Table 1S. Differences in GC levels between normal (control) lymphoblasts and N370S/N370S lymphoblasts treated for 10 or 15 days with ABX, IFG or DMSO (Mock) using ABX as the reference category[1].

GC Species	**Control (WT)**	**ABX vs. control**	**p**	**ABX vs. IFG**	**p**	**ABX vs. Mock**	**p**
	pmol/mg protein	**EST (95% CI)[2]**		**EST (95% CI)**		**EST (95% CI)**	
GC 16[3]	359 ± 17[4]	+324 (+305, +342)	<0.001	-252 (-215, -290)	<0.001	-404 (-362, -447)	<0.001
GC 18	45.5 ± 2	+65 (+58, +71)	<0.001	-48 (-33, -64)	<0.001	-26 (-13, -41)	<0.001
GC 20	59.2 ±3	+31 (+24, +37)	<0.001	-43 (-33, -54)	<0.001	-24 (-12, -37)	<0.001
GC 22	131 ± 5	+60 (+47, +71)	<0.001	-51 (-33, -70)	<0.001	-30 (-13, -48)	<0.001
GC 24	93.5 ± 4	+80 (+70, +89)	<0.001	-40 (-23, -58)	<0.001	-14 (-30, +2)	0.08
GC 24:1[5]	185 ± 6	-22 (-7, -39)	0.003	-39 (-22, -56)	0.001	-28 (-12, -45)	<0.001
GC total	873 ± 32	+539 (+508, +568)	<0.001	-625 (-569, -682)	<0.001	-374 (-324, -508)	<0.001

1. A separate model was created using the mock group as a reference to determine whether there were any differences between the mock- and IFG-group (data not shown). Significant increases were found in all but the GC 24:1 species in the IFG- versus Mock-group.
2. A linear regression model using maximum likelihood algorithm for parameter estimation was used to determine the significance of the differences between all the groups. The first value (EST) represents the average difference between groups, with the 95% confidence interval (95% CI). If all 3 values are positive or all 3 values are negative, the difference is statistically significant. For example, on average the major GC16 form is 324 pmol/mg protein higher in the ABX group than in the control, with a confidence interval of 305 to 342, which is statistically significant. Only the ABX vs. Mock difference for the GC 24 form is not significant.
3. Refers to the carbon chain length of the fatty acid moiety, which defines the individual forms of GC
4. Standard error
5. GC containing a 24-carbon fatty acid chain with 1 double bond

Table 2S. Deuteration levels of specific GCase segments in the presence of IFG, ABX and FNZ as a function of four exchange periods (30, 100, 300, 1,000 and 3,000 s).

numbering					isofagomine						fluphenazine						ambroxol					
-propeptide		+propeptide		Z	30	100	300	1000	3000	avg	30	100	300	1000	3000	avg	30	100	300	1000	3000	avg
34	**37**	73	76	1	4%	2%	3%	3%	6%	**4%**	0%	3%	-3%	-1%	7%	**1%**	5%	2%	-1%	6%	-1%	**2%**
39	**51**	78	90	2	2%	-1%	0%	1%	0%	**0%**	1%	-1%	1%	0%	0%	**0%**	2%	-3%	-1%	5%	-1%	**1%**
69	**91**	108	130	2	-1%	-3%	-1%	0%	-5%	**-2%**	-4%	-1%	0%	-1%	-2%	**-2%**	-1%	-3%	0%	1%	-5%	**-2%**
97	**103**	136	142	1	-3%	-3%	-3%	0%	-1%	**-2%**	-4%	-3%	-4%	-6%	0%	**-3%**	-5%	-1%	-4%	-2%	-2%	**-3%**
108	**117**	147	156	2	-7%	1%	-1%	4%	8%	**1%**	-3%	1%	-1%	8%	6%	**2%**	-6%	-3%	-5%	8%	3%	**-1%**
119	**127**	158	166	1	-10%	-8%	-13%	-9%	-22%	**-12%**	-1%	-2%	0%	-5%	-8%	**-3%**	2%	0%	-3%	-2%	-9%	**-2%**
130	**134**	169	173	1	-6%	-16%	-4%	2%	-2%	**-5%**	-7%	-14%	-2%	4%	5%	**-3%**	-2%	-9%	-5%	1%	-6%	**-4%**
135	**142**	174	181	1	-4%	-6%	-6%	-1%	-3%	**-4%**	-4%	-11%	-5%	-8%	-6%	**-7%**	-1%	-7%	-4%	5%	-7%	**-3%**
156	**167**	195	206	2	1%	-2%	-2%	3%	-3%	**0%**	3%	0%	-2%	1%	-3%	**0%**	-1%	-1%	-1%	3%	-1%	**0%**
170	**174**	209	213	1	4%	-3%	1%	3%	-3%	**1%**	-1%	-4%	0%	1%	-2%	**-2%**	3%	-3%	4%	1%	-12%	**-2%**
177	**185**	216	224	1	1%	-7%	-11%	-12%	-18%	**-9%**	0%	-4%	-7%	-6%	-5%	**-4%**	-1%	-6%	-7%	-3%	-8%	**-5%**
187	**197**	226	236	1	-18%	-18%	-9%	-6%	-9%	**-12%**	-11%	-11%	-3%	-4%	-2%	**-6%**	-15%	-12%	-8%	-1%	-8%	**-9%**
200	**212**	239	251	2	1%	-1%	-3%	-3%	-6%	**-2%**	3%	1%	-3%	-1%	-4%	**-1%**	4%	-2%	-3%	2%	-1%	**0%**
215	**219**	254	258	1	0%	0%	0%	-1%	0%	**0%**	0%	0%	0%	-1%	0%	**0%**	-1%	0%	-1%	-1%	-1%	**-1%**
222	**227**	261	266	1	0%	-4%	1%	1%	-1%	**-1%**	-3%	-4%	1%	-3%	-1%	**-2%**	0%	-1%	-2%	3%	-2%	**-1%**
230	**240**	269	279	1	-4%	-8%	-13%	-14%	-14%	**-10%**	-4%	-8%	-11%	-16%	-17%	**-11%**	-3%	-6%	-12%	-10%	-8%	**-8%**
243	**249**	282	288	1	-15%	-31%	-45%	-48%	-51%	**-38%**	-21%	-35%	-37%	-25%	-9%	**-26%**	-17%	-29%	-35%	-11%	-6%	**-19%**
252	**259**	291	298	2	-1%	-6%	-6%	-3%	-1%	**-4%**	-1%	-7%	-8%	-5%	-4%	**-5%**	-1%	0%	-1%	2%	-3%	**-1%**
281	**283**	320	322	1	-3%	-3%	-3%	3%	-4%	**-2%**	0%	-6%	5%	3%	1%	**1%**	4%	0%	6%	3%	2%	**3%**
284	**296**	323	335	2	-2%	-5%	-6%	-11%	-10%	**-7%**	-6%	-6%	-7%	-13%	-13%	**-9%**	-4%	-4%	-5%	-10%	-6%	**-6%**
299	**307**	338	346	1	-2%	-5%	-4%	3%	-6%	**-3%**	-1%	-3%	-5%	-2%	-4%	**-3%**	1%	-5%	2%	1%	-2%	**-1%**
310	**312**	349	351	1	1%	-2%	-11%	-19%	-28%	**-12%**	4%	-5%	-10%	-14%	-20%	**-9%**	0%	-6%	-11%	-18%	-19%	**-11%**
315	**336**	354	375	2	-8%	-15%	-3%	3%	-4%	**-6%**	-13%	-20%	-7%	2%	-3%	**-8%**	-2%	-8%	-1%	5%	-3%	**-2%**
343	**347**	382	386	1	1%	-6%	-6%	-11%	-22%	**-9%**	5%	-2%	-4%	-7%	-7%	**-3%**						
350	**362**	389	401	2	-7%	-9%	-7%	-7%	-10%	**-8%**	-4%	-7%	-5%	-3%	-1%	**-4%**	2%	-7%	-4%	4%	-5%	**-2%**
365	**371**	404	410	1	0%	-2%	-2%	0%	0%	**-1%**	0%	-1%	0%	-2%	0%	**-1%**	1%	-1%	-2%	0%	-1%	**-1%**
374	**383**	413	422	1	0%	-2%	-2%	-2%	-9%	**-3%**	-1%	-4%	-1%	-2%	-5%	**-3%**	-1%	-1%	-3%	-1%	-5%	**-2%**
386	**400**	425	439	2	-20%	-31%	-34%	-39%	-49%	**-34%**	2%	-9%	-7%	-9%	-6%	**-6%**	-5%	-14%	-14%	-11%	-13%	**-11%**
399	**405**	438	444	1	-1%	-4%	-2%	-1%	-2%	**-2%**	0%	-4%	-1%	-2%	-2%	**-2%**	-1%	-2%	-2%	0%	-1%	**-1%**
408	**411**	447	450	1	0%	-1%	0%	3%	0%	**0%**	1%	1%	3%	-1%	1%	**1%**	7%	1%	5%	7%	8%	**6%**
414	**417**	453	456	1	-5%	-14%	-20%	-28%	-31%	**-19%**	-2%	-10%	-5%	-3%	-1%	**-4%**	3%	0%	-4%	4%	8%	**2%**
420	**426**	459	465	1	1%	-6%	3%	5%	0%	**1%**	-2%	-4%	1%	2%	1%	**-1%**	3%	-2%	-3%	4%	0%	**0%**
429	**436**	468	475	2	4%	-2%	1%	1%	0%	**1%**	0%	0%	-1%	1%	1%	**0%**	2%	-1%	1%	2%	-4%	**0%**
435	**446**	474	485	2	2%	-3%	-1%	3%	1%	**1%**	0%	-3%	0%	0%	1%	**-1%**	1%	-5%	-2%	7%	-1%	**0%**
449	**457**	488	496	1	-3%	-3%	-1%	1%	0%	**-1%**	-3%	-4%	1%	-1%	1%	**-1%**	-1%	0%	0%	4%	0%	**0%**
459	**461**	498	500	1	2%	2%	0%	-1%	1%	**1%**	-1%	4%	2%	-1%	2%	**1%**	-4%	3%	-1%	-5%	-2%	**-2%**
464	**480**	503	519	2	1%	-2%	-1%	-1%	1%	**0%**	1%	-2%	-1%	-1%	3%	**0%**	0%	-3%	0%	1%	1%	**0%**
482	**493**	521	532	2	-2%	-6%	-2%	-2%	0%	**-2%**	0%	-2%	0%	-3%	-5%	**-2%**	-1%	0%	-2%	0%	-9%	**-2%**

Negative perturbations ≤ -9% are highlighted in blue.

Figure 1S

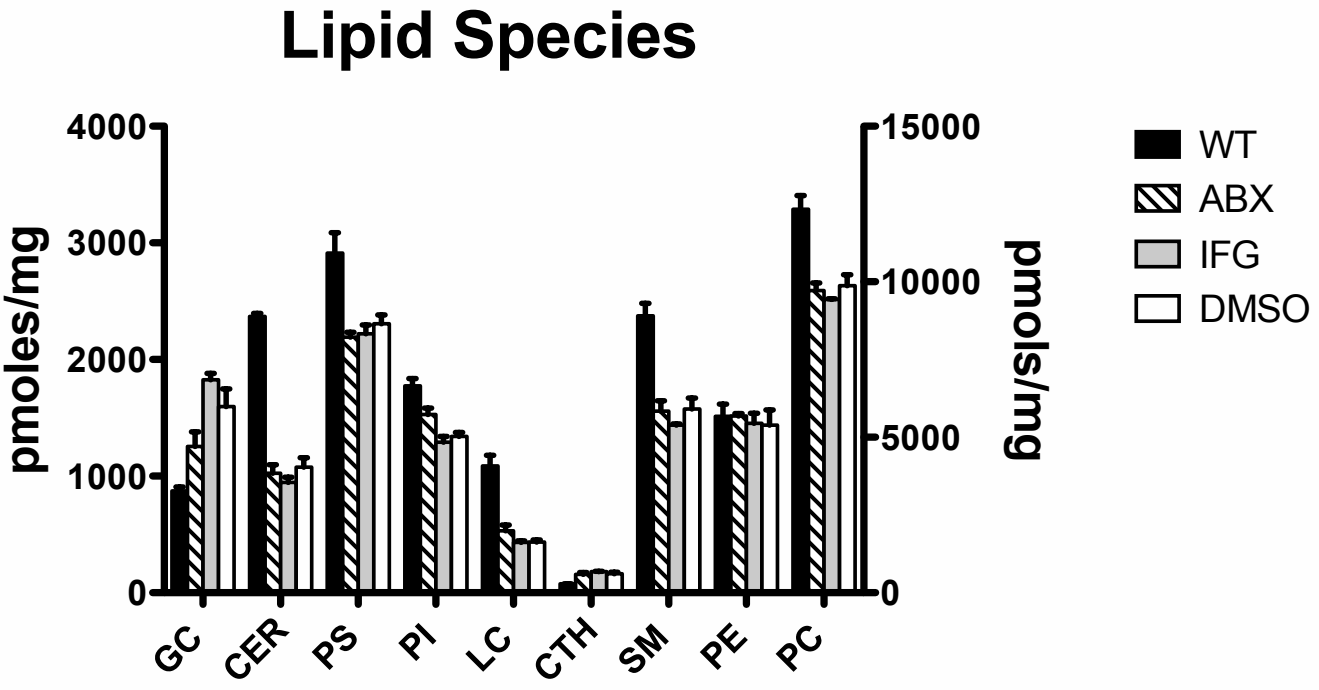
A) Histogram showing the total amounts (pmol/mg total protein) of different lipid species found in extracts from Wild Type (WT) (black bars), and ABX- (hatched), IFG- (grey) or Mock, DMSO- (white) treated N370S/N370S patient lymphoblasts grown for 10 days in culture. The total amount of each lipid is derived by summing the amounts of each of the lipid's isoforms, which were determined by triplicate assays (see accompanying figure showing levels of all isoforms that could be detected and quantified for each lipid). Standard error (n=3) is shown. The higher levels of lipids SM, PE and PC are shown on the right Y-axis, levels of other lipids are displayed on the left Y-axis. The abbreviations of individual lipid species used in this and accompanying supplementary figures are as follows: Glucosylceramide (GC), Ceramide (CER), Phosphatidylserine (PS), PhosphatidylInositol (PI), Lactosylceramide (LC), Ceramide TriHexoside (CTH), Sphingomyelin (SM), Phaphatidylcholine (PC) and PhosphatidylEthanolamine (PE).
B) Histogram showing amount (pmol/mg) of different GC isoforms from extracts of Wild Type (WT) (black bars), and ABX (hatched), IFG (grey) or DMSO (white) treated N370S/N370S patient lymphoblasts grown in the presence of the drug for 10 days. The amount of each isoform represents the average of three independent analyses. The total amount of GC is derived by summing the amounts of the different GC isoforms for the triplicate determinations. Standard error (n=3) is shown. The higher levels of lipids GC C16 and GC (total level) are shown on the right Y-axis, levels of the other GC isoforms are displayed on the left Y-axis.

Figure 2S.

Scatterplots showing the levels (n=3) of each of the Lipid's isoforms that could be identified and measured in extracts from Wild Type (Control_1, black bars), and ABX (ABX_1,hatched), IFG(IFG_1, grey) or DMSO (Mock_1, white) treated N370S/N370S patient fibroblasts, grown in culture for 10 days. Horizontal line denotes the average amount. The size of the lipid alkyl chains are prefixed with the abbreviation for chain(C) followed by the number of carbon atoms. The presence of double bonds in the alkyl chain is denoted by the number prefixed with a backslash.

Fig. 1.Suppl.

A.



B.

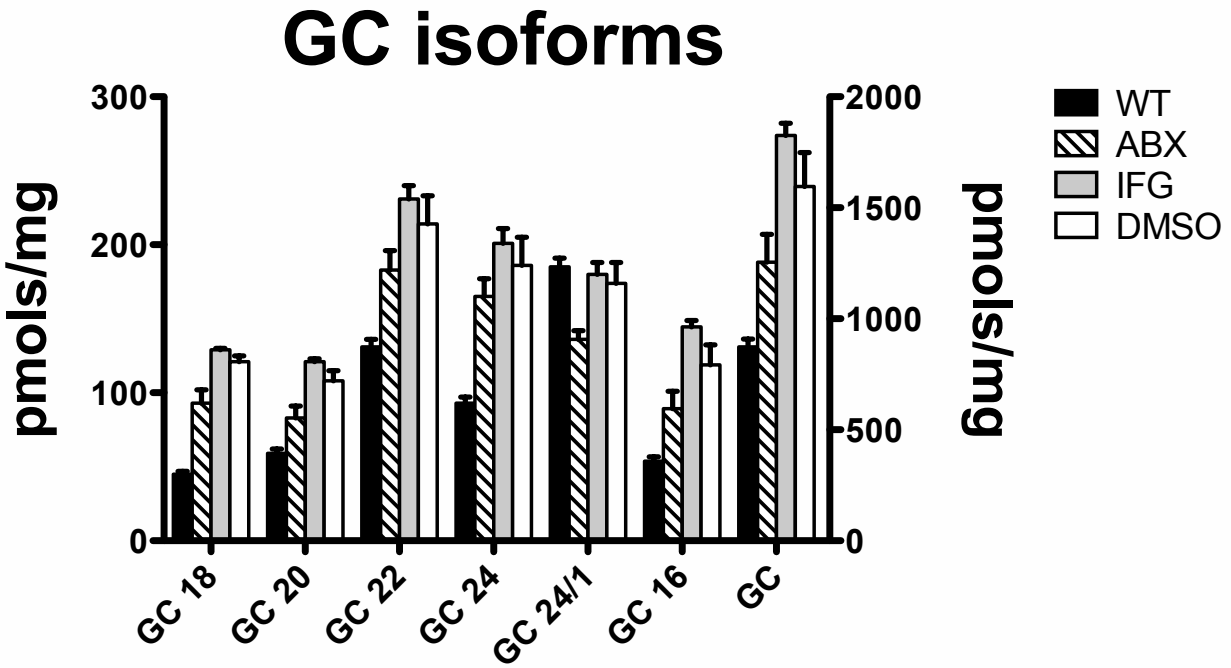
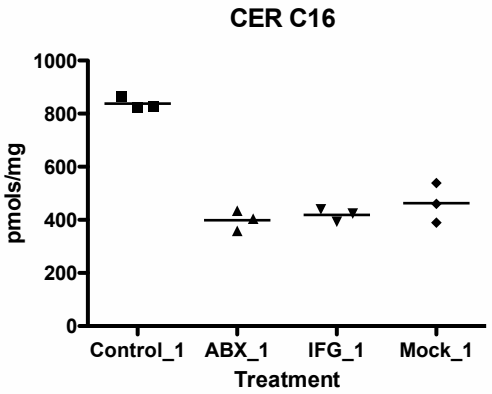
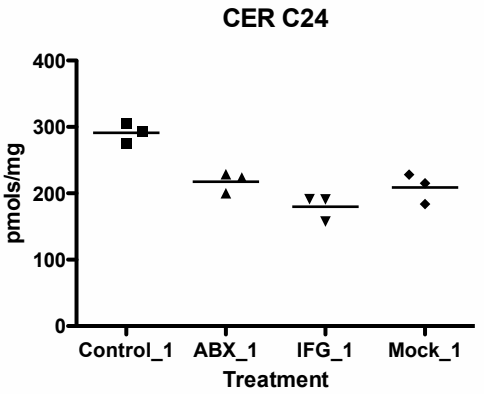
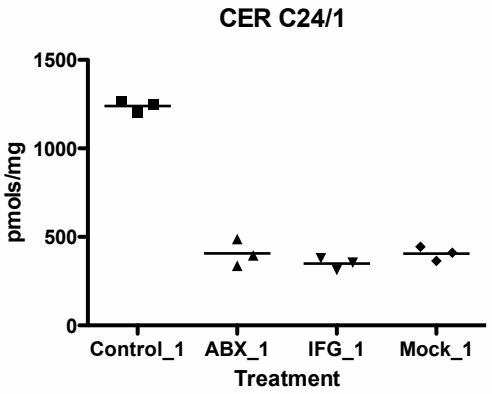
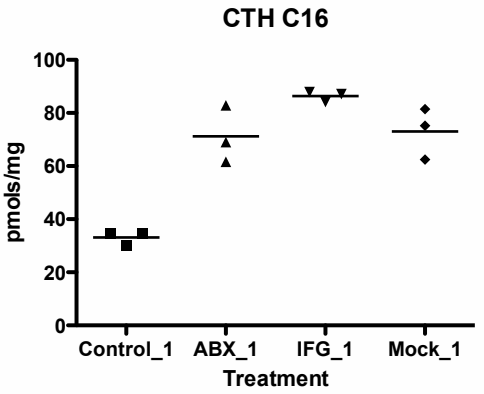


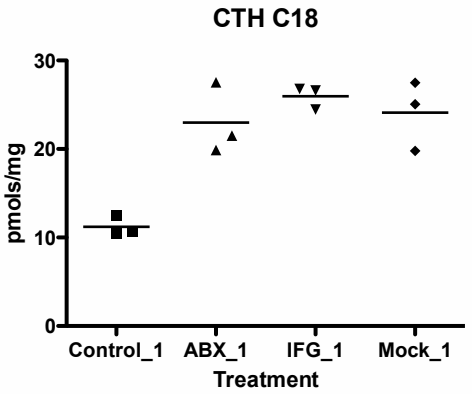
Fig. 2.Suppl. Page 1/7

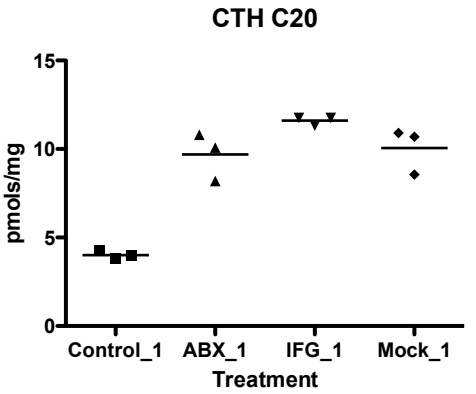


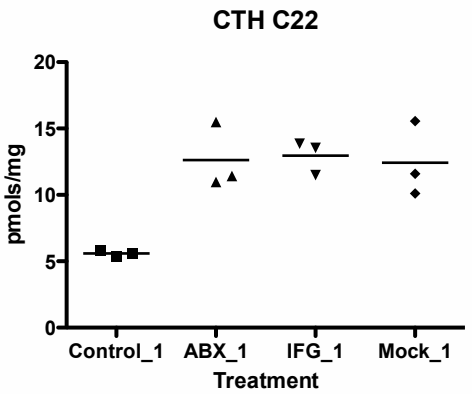












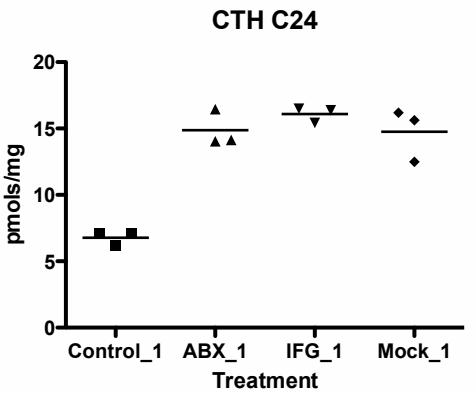
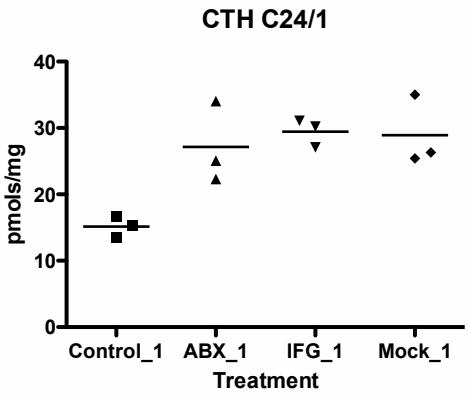
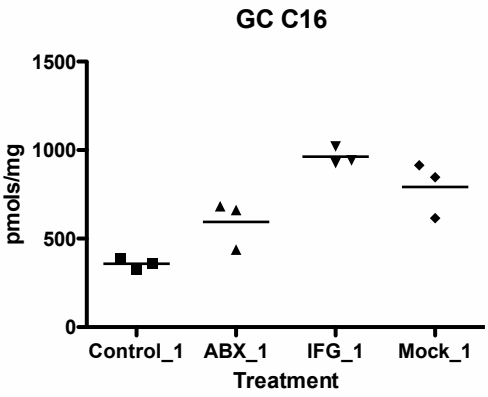
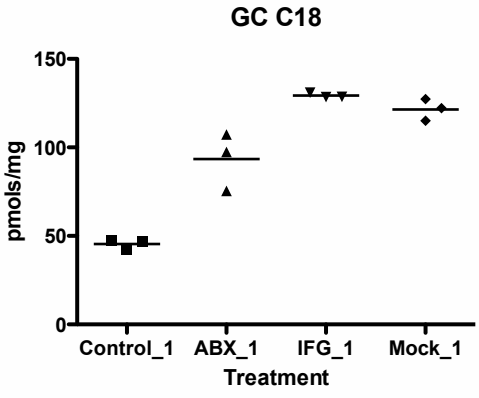
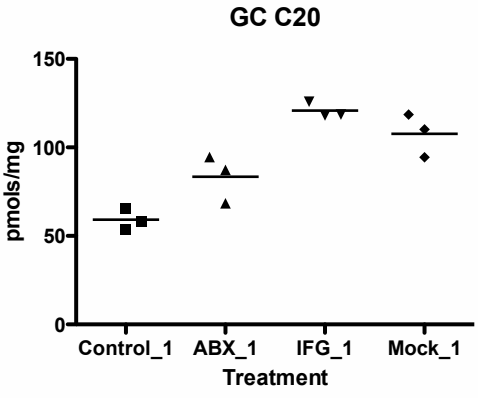


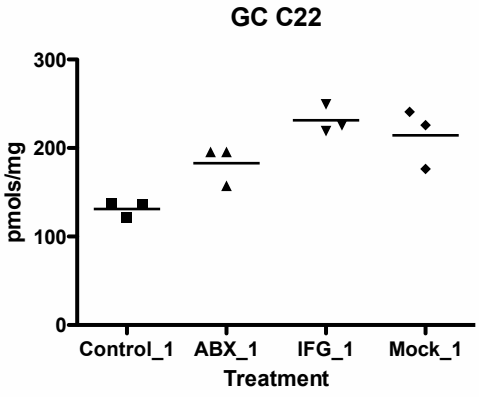
Fig. 2.Suppl. Page 2/7

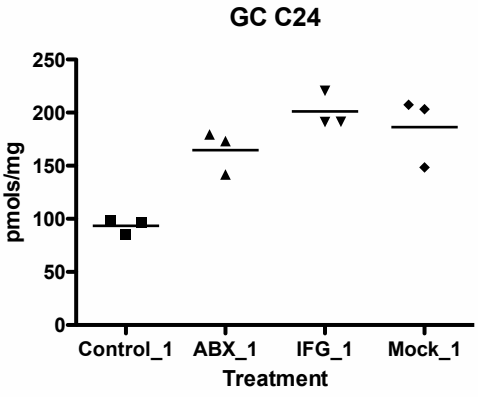


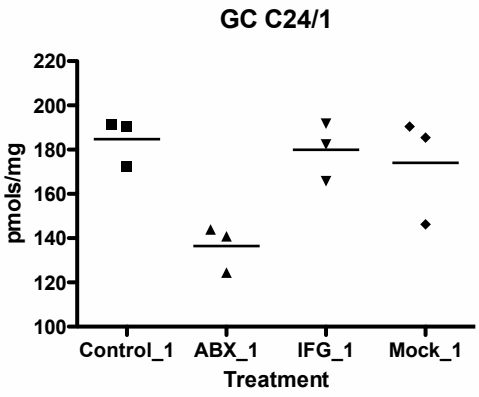


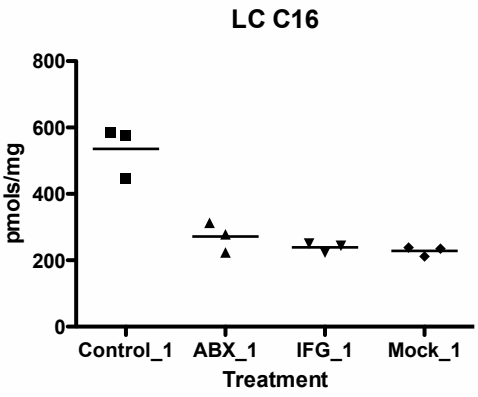


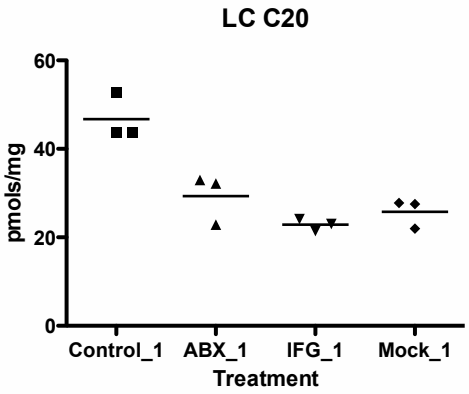


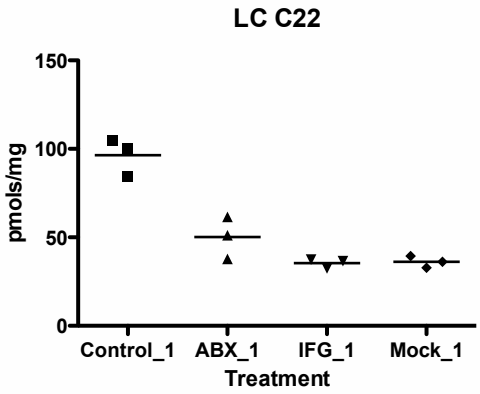









LC C20
pmols/mg
60
40
20
0
Control_1
ABX_1
IFG_1
Mock_1
Treatment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100
50
0
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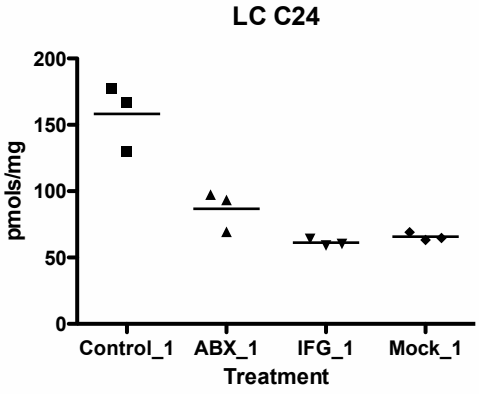
ABX_1
IFG_1
Mock_1
Treatment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pmols/mg
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150
100
50
0
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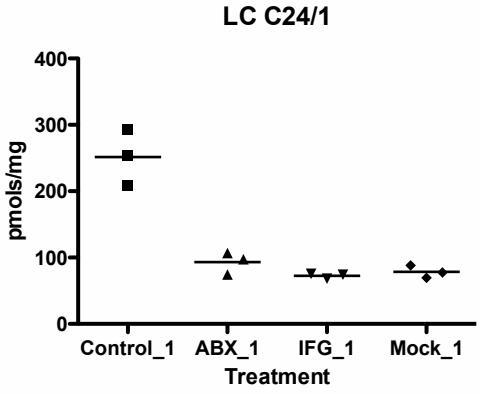
ABX_1
IFG_1
Mock_1
Treatment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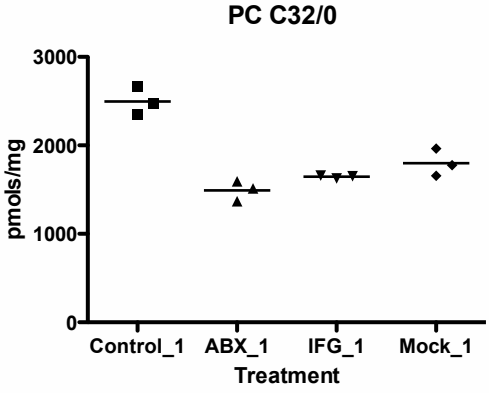
pmols/mg
400
300
200
100
0
Control_1
ABX_1
IFG_1
Mock_1
Treatment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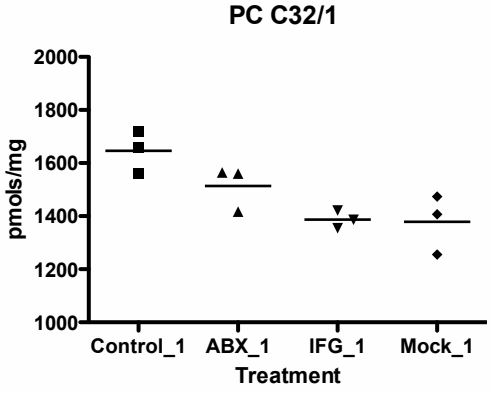
pmols/mg
3000
2000
1000
0
Control_1
ABX_1
IFG_1
Mock_1
Treatment


PC C32/1
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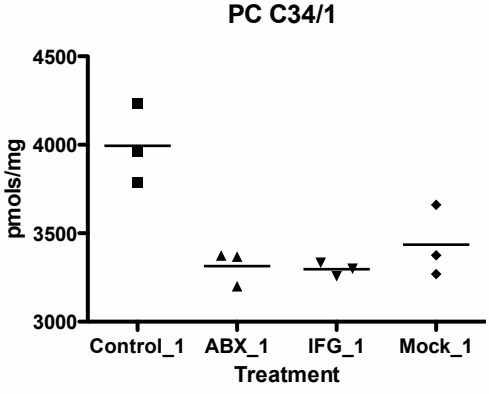
2000
1800
1600
1400
1200
1000
Control_1
ABX_1
IFG_1
Mock_1
Treatment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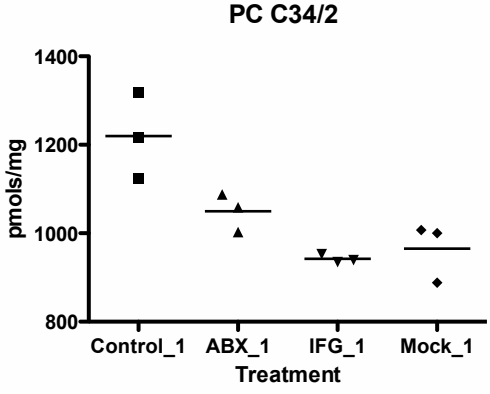
pmols/mg
4500
4000
3500
3000
Control_1
ABX_1
IFG_1
Mock_1
Treatment


PC C34/2
pmols/mg
1400
1200
1000
800
Control_1
ABX_1
IFG_1
Mock_1
Treatment

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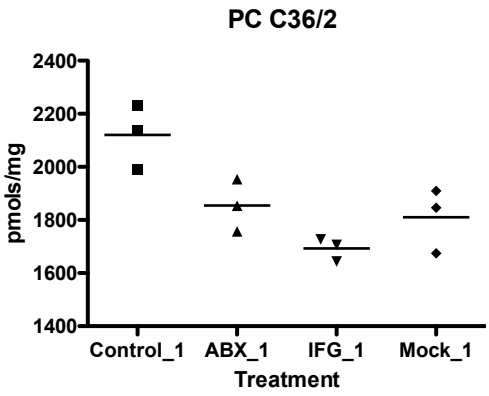

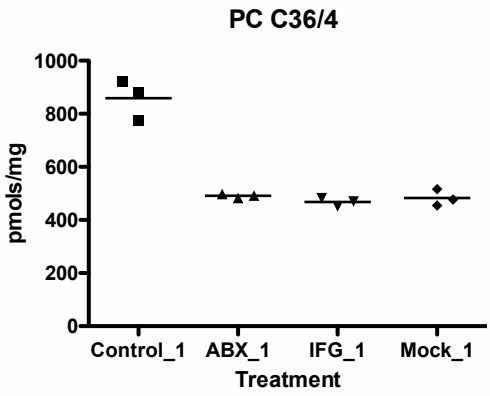

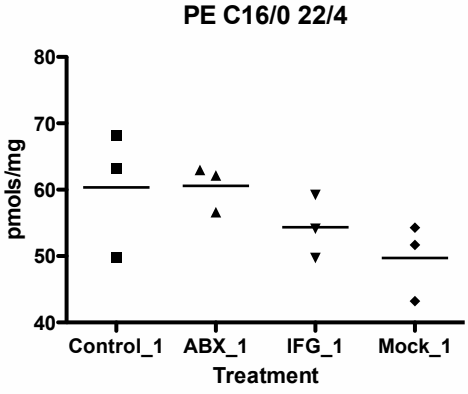

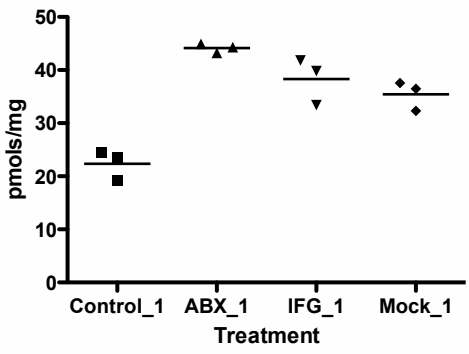

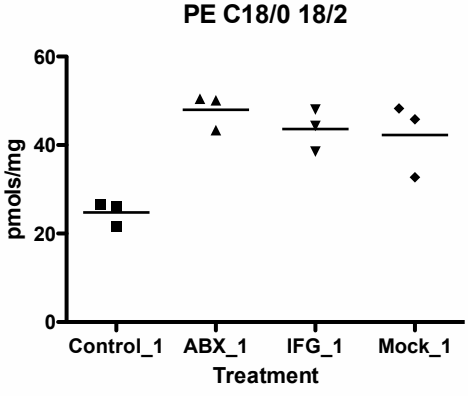

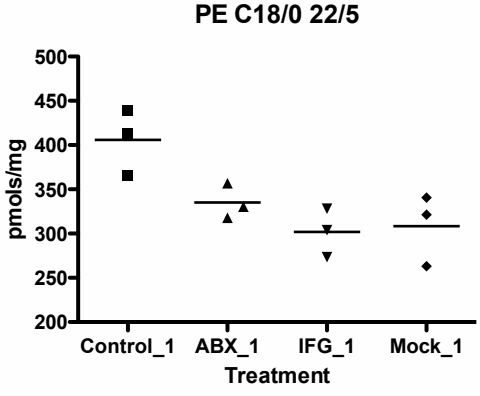

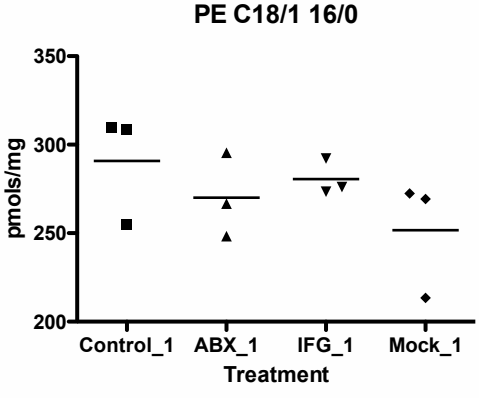

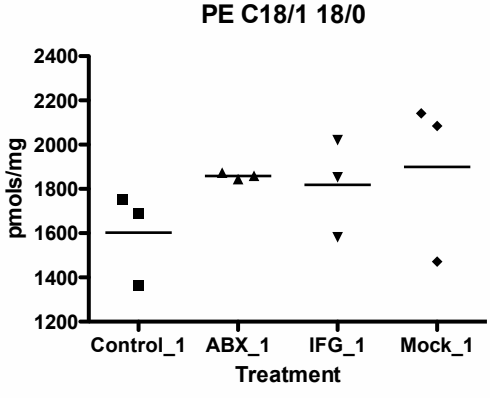

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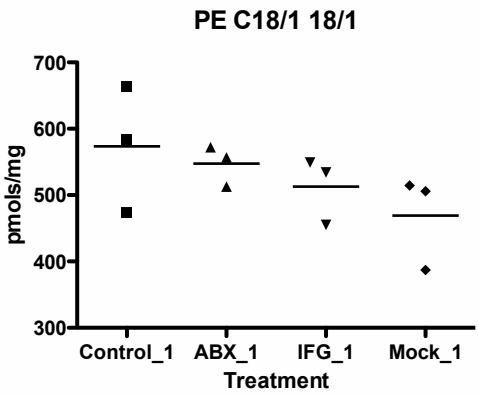

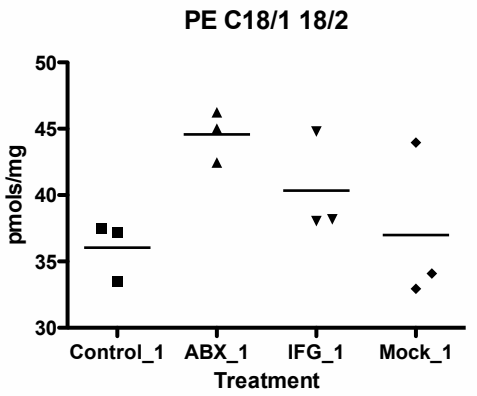

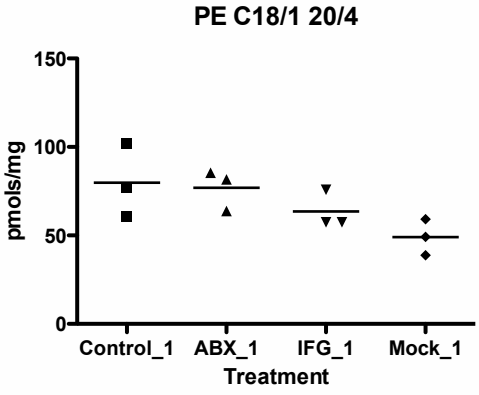

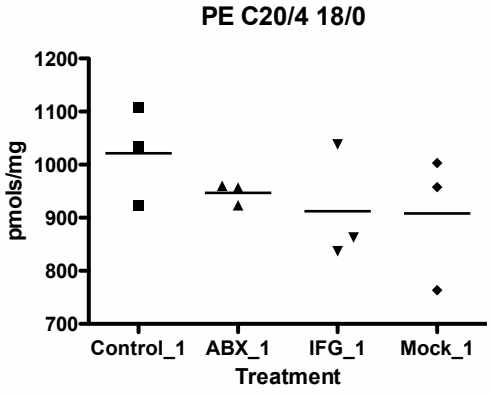

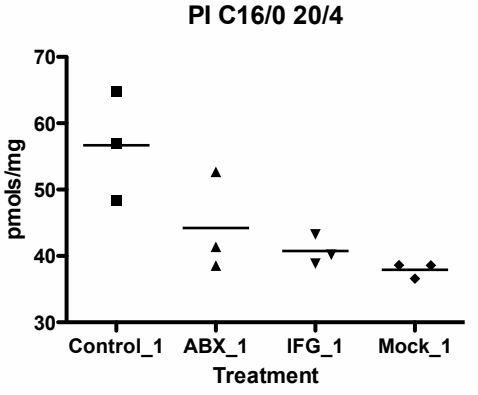

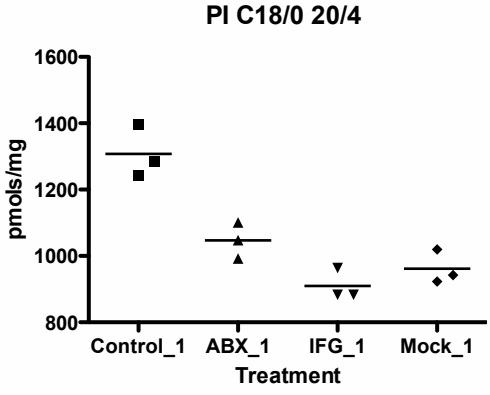

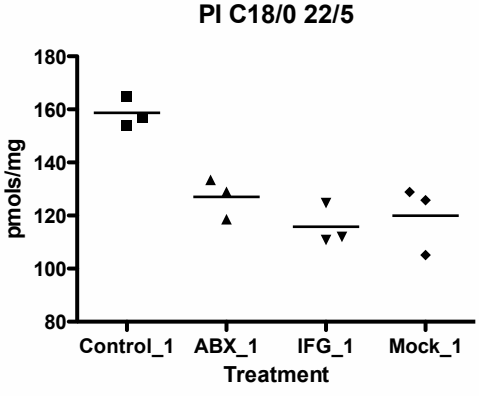

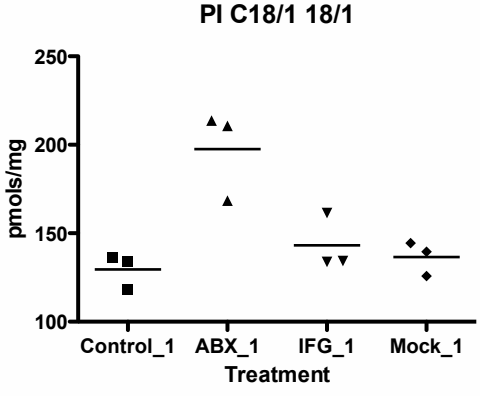

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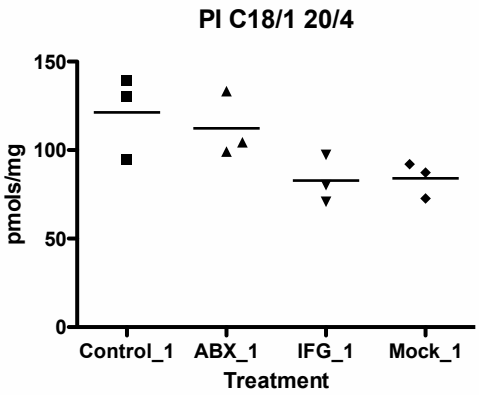

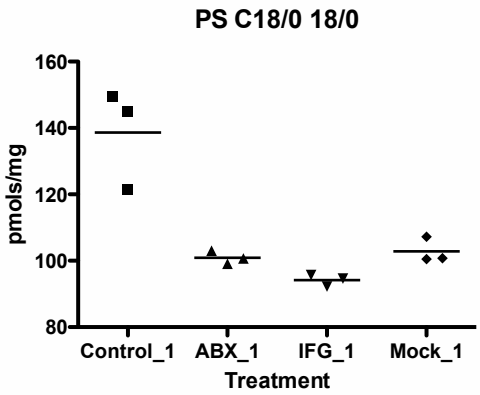

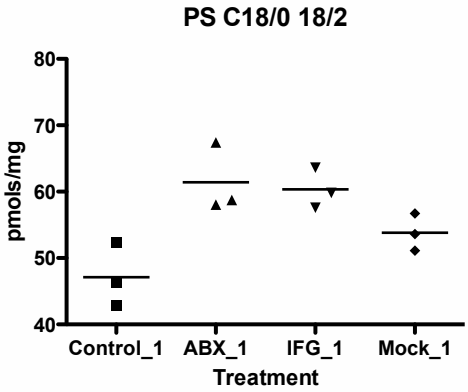

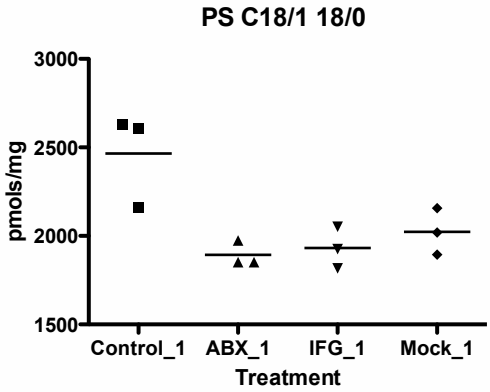

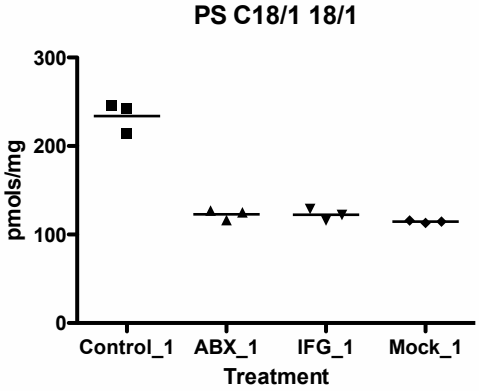

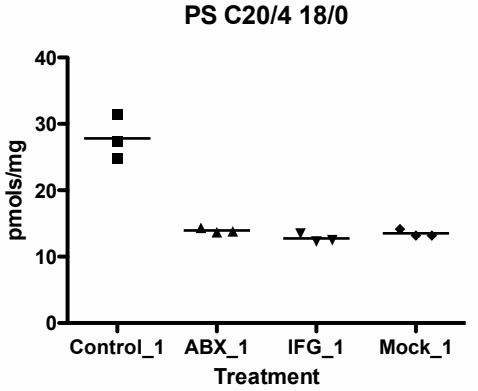

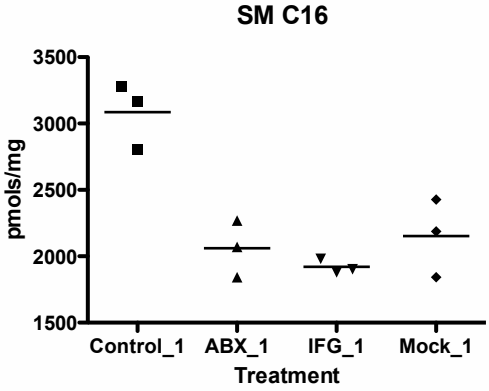

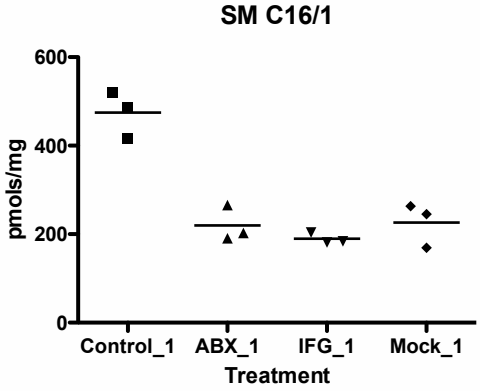

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