Effects of Isotretinoin on CYP2D6 Activity
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Dextromethorphan/dextrorphan metabolic ratio: All urine will be collected over 4 hours following DM administration for measurement of our endpoint, urinary DM/DX MR, as previously described. Urine pH will also be measured. We recognize that urinary DM/DX MR is influenced by renal clearance (blood flow, secretion and filtration), changes in CYP3A activity or changes in urine pH. Urine samples will be analyzed for DM, DX, 3-methoxymorphinan, 3-hydroxymorphinan and DX-O-glucuronide concentrations using our validated UHPLC-MS/MS assay.

CYP2D6 genotype: Buccal swabs will be collected from each subject for CYP2D6 genotyping prior to the first DM study. The following CYP2D6 genotypes will be determined: *CYP2D6*3* (2549delA), *CYP2D6*4* (1846G>A), *CYP2D6*5* (*CYP2D6* deleted), *CYP2D6*6* (1707delT), *CYP2D6*9* (2613 delAGA), *CYP2D6*10* (100C>T), *CYP2D6*17* (1023C>T), *CYP2D6*35* (-1584 C>G and 31G>A) and *CYP2D6*41* (2988 G>A) as previously described using commercially available TaqMan assays. The genotype will be used to predict the subject phenotype (PM, IM, EM or UM) as well as activity scores (0, 0.5, 1,1.5, 2 and 3) as described previously. Only extensive metabolizers with index scores based on genotype of 1,1.5 and 2 will proceed with the DM portion of the study.

DX/DM MRs were calculated by dividing the molar quantity (urine) of the metabolite by that of the parent. DX plus DX-O-glucuronide/DM urinary MR was calculated by dividing the sum of the molar quantity of metabolites by that of the parent. Urine samples with concentrations above or within 5% of the LLOQ were accepted, and concentrations lower than that were excluded from data analysis. DX/DM and DX plus DX-O-glucuronide/DM MRs were analyzed only in CYP2D6 EMs (AS = 1-2). The GMR and 90% CI were used to compare urinary MRs between study timepoint 1 (pre-treatment control) and study timepoint 2 (with isotretinoin treatment). The 90% CI of the GMR for the MR with isotretinoin treatment over pre-treatment control was compared to the bioequivalence range of 0.8 and 1.25 according to FDA Guidance of Clinical Drug Interaction Studies. If the 90% CI does not include 1, there is an indication of a potential drug interaction. Statistical analyses were all conducted on GraphPad Prism 9.5.1 (GraphPad Software, Inc., La Jolla, CA, USA).