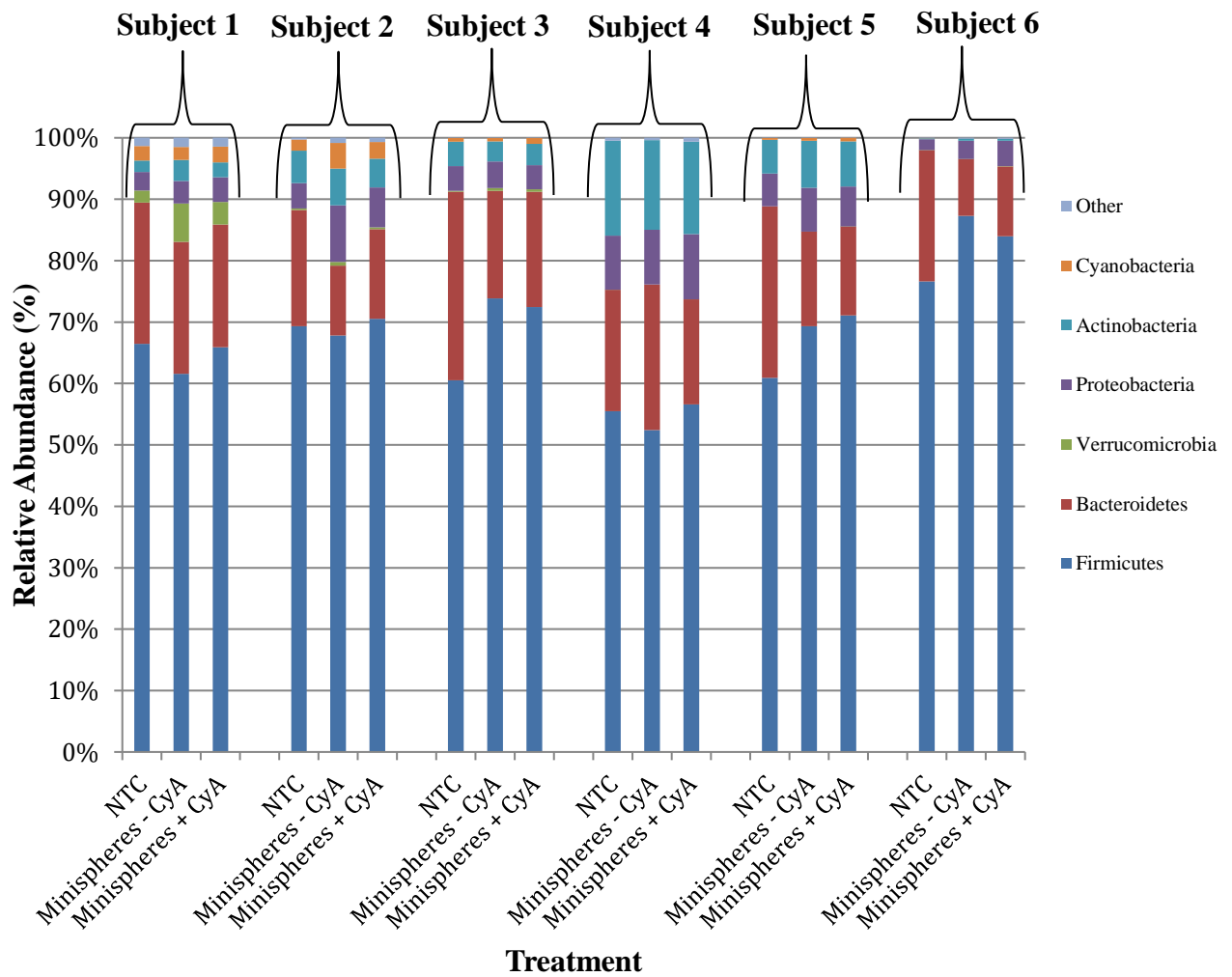
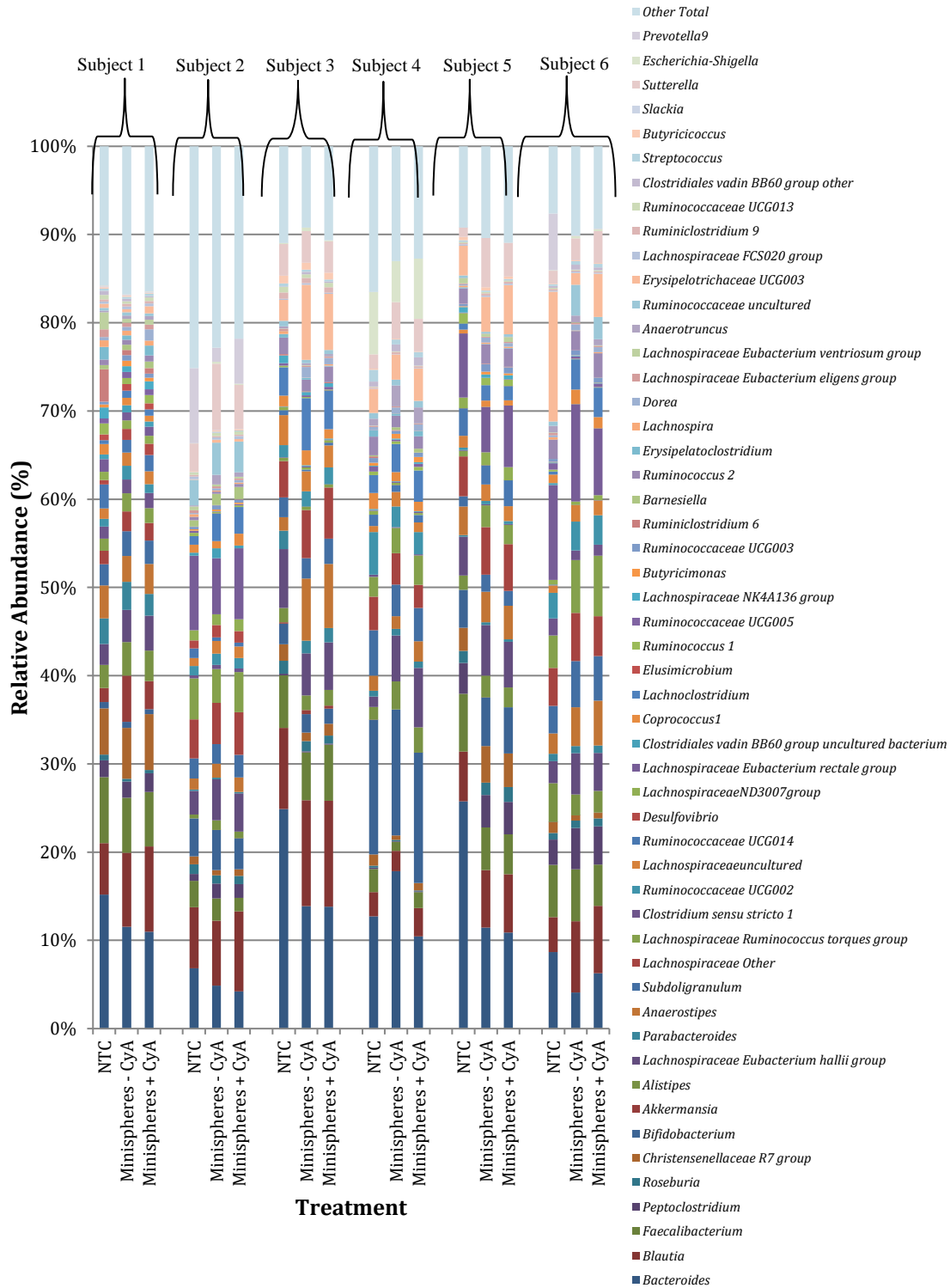


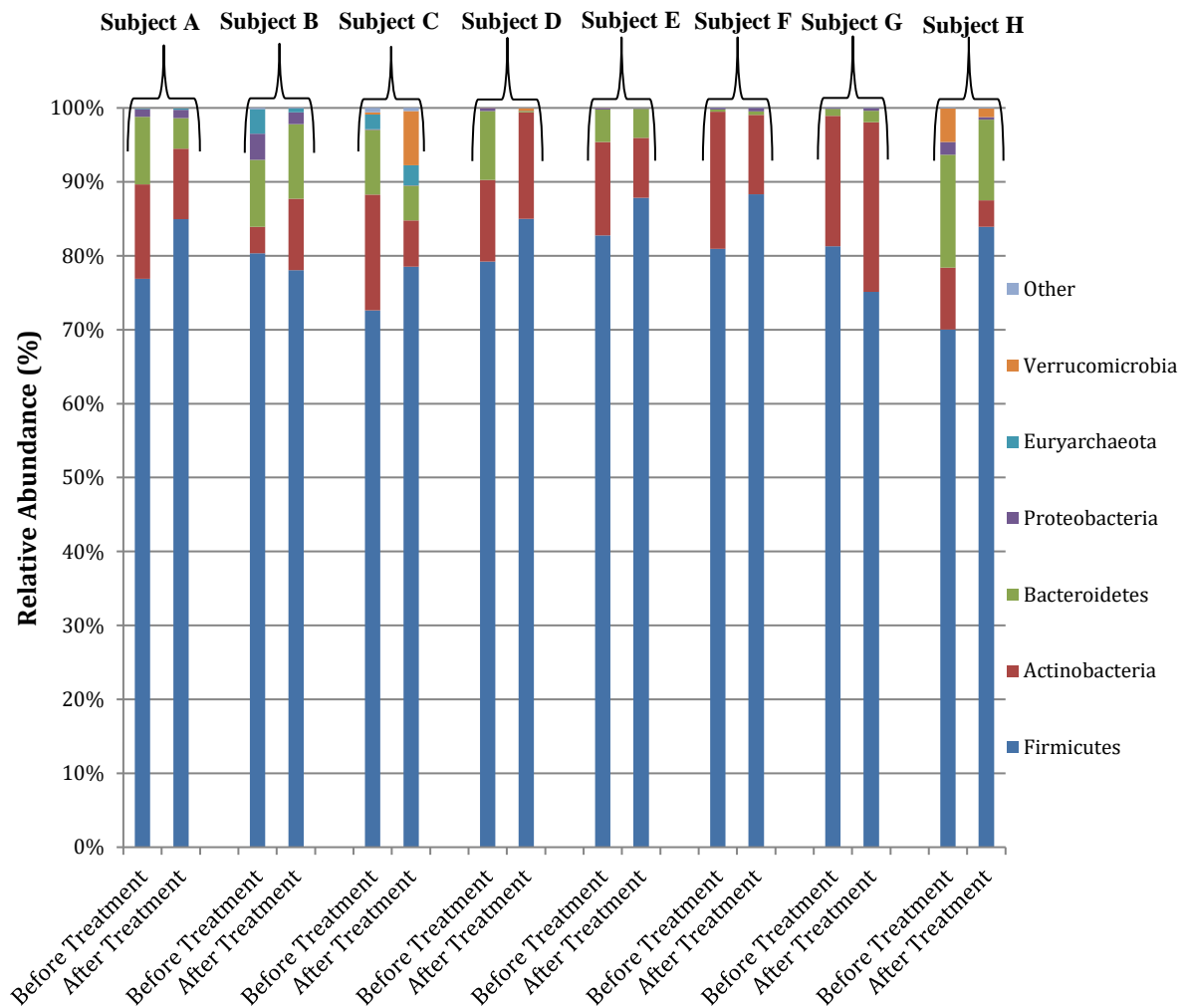
Supplementary Figure S1. PCoA plots based on unweighted UniFrac distance matrices. Each large circle represents an individual fecal donor. **(A)** samples presented by subject. Each sphere colour within the large circle represents an individual fecal donor sample at 0 and 24 h. **(B)** samples by treatment. Each large circle represents a subject and each sphere colour represents a treatment: orange: no treatment; blue: treated with minispheres with Cyclosporine A (CyA); green: treated with minispheres without CyA. **(C)** samples by time-point: red spheres, 0 hour; blue spheres, 24 hours.



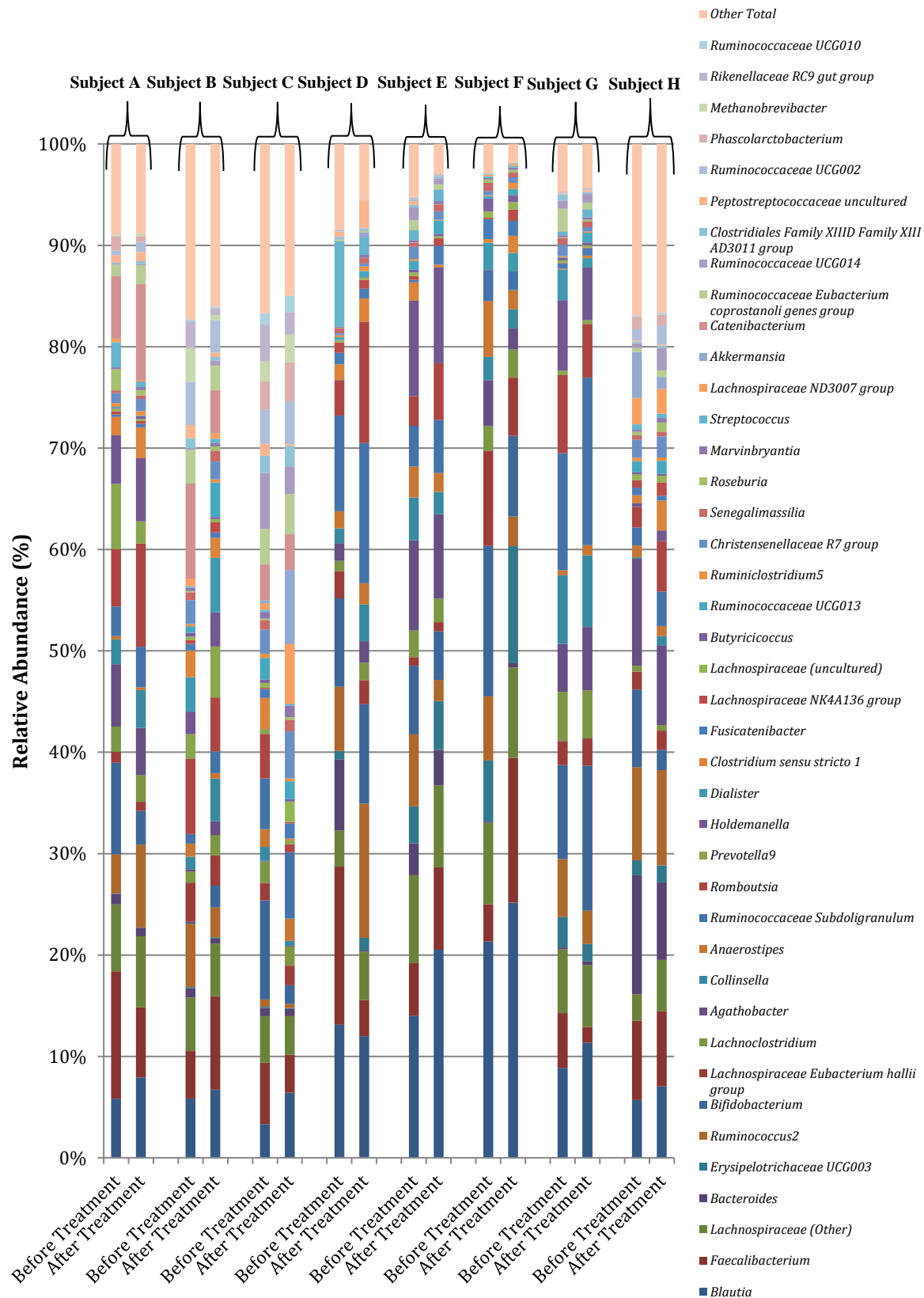
Supplementary Figure S2. Relative abundance (%) of the phyla across treatment groups in fecal samples from six subjects (1-6) following 24 hour fermentation in an *ex vivo* model. Groups: non-treatment control (NTC); Minispheres without (-) Cyclosporine A (CyA), Minispheres with (+) CyA.



Supplementary Figure S3. Relative abundance (%) of the bacterial genera identified in fecal samples in treatment groups from six individual subjects (Subjects 1-6) following 24h fermentation. Groups: non-treatment control; Minispheres without (-) Cyclosporine A (CyA); Minispheres with (+) CyA



Supplementary Figure S4. Relative abundance (%) of the bacterial phyla identified in fecal samples from human subjects (n=8) participating in the pilot study with SmPill® + CyA, before (Day 0) and after (Day 7) treatment.



Supplementary Figure S5. Relative abundance (%) of the bacterial genera identified in human fecal samples from eight subjects (A-H), before and after treatment with SmPill® + Cyclosporine A (CyA)

Supplementary Table S1

Alpha Diversity Indices (mean) for 6 fecal ferment samples across three treatment groups following 24 hour fermentation in an *ex vivo* model.

Index	No Minispheres	Minispheres with CyA	Minispheres without CyA	p value
Chao1 richness estimate	449.1	436.4	430.9	0.56
Simpson's Diversity Index	0.96	0.96	0.96	0.23
Shannon Index	5.8	5.9	5.8	0.38
Number of observed species	420.7	412.3	398.5	0.51

Supplementary Table S2. Concentration of SCFAs (mM) in fecal samples following 24 h fermentation in an *ex vivo* model.

SCFAs (mM)	nButyrate			iButyrate			Propionate			Acetate		
	MS* - CyA	MS + CyA	No MS	MS - CyA	MS + CyA	No MS	MS - CyA	MS + CyA	No MS	MS - CyA	MS + CyA	No MS
Subject												
1	30.1	31.4	24.5	1.8	1.7	1.7	16	16	13.6	61.9	60	40.8
2	21.5	22.1	15.3	1.3	1.3	1.3	8.9	8.9	8.1	25.1	25.6	22.6
3	25	27.2	16.4	1.9	1.8	2	13.3	12.9	11.9	27.8	29.2	26.7
4	18.9	21.2	13.3	1.4	1.3	1.02	14.3	12.5	9.4	68.5	63.4	46.8
5	36.3	33.2	20.9	2.2	2.2	1.5	20.5	16.1	12.5	53	38	37.4
6	29.4	31.3	21	1.57	1.41	1.22	15.2	15.2	10.9	47.4	49.6	33
Mean	26.9	27.7	18.6	1.7	1.6	1.5	14.7	13.6	11.1	47.3	44.3	34.6
SD	6.4	5.1	4.2	0.3	0.4	0.4	3.8	2.8	2.0	17.7	15.9	9.0
P-Value	0.02			0.50			0.13			0.32		

*MS=Minispheres; CyA = Cyclosporine A; SD = Standard Deviation

Supplementary Table S3. Alpha diversity of gut microbiota in fecal samples from 8 subjects who participated in the pilot study before (Day 0) and after treatment (Day 7) with SmPill® + CyA.

Alpha diversity	Before treatment (Day 0)	After treatment (Day 7)	P-Value
Chao1 richness estimate	431.30	430.61	0.99
Simpson's Diversity Index	0.96	0.96	0.84
Shannon Index	5.57	5.56	0.96
Number of observed species	404.88	394.75	0.88

Supplementary Table S4. Concentration of SCFAs (mM) in fecal samples from healthy subjects before (Day 0) and after (Day 7) participating in the pilot study with SmPill® + Cyclosporine A (CyA).

SCFAs (mM)		nButyrate	iButyrate	Propionate	Acetate	IsoValerate	Hexanoate	Pentanoate
Subject	Treatment							
1	Before	2.5	0.89	4.8	13.0	0.71	0.06	1.17
	After	1.5	0.43	3.0	9.1	0.30	0.06	0.64
2	Before	4.3	0.82	4.9	10.9	0.62	0.18	0.81
	After	7.7	0.84	17.5	36.4	0.58	0.62	1.73
3	Before	5.5	0.31	11.7	23.3	0.28	0.31	0.89
	After	14.1	0.75	38.5	51.4	0.49	0.59	2.04
4	Before	3.2	0.30	2.8	11.2	0.24	0.00	0.42
	After	4.5	0.37	4.5	21.6	0.25	0.00	0.36
5	Before	4.2	0.42	4.0	17.4	0.28	0.00	0.51
	After	7.6	0.29	5.7	22.3	0.20	0.00	0.52
6	Before	2.5	0.41	5.5	13.0	0.26	0.00	0.48
	After	10.7	0.46	8.5	31.4	0.38	0.00	0.91
7	Before	6.2	0.44	9.1	22.1	0.28	0.00	0.60
	After	11.2	0.41	16.0	32.3	0.26	0.00	0.83
8	Before	0.0	0.00	0.0	0.0	0.00	0.00	0.00
	After	1.5	0.18	1.7	6.8	0.15	0.11	0.26
Mean	Before	3.6	0.45	5.35	13.87	0.33	0.07	0.61
	After	7.35	0.47	11.93	26.41	0.33	0.17	0.91
SD	Before	1.96	0.29	3.61	7.35	0.23	0.11	0.35
	After	4.63	0.22	12.19	14.67	0.15	0.27	0.65
P value		0.05	0.90	0.17	0.05	0.97	0.28	0.27

Supplementary Table S5. Effect of SmPill® + CyA on amino acids and other metabolites detected in fecal samples from healthy subjects (A-H) participating in a seven day pilot study.

Subject	A		B		C		D		E		F		G		H	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Compound (mM)																
Alanine	0.756	0.510	0.367	3.063	0.827	2.705	1.114	4.417	0.959	0.884	1.358	1.219	1.956	1.386	0.034	1.064
Glycine	0.370	0.258	0.146	1.314	0.411	1.288	0.615	1.899	0.566	0.344	0.764	0.727	0.753	0.671	0.010	0.647
Valine	0.345	0.247	0.143	1.019	0.276	0.992	0.512	1.440	0.429	0.311	0.711	0.540	0.594	0.370	0.017	0.478
Leucine	0.370	0.256	0.152	1.022	0.284	0.974	0.554	1.473	0.386	0.348	0.736	0.655	0.698	0.475	0.017	0.465
Isoleucine	0.232	0.162	0.100	0.727	0.202	0.690	0.353	1.021	0.269	0.190	0.534	0.285	0.433	0.271	0.009	0.310
Threonine	0.197	0.132	0.065	0.660	0.178	0.573	0.262	0.500	0.146	0.167	0.417	0.309	0.373	0.260	<LOD	0.150
Proline	0.211	0.161	0.084	0.093	0.132	0.385	0.212	0.913	0.135	0.045	0.326	0.158	0.251	0.123	0.007	0.263
Asparagine	0.013	0.020	0.012	0.025	0.016	0.028	0.011	0.102	0.008	0.009	0.013	0.019	0.012	0.011	0.001	0.013
Glutamine	0.327	0.262	0.257	1.040	0.288	0.934	0.417	1.476	0.565	0.390	0.471	0.545	0.818	0.510	<LOD	0.357
Serine	0.244	0.146	0.086	0.430	0.139	0.319	0.176	0.341	0.108	0.163	0.445	0.389	0.281	0.220	<LOD	0.120
Glutamic acid	1.040	0.655	0.415	2.557	0.779	2.249	1.821	4.253	1.682	1.207	1.569	1.543	1.793	1.290	0.018	1.462
Methionine	0.055	0.052	0.067	0.338	0.111	0.365	0.203	0.504	0.122	0.138	0.246	0.332	0.252	0.184	0.033	0.120
Phenylalanine	0.148	0.100	0.072	0.371	0.123	0.393	0.250	0.562	0.156	0.176	0.322	0.494	0.300	0.223	0.018	0.183
Ornithine	0.081	0.051	0.062	0.416	0.115	0.371	0.219	0.271	0.124	0.168	0.154	0.099	0.188	0.177	0.030	0.213
Lysine	0.393	0.237	0.161	1.445	0.313	1.159	0.624	1.845	0.530	0.405	0.900	0.951	0.986	0.766	0.019	0.563
Histidine	0.323	0.189	<LOD	0.462	<LOD	0.338	0.197	3.294	<LOD	<LOD	0.344	1.545	<LOD	0.407	<LOD	<LOD
Tyrosine	0.121	0.083	0.060	0.278	0.100	0.305	0.242	0.576	0.139	0.159	0.274	0.363	0.277	0.201	0.014	0.154
Tryptophan	0.058	0.054	0.052	0.098	0.059	0.104	0.078	0.143	0.061	0.073	0.083	0.091	0.097	0.090	<LOD	0.062
Aspartate	0.311	0.220	0.096	0.724	0.092	0.640	0.208	1.234	0.123	0.134	0.730	0.967	0.220	0.243	0.017	0.148
Succinic acid	0.135	0.148	0.061	2.303	1.214	2.855	1.934	2.593	2.487	2.911	0.452	14.459	2.025	1.838	0.011	1.663
Lactic acid	0.069	0.032	0.100	2.299	3.489	2.253	0.311	0.326	0.875	1.661	0.157	0.719	0.710	0.925	0.041	0.394
Fumaric acid	0.015	0.009	<LOD	0.025	0.011	0.027	0.007	0.063	0.012	<LOD	0.008	0.077	0.029	0.018	<LOD	0.019
Malic acid	0.419	0.265	0.177	0.322	0.245	0.423	0.201	0.352	0.275	0.112	0.196	0.607	0.600	0.569	0.016	0.237
2-oxoglutarate	0.080	0.058	0.021	0.083	0.028	0.060	0.028	0.089	0.050	0.032	0.041	0.046	0.063	0.047	<LOD	0.041
cis-Aconitic acid	0.019	0.022	0.020	0.031	0.023	0.036	0.016	0.024	0.017	0.018	0.020	0.023	0.021	0.020	0.011	0.015
Isocitric acid	0.037	0.039	0.032	0.055	0.035	0.050	0.043	0.045	0.037	0.038	0.040	0.044	0.050	0.042	0.028	0.038
Citric acid	0.055	0.053	0.045	0.067	0.036	0.060	0.046	0.069	0.040	0.043	0.059	0.049	0.047	0.053	0.026	0.044
Heptanoic acid (C7:0)	0.743	0.403	0.915	4.357	1.262	2.974	<LOD	0.101	<LOD	0.098	0.168	0.227	0.110	0.104	<LOD	0.884
Octanoic acid (C8:0)	<LOD	<LOD	0.305	0.739	<LOD	0.569	<LOD	0.769	<LOD	0.900	<LOD	6.133	<LOD	<LOD	<LOD	0.525
Linoleic acid (C12:2)	0.665	0.415	0.119	1.421	0.134	0.411	0.649	0.868	0.254	1.260	0.457	1.662	0.362	0.292	<LOD	0.293
Phenylacetic acid	2.195	1.078	1.562	1.830	0.229	1.082	0.675	0.640	0.700	0.529	0.881	0.510	0.889	0.552	0.032	0.422
4-Hydroxyphenylacetic acid	0.320	0.599	0.806	1.887	0.228	1.131	0.106	1.422	0.331	0.119	3.039	1.098	0.719	0.492	<LOD	0.129
Indole-3-acetic acid	0.233	0.202	0.046	4.414	<LOD	0.861	0.273	0.392	0.250	1.542	0.123	0.558	1.836	1.075	<LOD	0.126

Supplementary Table S6. The effect of uncoated minispheres with (+) and without (-) Cyclosporine A (CyA) (0.75 mg ml^{-1}) on the growth of *Bacteroides* sp *in vitro* (cfu/ml)

Bacteroides Strain	Treatment	TBC (cfu/ml)
		T48
<i>Bacteroides distasonis</i>	No Treatment control	6.6×10^9
	Minispheres without cyclosporine (uncoated)	2.2×10^9
	Minispheres with cyclosporine (uncoated)	2.6×10^8
<i>Bacteroides dorei</i>	No Treatment control	4.86×10^8
	Minispheres without cyclosporine (uncoated)	3.78×10^6
	Minispheres with cyclosporine (uncoated)	1.78×10^6
<i>Bacteroides fragilis</i>	No Treatment control	2.58×10^6
	Minispheres without cyclosporine (uncoated)	4.04×10^6
	Minispheres with Cyclosporine (uncoated) beads	3.12×10^6