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Supplementary Data

A Canine Model to Evaluate Efficacy and Safety of γ-Secretase Inhibitors and Modulators

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Supplementary Table 1
PK/PD analysis, estimated I_{max} or E_{max} and IC_{50} or EC_{50} per parameter and treatment

	BMS-708163				LY-450139			
	$A\beta_{37}$	$A\beta_{38}$	$A\beta_{40}$	$A\beta_{42}$	$A\beta_{37}$	$A\beta_{38}$	$A\beta_{40}$	$A\beta_{42}$
E_0 (6 h)	115	117	102	93	116	119	100	94
I_{max}	64[(2)]	55	48	34	64	84	59	67
IC_{50} (0–6 h)	[nd][(1)]	149	579	404	946	3544	5391	6651
	E-2012				JNJ-42601572			
	$A\beta_{37}$	$A\beta_{38}$	$A\beta_{40}$	$A\beta_{42}$	$A\beta_{37}$	$A\beta_{38}$	$A\beta_{40}$	$A\beta_{42}$
E_0 (8 h)	101	100	106	110	102	101	107	109
I_{max}			39	35			36	61
E_{max}	378	30			700[(2)]	150[(2)]		
IC_{50} (0–8 h)			27569	1995			3132	6913
EC_{50} (0–8 h)	28930	19920			183047	58000		

E_0 = the peptide in CSF expressed as % of baseline in the absence of treatment; I_{max} = the maximum % decrease of E_0; E_{max} = the maximum % increase of E_0; IC_{50}/EC_{50} = the AUC value at which 50% of the maximum effect is obtained (ng*h/ml) [(1)]na = not available (linear model); [(2)]increase at the maximum observed AUC.

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Supplementary Table 2
Maximal changes in Aβ in CSF on the measured timepoints expressed as mean % change from baseline (day before dosing). Values in italic are changes in corresponding vehicle group from baseline

	GSIs				GSMs			
	BMS-708163		LY-450139		E-2012		JNJ-42601572	
Dose (mg/kg)	0.63	2.5	1.25	5	20	80	10	20
Time	6 h	12 h	6 h	6 h	8 h	8 h	8 h	8 h
Assay	LC-MS/MS				AlphaLISA			
$A\beta_{1\text{-}38}$	−3 *(29)*	−48 *(21)*	−36 *(29)*	−55 *(19)*	14 *(−2)*	21 *(−2)*	22 *(−2)*	52 *(−2)*
$A\beta_{1\text{-}40}$	nd	Nd	nd	nd	−7 *(3)*	−21 *(3)*	−12 *(3)*	−27 *(3)*
$A\beta_{1\text{-}42}$	nd	Nd	nd	nd	−12 *(10)*	−41 *(10)*	−13 *(10)*	−28 *(10)*

Nd = no data due to technical problems.

Supplementary Table 3
Details of pathways analysis (using Ingenuity Pathway knowledge database): most enriched pathways ($p < 0.001$ using MLP gene set enrichment algorithm [32]) comparing GSI-treated to vehicle group. Number of genes tested per pathway and p-value per group and pathway are listed

Pathway	*N* genes	BMS-708163	LY-450139	
		0.63	1.25	5
Positive acute phase response proteins	28	1.17E-09		3.78E-12
Antigen presentation	27	8.59E-10		
Hepatic fibrosis	81	4.25E-09		
Interferon signaling	28	1.56E-08		
Cell cycle control of chromosomal replication	27	2.99E-07		
T-helper cell differentiation	66	4.54E-07		
B-cell development	21	4.04E-05		
TREM1 signaling	52	5.19E-05		
Dendritic cell maturation	128	6.32E-05		
Hepatic stellate cell activation	34	8.87E-05		
Atherosclerosis signaling	70	0.0001		
Cholesterol biosynthesis	19		2.24E-07	1.49E-06
Pentose and glucuronate interconversions	128		3.38E-06	1.18E-05
Butanoate metabolism	308		0.00092	0.00026
FXR/RXR Activation	71		0.00028	0.00032
PXR/RXR Activation	49		8.81E-05	
Inositol metabolism	365			1.38E-05
Aminophosphonate metabolism	127			0.00012
Extrinsic prothrombin activation pathway	17			0.00021
Lysine degradation	212			0.00022
Arginine and proline metabolism	128			0.00027
Coagulation system	33			0.00038
Ascorbate and aldarate metabolism	199			0.00040
LPS/IL-1 Mediated inhibition of RXR function	160			0.00088

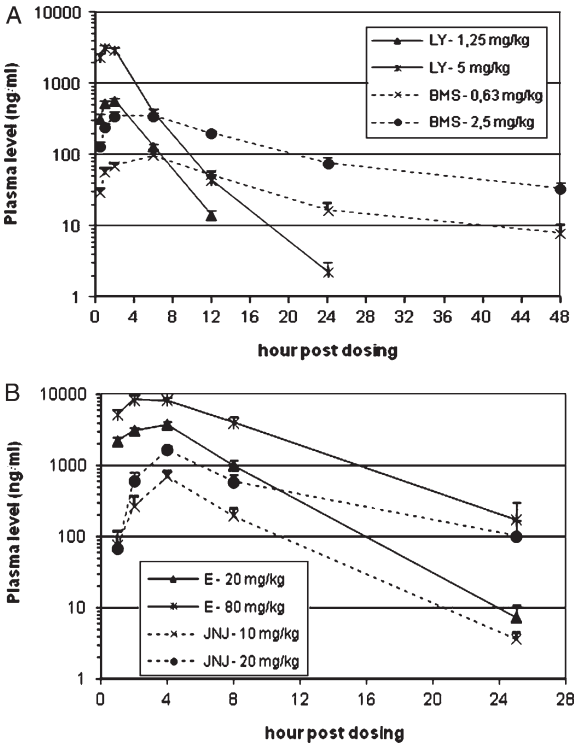
Note: no significant pathways ($p < 0.001$) in the 2.5 mg/kg BMS-708163 dose group.

Supplementary Table 4
Details of Pathways analysis (using Ingenuity Pathway knowledge database): most enriched pathways ($p < 0.001$ using MLP gene set enrichment algorithm [32]) comparing GSM-treated to vehicle group. Number of genes tested per pathway and p-value per group and pathway are listed

Pathway	N genes	E-2012		JNJ-42601572	
		20	80	10	20
Inositol metabolism	365	6.34E-16	2.31E-96		4.66E-09
Ubiquinone biosynthesis	210	1.57E-15	1.87E-20		0.00031
Tyrosine metabolism	265	3.59E-10	3.19E-28		1.57E-05
Glycine, serine and threonine metabolism	255	4.89E-08	3.55E-24		8.97E-06

Table 4
(*Continued*)

Pathway	N genes	E-2012		JNJ-42601572	
		20	80	10	20
Stilbene, coumarine and lignin biosynthesis	115	4.85E-07	5.97E-10		6.87E-06
Androgen and estrogen metabolism	135	7.49E-06	1.41E-07		0.00021
Bile acid biosynthesis	180	4.49E-05	1.14E-26		6.45E-07
Lysine degradation	212	4.56E-05	3.77E-14		0.00013
Biosynthesis of steroids	118	6.86E-05	6.73E-17		5.78E-07
Fatty acid metabolism	85	0.00012	2.53E-18		1.23E-10
Linoleic acid metabolism	138	0.00048	7.19E-08		1.89E-05
FXR/RXR Activation	71	0.00097	0.00076		4.26E-05
Ascorbate and aldarate metabolism	199	1.03E-12			7.88E-09
Tryptophan metabolism	236	1.16E-06			2.67E-05
Valine, leucine and isoleucine degradation	114		4.71E-17		0.00056
Butanoate metabolism	308		1.97E-11		0.00045
Xenobiotic metabolism signaling	45		1.51E-05		6.04E-06
Phenylalanine metabolism	139	1.28E-08	6.11E-18		
Pyruvate metabolism	95	1.24E-07	7.03E-09		
Histidine metabolism	204	4.45E-07	6.00E-20		
Aminophosphonate metabolism	127	3.82E-06	6.07E-11		
Folate biosynthesis	186	8.80E-05	2.94E-07		
Propanoate metabolism	81	0.00013	4.37E-16		
Oxidative phosphorylation	100	0.00017	3.90E-05		
LPS/IL-1 Mediated inhibition of RXR function	160	0.00049	2.87E-10		
Selenoamino acid metabolism	77	0.00063	4.24E-05		
Starch and sucrose metabolism	241	0.00065	3.13E-05		
Nucleotide sugars metabolism	156	0.00045			
Methane metabolism	111	0.00062			
Arginine and proline metabolism	128		1.03E-15		
Protein ubiquitination pathway	146		3.52E-08		
β-alanine metabolism	50		1.34E-07		
Folate biosynthesis	186		2.94E-07		
Purine metabolism	370		1.69E-06		
Galactose metabolism	132		1.58E-05		
Nitrogen metabolism	121		4.00E-05		
Selenoamino acid metabolism	77		4.24E-05		
Lysine biosynthesis	71		0.00010		
Antigen presenting pathway	27		0.00057		
Pentose and glucuronate interconversions	128		0.00062		
CYP450 panel – substrate is a xenobiotic	11			3.08E-05	1.57E-09
PXR/RXR activation	49				1.17E-06
Hepatic cholestasis	123				9.57E-05
NRF2-mediated oxidative stress response	152				0.00016



Supplementary Figure 1. Plasma profiles of LY-450139 and BMS-708163 (A) and E-2012 and JNJ-42601572 (B) (mean + SEM; $n = 6$).