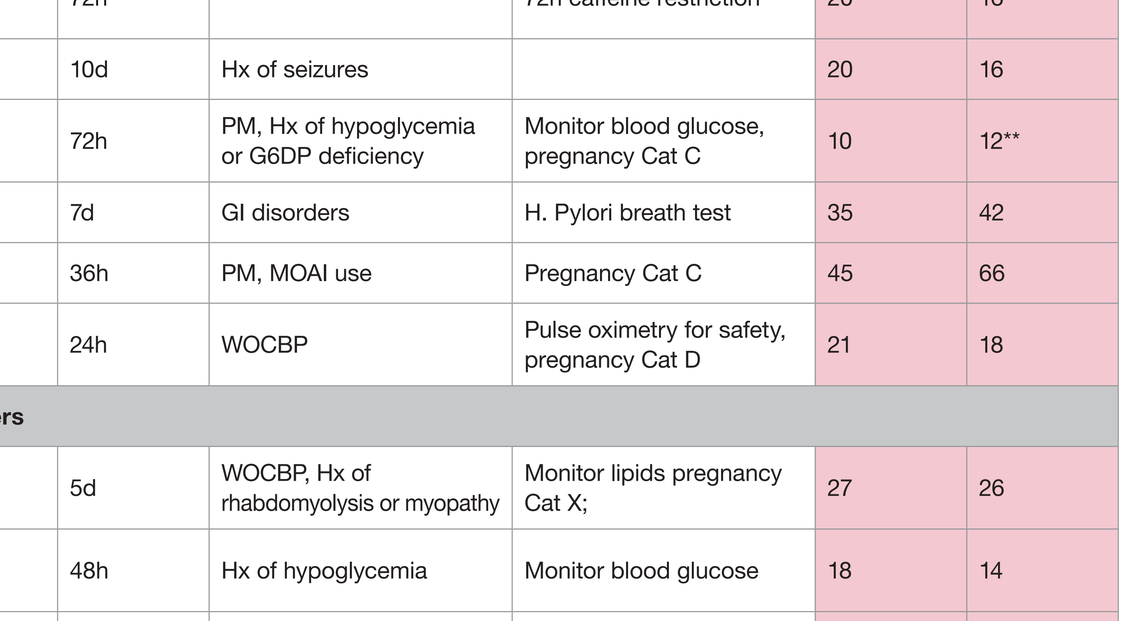
CYP / Transporter	Substrate	Drug Class	Oral Dose (mg)	T_{max} (h)	$t_{1/2}$ (h)	PK Sampling (h)	Washout Period	Key Exclusion Criteria	Comments	C_{max} Mean intraCV%	Size n*
CYP Enzymes											
CYP1A2	Caffeine	Stimulant, food additive	100	2	5	48	72h		72h caffeine restriction	20	16
CYP2B6	Bupropion	Anti-depressant	100	1.5	21	96	10d	Hx of seizures		20	16
CYP2C9	Tolbutamide	Anti-hyperglycemic agent	500	3	5	48	72h	PM, Hx of hypoglycemia or G6DP deficiency	Monitor blood glucose, pregnancy Cat C	10	12**
CYP2C19	Omeprazole	Proton pump inhibitor	40	2	0.75	24	7d	GI disorders	H. Pylori breath test	35	42
CYP2D6	Dextromethorphan	Antitussive	30	4	4	24	36h	PM, MOAI use	Pregnancy Cat C	45	66
CYP3A	Midazolam	Sedative	2	0.7	5	24	24h	WOCBP	Pulse oximetry for safety, pregnancy Cat D	21	18
Transporters											
BCRP / OATP1B	Rosuvastatin	Lipid-lowering agent	10	4	15	96	5d	WOCBP, Hx of rhabdomyolysis or myopathy	Monitor lipids pregnancy Cat X;	27	26
OCT / MATE1/2K	Metformin HCl	Anti-hyperglycemic agent	500 or 1000	2.5	4	48	48h	Hx of hypoglycemia	Monitor blood glucose	18	14
P-gp	Digoxin	Cardiac glycoside	0.25	1	38	168	10d	Long QT, hypo-Ca^{2+}/Mg^{2+}	Include urine PK if MD perpetrator	26	24

G6DP, glucose 6-phosphate dehydrogenase; **GI**, gastrointestinal; **Hx**, history; **MD**, multiple dose; **MOAI**, monoamine oxidase inhibitors; **PM**, poor metabolizers (genetic variants); **WOCBP**, women of childbearing potential.

*Recommended sample size to complete the study; **n=6 is required to complete, however recommend dosing n=12 for a more representative sample size.

- The number of participants recommended for a substrate DDI study to show no effect ranged from n=16 to 35 (Table 1).
- Metformin (OCT / MATE 1/2K) had the lowest Cmax intraCV% (18, n=16).
- Omeprazole (CYP2C19) had the highest variability (30%, n=35).
- Sample sizes applied in trials listed on CTG are in line with those calculated for digoxin, rosuvastatin and midazolam, however, omeprazole DDI studies on CTG appear to be underpowered whereas CTG metformin studies appear slightly overpowered.

Figure 1: CTG-Reported Sample Sizes for Selected Index Substrates



Box and whisker plot showing the median, 25-75 percentile and min-max whiskers of enrollment numbers in DDI studies reported on CTG for substrates digoxin, metformin, rosuvastatin, midazolam and omeprazole; and sample sizes calculated from studies conducted at Celerion (■)

CONCLUSION

- For a non-powered study, we typically recommend a sample size of n=12-16. For a powered study, recommended sample sizes, in some cases, are up to 2-4 times greater for a specific substrate.
- The relatively high variability in omeprazole and dextromethorphan PK can probably be attributed to genetic polymorphisms for CYP2C19 and CYP2D6 among study participants, respectively.
- This information will help drug developers plan for future DDI studies.

REFERENCE

[1] FDA Final Guidance for Industry: M12 Drug Interaction Studies, https://www.fda.gov/media/161199/download

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