

Supplemental Table 1: Studies Characteristics

Study Number/Study	Lead-in? Type of lead-in (OL, SB)	Duration of lead-in (weeks)	Total N enrolled in lead-in	Duration to primary endpoint (weeks)	Agent	Dose (mg)	Scale	N Drug/N Control	Positive Primary Outcome?
1 ^a	Papakostas GJ et al. 2012-A (SPCD stage II)	N	148	4	L-methylfolate	7.5	HAMD	13	98
1 ^a	Papakostas GJ et al. 2012-A (SPCD stage II)	Y	148	4	L-methylfolate	7.5	HAMD	30	30
2 ^a	Papakostas GJ et al. 2012-B (SPCD stage II)	N	75	4	L-methylfolate	7.5	HAMD	19	156
2 ^a	Papakostas GJ et al. 2012-B (SPCD stage II)	Y	75	4	L-methylfolate	7.5	HAMD	19	156
3 ^a	Fava M et al. 2012 (SPCD stage I)	N	221	4	Primaprazole	2	MADRS	54	167
3 ^a	Fava M et al. 2012 (SPCD stage I)	Y	221	4	Primaprazole	2	MADRS	61	163
4 ^a	Fava M et al. 2016 (SPCD stage I)	N	142	4	L-methylfolate	2/2	MADRS	24	98
4 ^a	Fava M et al. 2016 (SPCD stage I)	Y	142	4	L-methylfolate	2/2	MADRS	23	20
5 ^a	Fava M et al. 2016 (SPCD stage I)	N	98	4	L-methylfolate	8/8	MADRS	19	98
5 ^a	Fava M et al. 2016 (SPCD stage I)	Y	98	4	L-methylfolate	8/8	MADRS	22	20
6 ^a	Fava M et al. 2018-A (SPCD stage II)	N	385	5	L-methylfolate	15/0.5	MADRS	59	266
6 ^a	Fava M et al. 2018-A (SPCD stage II)	Y	385	5	L-methylfolate	15/0.5	MADRS	56	266
7 ^a	Fava M et al. 2018-A (SPCD stage II)	N	407	5	L-methylfolate	2/2	MADRS	60	166
7 ^a	Fava M et al. 2018-A (SPCD stage II)	Y	407	5	L-methylfolate	2/2	MADRS	58	166
8 ^a	Fava M et al. 2018-B (SPCD stage II)	N	207	5	L-methylfolate	1/1	MADRS	62	161
8 ^a	Fava M et al. 2018-B (SPCD stage II)	Y	207	5	L-methylfolate	1/1	MADRS	62	161
9 ^a	Fava M et al. 2019 (SPCD stage II)	N	None	5	Primaprazole	2/2	MADRS	63	281
9 ^a	Fava M et al. 2019 (SPCD stage II)	Y	None	5	Primaprazole	2/2	MADRS	63	281
10 ^a	Baron M et al. 2009-A	N	None	None	Primaprazole	14	HAMD	29	29
10 ^a	Baron M et al. 2009-A	Y	None	None	Primaprazole	14	HAMD	29	29
11 ^a	Baron M et al. 2009-B	N	None	None	Primaprazole	150	MADRS	160	160
11 ^a	Baron M et al. 2009-B	Y	None	None	Primaprazole	150	MADRS	160	160
12 ^a	Baron M et al. 2010-A	N	None	None	Primaprazole	150	MADRS	143	143
12 ^a	Baron M et al. 2010-A	Y	None	None	Primaprazole	150	MADRS	143	143
13 ^a	Durgam S, 2016-A	N	None	None	Primaprazole	1 to 2	MADRS	273	264
13 ^a	Durgam S, 2016-A	Y	None	None	Primaprazole	1 to 2	MADRS	273	264
14 ^a	Conner AM, 2017	N	None	None	Primaprazole	2 to 4.5	MADRS	271	264
14 ^a	Conner AM, 2017	Y	None	None	Primaprazole	2 to 4.5	MADRS	271	264
15 ^a	Quireza JA, 2016-A	N	None	None	Primaprazole	10	MADRS	64	64
15 ^a	Quireza JA, 2016-A	Y	None	None	Primaprazole	10	MADRS	64	64
16 ^a	Quireza JA, 2016-B	N	None	None	Primaprazole	0.5	MADRS	112	109
16 ^a	Quireza JA, 2016-B	Y	None	None	Primaprazole	0.5	MADRS	112	109
17 ^a	Umbreit, 2015-A	N	None	None	Primaprazole	1.5	MADRS	89	86
17 ^a	Umbreit, 2015-A	Y	None	None	Primaprazole	1.5	MADRS	88	86
18 ^a	Umbreit, 2015-B	N	None	None	Primaprazole	1.5	MADRS	87	86
18 ^a	Umbreit, 2015-B	Y	None	None	Primaprazole	1.5	MADRS	87	86
19 ^a	Fava M, 2018-A	N	502	8	Primaprazole	0.1 to 0.3	MADRS	76	81
19 ^a	Fava M, 2018-A	Y	502	8	Primaprazole	0.1 to 0.3	MADRS	76	81
20 ^a	Fava M, 2018-B	N	463	8	Primaprazole	1 to 2	MADRS	73	81
20 ^a	Fava M, 2018-B	Y	463	8	Primaprazole	1 to 2	MADRS	73	81
21 ^a	Mahmoud RA, 2007	N	287	8	Primaprazole	1 to 4	MADRS	62	63
21 ^a	Mahmoud RA, 2007	Y	287	8	Primaprazole	1 to 4	MADRS	62	63
22 ^a	Wells E, 2014(1)	N	710	8	Primaprazole	2 to 8	MADRS	151	157
22 ^a	Wells E, 2014(1)	Y	710	8	Primaprazole	2 to 8	MADRS	151	157
23 ^a	Baron G, 2011	N	167	8	Primaprazole	2 to 8	MADRS	145	145
23 ^a	Baron G, 2011	Y	167	8	Primaprazole	2 to 8	MADRS	145	145
24 ^a	Thase ME, 2007(1)	N	1513	10	Primaprazole	1 to 400	MADRS	148	148
24 ^a	Thase ME, 2007(1)	Y	1513	10	Primaprazole	1 to 400	MADRS	148	148
25 ^a	Thase ME, 2007(2)	N	1289	8	Primaprazole	0.5 to 0.650	MADRS	174	174
25 ^a	Thase ME, 2007(2)	Y	1289	8	Primaprazole	0.5 to 0.650	MADRS	174	174
26 ^a	Modell, 2015(1)-A	N	1317	8	Primaprazole	2	MADRS	170	174
26 ^a	Modell, 2015(1)-A	Y	1317	8	Primaprazole	2	MADRS	170	174
27 ^a	Modell, 2015(1)-B	N	781	8	Primaprazole	0.1	MADRS	155	157
27 ^a	Modell, 2015(1)-B	Y	781	8	Primaprazole	0.1	MADRS	155	157
28 ^a	Modell, 2015(2)-C	N	827	8	Primaprazole	1	MADRS	156	157
28 ^a	Modell, 2015(2)-C	Y	827	8	Primaprazole	1	MADRS	156	157
29 ^a	Berman M, 2007	N	1115	8	Primaprazole	2 to 15	MADRS	181	172
29 ^a	Berman M, 2007	Y	1115	8	Primaprazole	2 to 15	MADRS	181	172
30 ^a	Berman M, 2009	N	830	8	Primaprazole	2 to 20	MADRS	174	169
30 ^a	Berman M, 2009	Y	830	8	Primaprazole	2 to 20	MADRS	174	169
31 ^a	Kanjina K, 2013-A	N	830	8	Primaprazole	3	MADRS	197	195
31 ^a	Kanjina K, 2013-A	Y	830	8	Primaprazole	3	MADRS	197	195
32 ^a	Kanjina K, 2013-B	N	830	8	Primaprazole	3 to 15	MADRS	194	195
32 ^a	Kanjina K, 2013-B	Y	830	8	Primaprazole	3 to 15	MADRS	194	195
33 ^a	Baron M, 2018	N	837	8	Primaprazole	1.5 to 4.5	MADRS	267	258
33 ^a	Baron M, 2018	Y	837	8	Primaprazole	1.5 to 4.5	MADRS	267	258
34 ^a	Thase ME, 2019(1)	N	860	8	Primaprazole	0.15	MADRS	191	202
34 ^a	Thase ME, 2019(1)	Y	860	8	Primaprazole	0.15	MADRS	191	202
35 ^a	Thase ME, 2019(2)	N	773	8	Primaprazole	0.25 to 0.75	MADRS	184	189
35 ^a	Thase ME, 2019(2)	Y	773	8	Primaprazole	0.25 to 0.75	MADRS	184	189
36 ^a	Thase ME, 2019(3)	N	1512	8	Primaprazole	1 to 3	MADRS	158	147
36 ^a	Thase ME, 2019(3)	Y	1512	8	Primaprazole	1 to 3	MADRS	158	147
37 ^a	Thase ME, 2015-A	N	826	8	Primaprazole	1	MADRS	211	203
37 ^a	Thase ME, 2015-A	Y	826	8	Primaprazole	1	MADRS	211	203
38 ^a	Thase ME, 2015-B	N	1239	8	Primaprazole	2	MADRS	175	176
38 ^a	Thase ME, 2015-B	Y	1239	8	Primaprazole	2	MADRS	175	176
39 ^a	Richard C, 2014(1)	N	1095	8	Primaprazole	24 to 70	MADRS	200	209
39 ^a	Richard C, 2014(1)	Y	1095	8	Primaprazole	24 to 70	MADRS	200	209
40 ^a	Richard C, 2017-A	N	1778	8	Primaprazole	10	MADRS	177	78
40 ^a	Richard C, 2017-A	Y	1778	8	Primaprazole	10	MADRS	177	78
41 ^a	Richard C, 2017-B	N	1416	8	Primaprazole	30	MADRS	76	78
41 ^a	Richard C, 2017-B	Y	1416	8	Primaprazole	30	MADRS	76	78
42 ^a	Richard C, 2017-C	N	10	8	Primaprazole	50	MADRS	78	78
42 ^a	Richard C, 2017-C	Y	10	8	Primaprazole	50	MADRS	78	78
43 ^a	Richard C, 2017-D	N	239	8	Primaprazole	70	MADRS	80	78
43 ^a	Richard C, 2017-D	Y	239	8	Primaprazole	70	MADRS	80	78
44 ^a	Kanjina K, 2018	N	899	8	Primaprazole	20 to 50	MADRS	165	164
44 ^a	Kanjina K, 2018	Y	899	8	Primaprazole	20 to 50	MADRS	165	164
45 ^a	Robert M, 2018 (2)-A	N	2174	8	Primaprazole	1 to 12/100	MADRS	208	201
45 ^a	Robert M, 2018 (2)-A	Y	2174	8	Primaprazole	1 to 12/100	MADRS	208	201
46 ^a	Robert M, 2018 (2)-B	N	8 to 10	8	Primaprazole	2 to 3	MADRS	191	205
46 ^a	Robert M, 2018 (2)-B	Y	8 to 10	8	Primaprazole	2 to 3	MADRS	191	205
47 ^a	Ball S, 2016-A	N	227	3	Primaprazole	150 to 300	MADRS	69	205
47 ^a	Ball S, 2016-A	Y	227	3	Primaprazole	150 to 300	MADRS	69	205
48 ^a	Ball S, 2016-B	N	1416	3	Primaprazole	6 to 18	MADRS	63	68
48 ^a	Ball S, 2016-B	Y	1416	3	Primaprazole	6 to 18	MADRS	63	68
49 ^a	Ball S, 2016-C	N	1480	3	Primaprazole	12	MADRS	230	240
49 ^a	Ball S, 2016-C	Y	1480	3	Primaprazole	12	MADRS	230	240
50 ^a	Ball S, 2016-D	N	1566	3	Primaprazole	18	MADRS	200	228
50 ^a	Ball S, 2016-D	Y	1566	3	Primaprazole	18	MADRS	200	228
51 ^a	Thase ME, 2018	N	376	8	Primaprazole	17 to 18	MADRS	125	128
51 ^a	Thase ME, 2018	Y	376	8	Primaprazole	17 to 18	MADRS	125	128
52 ^a	Thase ME, 2018	N	145	8	Primaprazole	800	MADRS	118	116
52 ^a	Thase ME, 2018	Y	145	8	Primaprazole	800	MADRS	118	116
53 ^a	Thase ME, 2018	N	145	8	Primaprazole	145	MADRS	148	148
53 ^a	Thase ME, 2018	Y	145	8	Primaprazole	145	MADRS	148	148

N=None; Y=Yes; OL=Open label; SB=Single-blind; DR=Double-blind

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