Supplemental Information

Clinical Pharmacokinetics and the Impact of Genetic Polymorphisms on a CYP2C19 Substrate, BMS-823778, in Healthy Subjects

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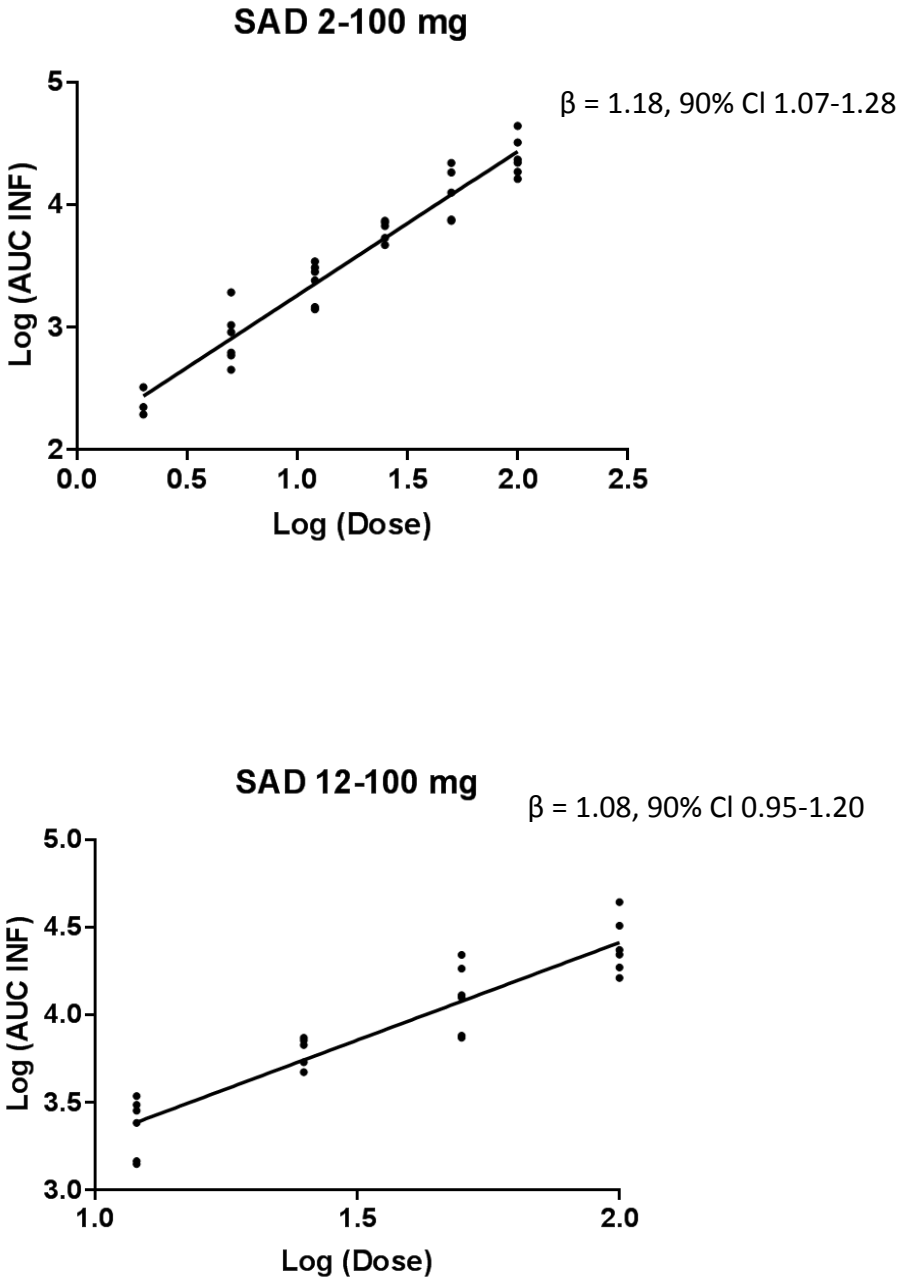
Figure S1 Representative plots for the dose proportionality analysis with a power model: log(AUC) = α + βlog(dose), for SAD/MAD data.



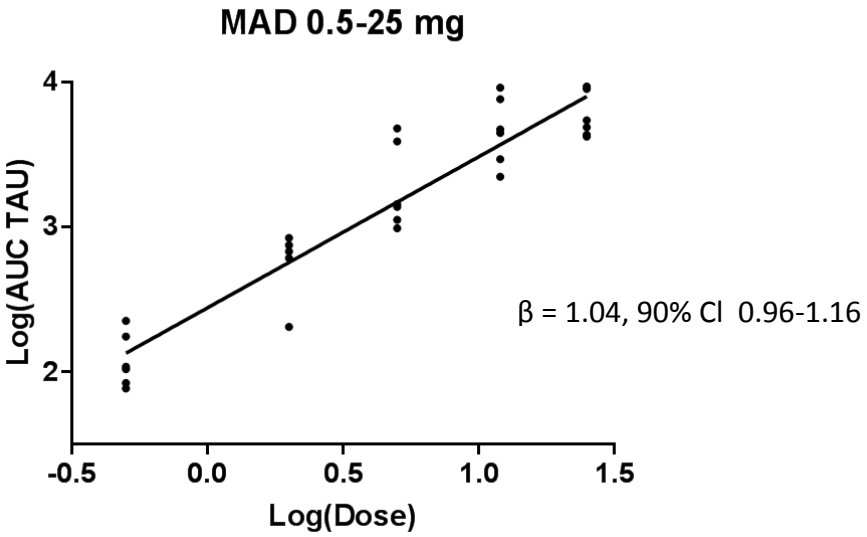

MAD 0.5-25 mg
Log(AUC TAU)
Log(Dose)
4
3
2
-0.5
0.0
0.5
1.0
1.5
β = 1.04, 90% CI 0.96-1.16

Figure S2. Individual and mean CLT/F of BMS-823778 in healthy Japanese subjects grouped according to (A) UGT1A4 or (B) CYP3A5 genotype (P = 0.38 and 0.71, respectively, when CLT/F values of subjects with UGT1A4 or CYP3A5 polymorphism were compared to subjects with wild-type genotype)

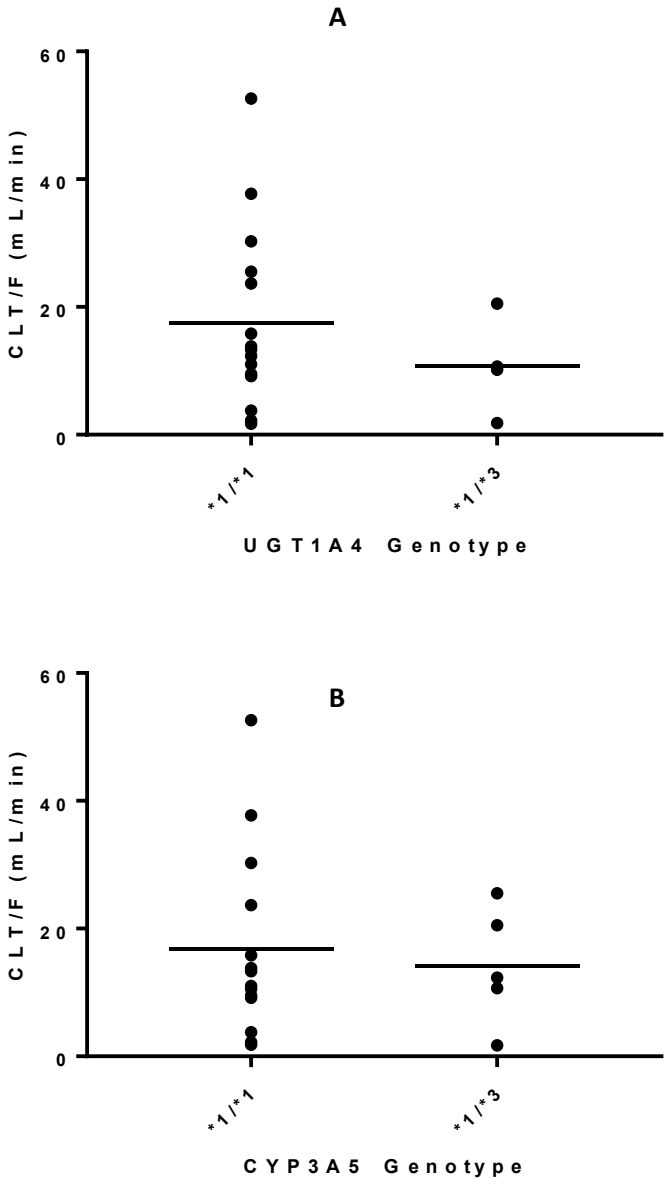


Table S1 Number (Percentage) of Subjects in SAD Study with Laboratory Marked Abnormalities

Category Lab Test Description	Placebo SAD (n=16)	BMS-832778 SAD								
		0.1 mg (n=6)	0.5 mg (n=6)	2 mg (n=6)	5 mg (n=6)	12 mg Fasted (n=6)	12 mg Fed (n=6)	25 mg (n=6)	50 mg (n=6)	100 mg (n=6)
Hematology										
Leuckocytes, low	0	0	0	1 (17)	0	0	0	0	0	1 (17)
Neutrophils, low	0	0	0	1 (17)	0	0	0	0	0	0
Eosinophils, high	0	0	0	0	0	0	0	0	1 (17)	0
Liver and Kidney function tests										
Alanine Aminotransferase, high	3 (19)	0	1 (17)	0	0	0	1 (17)	1 (17)	3 (50)	1 (17)
Aspartate Aminotransferase, high	0	0	0	0	0	0	0	0	0	1 (17)
Total Bilirubin, high	0	0	0	0	0	1 (17)	1 (17)	0	0	0
Other Chemistry Testing										
Creatine Kinase, high	0	0	0	0	0	0	0	0	1 (17)	1 (17)

Table S2 Number (Percentage) of Subjects in MAD Study with Laboratory Marked Abnormalities

Category Lab Test Description	Placebo MAD (n=10)	BMS-823778 MAD 0.5 mg (n=6)	2 mg (n=6)	5mg (n=6)	12 mg (n=6)	25 mg (n=6)
Hematology						
Hematocrit, low	0	2 (33)	0	0	0	0
Leukocytes, high	0	0	1 (17)	0	0	0
Eosinophils, high	0	0	1 (17)	0	0	0
Lymphocytes, low	0	0	0	0	1 (17)	0
Platelet Count, low	0	0	0	0	0	1 (17)
Liver and Kidney function tests						
Alanine Aminotransferase, high	1 (10)	0	1 (17)	2 (33)	5 (83)	1 (17)
Aspartate Aminotransferase, high	1 (10)	0	0	1 (17)	2 (33)	1 (17)
Total Bilirubin, high	0	0	1 (17)	0	0	0
Blood urea nitrogen, high	1 (10)	0	0	1 (17)	0	0
Other Chemistry Testing						
Creatine Kinase, high	0	0	0	1 (17)	0	0
Special Studies						
Albumin, Urine Conc., high	0	0	0	0	1 (17)	0

Table S3 Number (Percentage) of Subjects in the Chinese Study with Laboratory Marked Abnormalities

Category Lab Test Description	**Placebo (n=10)**	**BMS-823778 Multiple Dose**	
		2 mg (n=15)	**15 mg (n=15)**
Total subjects with an event	**4 (40.0)**	**2 (13.3)**	**7 (46.7)**
Eye Disorders	0	1 (6.7)	1 (6.7)
Eye inflammation	0	1 (6.7)	0
Conjunctivitis	0	0	1 (6.7)
Respiratory, Thoracic, and Mediastinal disorders	1 (10.0)	0	0
Rhinitis Allergic	1 (10.0)	0	0
Infections and infestations	2 (20.0)	1 (6.7)	5 (33.3)
Upper Respiratory Tract Infection	1 (10.0)	1 (6.7)	3 (20.0)
Conjunctivitis Viral	0	0	1 (6.7)
Viral Pharyngitis	1 (10.0)	0	0
Sinusitis	0	0	1 (6.7)

Table S4 Number (Percentage) of Subjects in the Japanese Study with Laboratory Marked Abnormalities

Category Lab Test Description	Placebo (n=6)	BMS-823778 Multiple Dose		
		2 mg (n=6)	12 mg (n=6)	25 mg (n=6)
Total subjects with an event	**4 (66.7)**	**1 (16.7)**	**0**	**3 (50.0)**
Investigations	3 (50.0)	0	0	2 (33.3)
Blood creatinine phosphokinase increased	2 (33.3)	0	0	1 (16.7)
Alanine aminotransferase increased	1 (16.7)	0	0	0
Blood uric acid increased	0	0	0	1 (16.7)
Liver function test abnormal	0	0	0	0
Gastrointestinal disorders	2 (33.3)	1 (16.7)	0	0
constipation	2 (33.3)	1 (16.7)	0	0
General dusirders and administration site conditions	0	0	0	1 (16.7)
Puncture site pain	0	0	0	1 (16.7)
Infections and infestations gingivitis	0	0	0	0

In Vitro Assessment of BMS-823778 as an Inducer of Cytochrome P450 Expression in Primary Human Hepatocytes

BMS-823778 (at concentrations of 0.2, 1, 5, and 15 μM), known prototypical CYP inducers, 3-methylcholanthrene (3-MC), phenobarbital (PB), and rifampicin (RIF), and solvent controls were incubated in three separate preparations of primary human hepatocytes for three consecutive days. During the incubation period, the media containing the test article was replaced every 24 hours. Cytotoxicity was evaluated by microscopic observations of the hepatocytes and measurement of lactate dehydrogenase (LDH) leakage. After the incubation period, microsomes were isolated and the enzymatic activities of CYP1A2 (phenacetin *O*-dealkylation), CYP2B6 (bupropion hydroxylation), and CYP3A4 (testosterone 6ß-hydroxylation) were measured and compared for each treatment group. Additionally, cells were harvested from each treatment group and the messenger RNA (mRNA) encoding CYP1A2, CYP2B6, CYP3A4 was measured by TaqMan®-based quantitative Reverse Transcription-Polymerase Chain Reaction (qRT-PCR) to compare mRNA expression across each treatment group. For each of the positive controls mentioned above, mean induction data were generated, and from those means, the corresponding mean vehicle control values were subtracted to yield "adjusted positive control responses." Induction results for BMS-823778 assays were averaged from triplicate samples and compared to the corresponding adjusted positive controls. Increases in enzyme activity or mRNA levels ≥ 40% of the respective positive control samples are considered an indication of demonstrable induction.

Overall, the cell viability analysis in the presence of BMS-823778 at concentrations of 0.2, 1, 5, and 15 μM showed no toxicity. Hepatocyte morphological integrity was maintained throughout the incubations period, and the extent of LDH leakage in the presence of BMS-823778 was comparable to that produced from cells in the vehicle control treatment group.

There appeared to be no potential for induction of CYP1A2 and CYP3A4 by BMS-823778 at concentrations of 0.2, 1, 5, and 15 μM given that the fold change on both enzyme activity and mRNA expression under these concentrations were below 40% of those with positive controls (Table S5 & S6). However, there was a dose-related increase in the CYP2B6 enzyme activity from 0.2 to 5 μM with a subsequent decrease at 15 μM. In addition, there was an increase at the mRNA level of CYP2B6 in two of the donors examined (Hu827 and Hu831) at 5 and 1 μM, respectively. However, these inductions for CYP2B6 were not as high as seen for the CYP450 enzymes with the prototype inducers.

Table S5. Summary of Enzyme Activity (fold induction) after Treatment with BMS-823778

Treatment	CYP1A2			CYP2B6			CYP3A4		
	Hu825	Hu827	Hu831	Hu825	Hu827	Hu831	Hu825	Hu827	Hu831
3-MC (2 μM)	74.7	11.8	43.6	1.5	1.5	1.3	1.0	0.7	1.3
Phenobarbital (1000 μM)	4.9	1.8	5.8	33.9	25.7	21.2	12.1	10.9	10.3
Rifampicin (10 μM)	3.3	0.9	2.0	14.3	7.6	5.0	14.8	16.9	14.9
BMS-823778 (0.2 μM)	1.6	0.7	1.7	2.2	3.0	1.2	2.0	1.1	2.0
BMS-823778 (1 μM)	1.0	0.8	1.2	2.9	4.9	2.4	1.7	1.5	2.0
BMS-823778 (5 μM)	1.5	0.6	2.1	8.7	28.2	8.0	4.2	2.4	3.1
BMS-823778 (15 μM)	2.0	1.3	2.9	5.5	5.6	5.1	5.0	3.7	3.4

Table S6. Summary of mRNA Content (fold induction) after Treatment with BMS-823778

Treatment	CYP1A2			CYP2B6			CYP3A4		
	Hu825	Hu827	Hu831	Hu825	Hu827	Hu831	Hu825	Hu827	Hu831
3-MC (2 μM)	165	536	512	0.762	2.14	3.45	0.254	0.591	2.18
Phenobarbital (1000 μM)	1.43	1.12	0.834	52.1	35.7	19.5	33.9	50.0	23.9
Rifampicin (10 μM)	0.596	0.823	4.92	7.50	15.6	33.1	30.2	59.4	91.0
BMS-823778 (0.2 μM)	0.198	0.645	0.571	1.18	1.06	2.08	1.62	1.02	1.32
BMS-823778 (1 μM)	0.150	0.541	0.731	2.25	12.5	18.8	2.39	4.21	9.33
BMS-823778 (5 μM)	0.238	0.860	0.516	8.67	34.5	4.99	8.25	19.2	2.56
BMS-823778 (15 μM)	0.198	0.263	0.101	0.762	9.99	8.33	2.94	10.5	14.2