Figure S1. Participant Flow Through Study

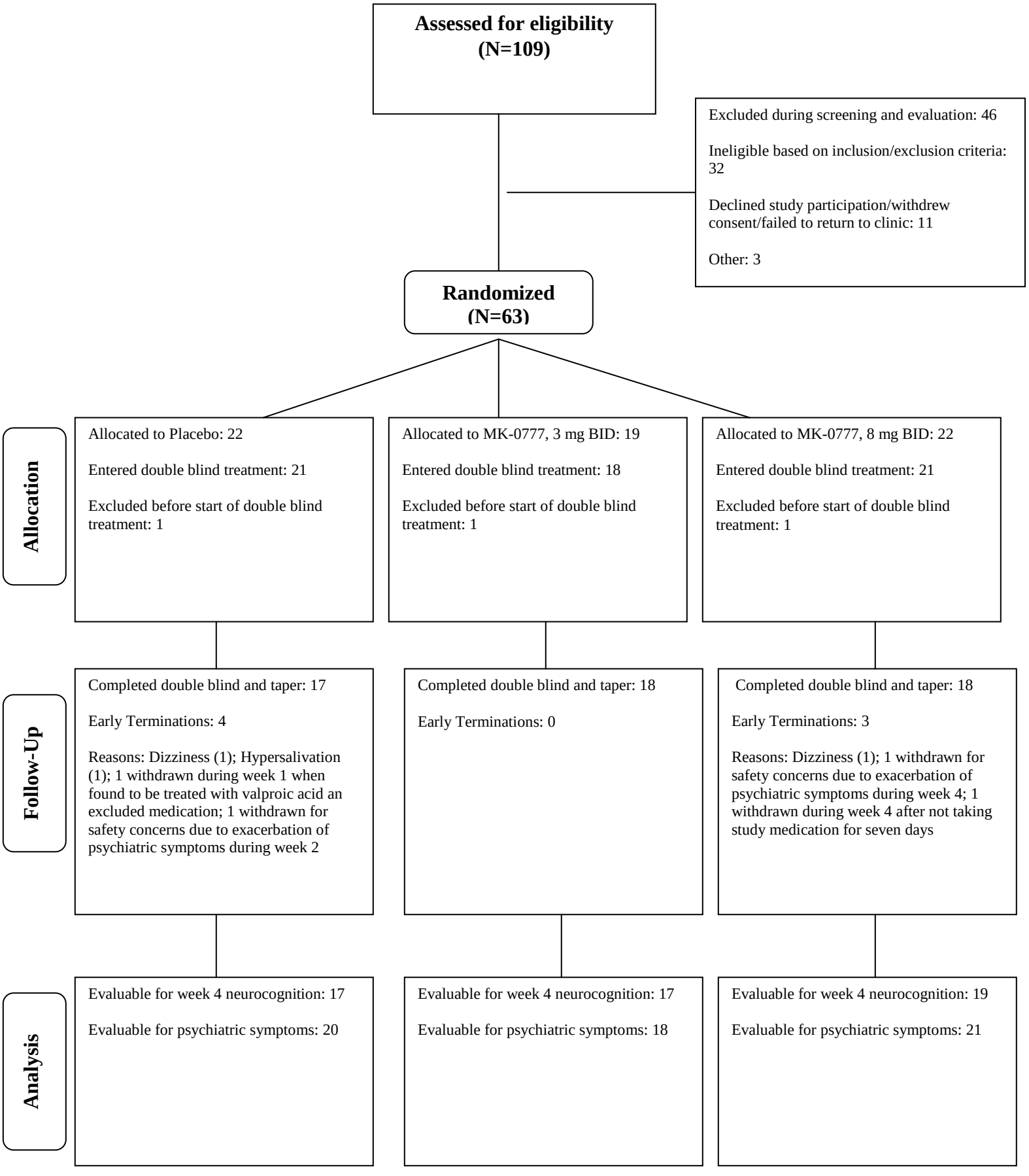

Table S1. MCCB: Reliability and Learning Effects

Domain (measure)	Test-Retest Reliability	Learning Effects in Placebo Group		
		Mean Diff.	SD (diff)	*p* value
MCCB Composite Score	0.95	2.47	1.94	<0.001
Attention/Vigilance (CPT-IP)	0.80	-0.71	7.09	0.69
Processing Speed	0.89	1.12	4.76	0.35
Visual Learning (BVMT-R)	0.84	3.24	6.72	0.06
Verbal Learning (HVLT-R)	0.72	3.47	6.76	0.05
Social Cognition (MSCEIT)	0.78	-1.24	7.38	0.50
Reasoning/Problem-Solving (NAB Mazes)	0.84	3.94	3.80	<0.001
Working Memory	0.90	1.00	5.53	0.47

BVMT-R, Brief Visuospatial Memory Test Revised; CPT-IP, Identical Pairs Continuous Performance Test; HVLT-R, Hopkins Verbal Learning Test, Revised; MCCB, MATRICS Consensus Cognitive Battery; MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test; NAB, Neuropsychological Assessment Battery.

Test-retest reliability was calculated using the Pearson correlation coefficient (r) and is based on data from all participants who had valid baseline and end-of-study data.

Table S2. AX-CPT and N-Back: Reliability and Learning Effects

	Test-Retest	**Learning Effects in Placebo Group**		
Domain (measure)	**Reliability**	**Mean Diff.**	**SD (diff)**	***p* value**
AX-CPT d-prime	0.67	-0.24	1.24	0.45
N-Back d-prime				
0-back (all non-targets)	0.68	-0.01	0.50	0.94
1-back (all non-targets)	0.84	0.08	0.52	0.55
2-back (all non-targets)	0.82	0.24	0.46	0.04
2-Back response times				
Target hit	0.78	43.8	188.7	0.35
Novel correct rejection	0.54	-137.2	454.3	0.23
Repeated correct rejection	0.78	-11.4	231.9	0.84

AX-CPT, modified Continuous Performance Test.

Test-retest reliability was calculated using the Pearson correlation coefficient (r) and is based on data from all participants who had valid baseline and end-of-study data.

Table S3. UPSA Summary and Component Scores, mean (±SD)*

Measure	Week	Placebo	MK-0777, 3 mg BID	MK-0777, 8 mg BID	ANCOVA F	df	*p*
UPSA Summary	0	95.0 (16.2)	85.0 (18.8)	91.7 (13.4)	0.77	2,50	0.47
	4	96.5 (15.5)	86.3 (18.7)	90.4 (12.8)			
Communication	0	14.0 (3.8)	12.4 (4.1)	13.9 (4.2)	0.36	2,50	0.70
	4	14.4 (2.8)	13.1 (4.2)	13.7 (2.9)			
Comprehension/ Planning	0	15.1 (3.4)	12.9 (3.4)	12.9 (3.9)	3.76	2,50	0.03
	4	16.6 (2.9)	13.1 (3.9)	12.3 (4.5)			
Financial Skills	0	18.1 (2.8)	16.4 (4.6)	16.9 (2.8)	0.11	2,50	0.90
	4	17.6 (3.3)	16.3 (3.1)	16.9 (2.8)			
Household	0	15.6 (5.3)	15.3 (5.3)	15.8 (3.4)	0.10	2,50	0.90
	4	15.9 (5.4)	15.3 (4.0)	16.1 (3.9)			
Medication Management	0	16.4 (3.3)	14.0 (5.0)	16.6 (2.1)	0.00	2,50	1.00
	4	16.4 (3.5)	14.5 (4.5)	16.5 (2.4)			
Transportation	0	15.8 (2.8)	14.0 (3.9)	15.6 (3.1)	0.21	2,50	0.81
	4	15.6 (3.3)	14.1 (2.9)	14.9 (4.0)			

UPSA, UCSD Performance-Based Skills Assessment.

The UPSA Summary score has a range from 0 to 120, and each domain score has a range from 0 to 20.

* There was no significant variation in the magnitude of treatment differences among the UPSA component scores: $F = 0.81$, $df = 10, 66.8$, $p = 0.62$.

Table S4. SCoRS Ratings by Treatment, mean (±SD)

Measure	Week	Placebo	MK-0777, 3 mg BID	MK-0777, 8 mg BID	ANCOVA F	df	*p*
Interviewer Global Rating	0	3.8 (2.3)	4.8 (2.3)	4.1 (2.3)			
	4	3.6 (1.8)	4.6 (2.1)	4.0 (2.4)	0.17	2,47	0.84
Interviewer Change Rating	-	4.3 (0.6)	4.2 (0.8)	4.4 (1.0)	0.48	2,47	0.62
Subject Change Rating	-	4.8 (1.0)	4.6 (1.6)	4.6 (1.1)	0.49	2,47	0.17
Informant Change Rating	-	4.1 (0.4)	3.7 (1.3)	4.3 (1.6)	1.11	2,25	0.34

SCoRS, Schizophrenia Cognition Rating Scale.

The SCoRS Interviewer Global Rating of function has a range 1 to 10. The SCoRS interviewer, participant and informant change ratings range from 1 to 7.

Table S5. Frequency of Participants Reporting New or Worsened Side Effects During Treatment by Group

	Placebo			3 mg MK-0777			8 mg MK-0777			Fisher's exact
Side effects	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**test p-value**
Anorexia	21	3	14.3	18	2	11.1	21	3	14.3	1.000
Blurred vision	21	1	4.8	18	1	5.6	21	2	9.5	1.000
Bruising easily	21	0	0.0	18	1	5.6	21	1	4.8	0.751
Constipation	21	2	9.5	18	4	22.2	21	2	9.5	0.454
Diarrhea	21	0	0.0	18	3	16.7	21	3	14.3	0.147
Difficulty reading	21	0	0.0	18	2	11.1	21	2	9.5	0.446
Dizziness	21	4	19.0	18	4	22.2	21	6	28.6	0.807
Dry mouth	21	4	19.0	18	3	16.7	21	5	23.8	0.922
Enuresis	21	0	0.0	18	2	11.1	21	3	14.3	0.255
Eye redness	21	0	0.0	18	1	5.6	21	0	0.0	0.300
Eyebrow pain	21	0	0.0	18	0	0.0	21	0	0.0	1.000
Fever	21	0	0.0	18	2	11.1	21	1	4.8	0.289
Headache	21	7	33.3	18	4	22.2	21	3	14.3	0.355
Hypersalivation	21	0	0.0	18	1	5.6	21	3	14.3	0.199
Insomnia	21	2	9.5	18	5	27.8	21	4	19.0	0.350
Light sensitivity	21	0	0.0	18	1	5.6	21	2	9.5	0.510
Malaise	21	1	4.8	18	5	27.8	21	2	9.5	0.143
Mucosal ulceration	21	0	0.0	18	1	5.6	21	0	0.0	0.300
Nausea	21	1	4.8	18	3	16.7	21	4	19.0	0.401
Rash	21	1	4.8	18	0	0.0	21	0	0.0	1.000
Restlessness	21	4	19.0	18	3	16.7	21	4	19.0	1.000
Sedation	21	3	14.3	18	5	27.8	21	4	19.0	0.661
Sore throat	21	3	14.3	18	3	16.7	21	2	9.5	0.894
Stiffness	21	3	14.3	18	3	16.7	21	3	14.3	1.000
Tremor	21	5	23.8	18	1	5.6	21	2	9.5	0.254
Urticaria	21	0	0.0	18	2	11.1	21	2	9.5	0.446
Vomiting	21	2	9.5	18	4	22.2	21	3	14.3	0.599

Table S6. Vital Signs Means at Baseline and Taper Visit

		Placebo			3 mg MK-0777			8 mg MK-0777			ANCOVA Test for Treatment Effect		
Measure	**Visit**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**F**	**df**	***p* value**
Sitting Diastolic	Base	21	80.2	8.8	18	76.5	7.4	21	76.95	8.6			
Blood Pressure	EOS	17	82.1	9.3	18	74.7	8.5	20	75.10	11.5	0.78	2 55.9	0.47
Standing Diastolic	Base	21	81.6	8.4	18	78.6	6.4	21	78.33	8.1			
Blood Pressure	EOS	17	85.5	8.8	18	76.2	11.2	20	77.70	10.0	3.43	2 55.8	0.04*
Sitting Systolic	Base	21	125.4	13.1	18	122.8	14.8	21	119.4	12.3			
Blood Pressure	EOS	17	127.4	15.4	18	120.4	17.7	20	119.0	16.4	2.67	2 55.5	0.08
Standing Systolic	Base	21	123.7	13.3	18	121.4	15.2	21	116.7	13.3			
Blood Pressure	EOS	17	126.5	14.3	18	122.8	18.7	20	116.4	16.8	0.10	2 55.8	0.90
Weight (kg)	Base	21	99.8	22.5	18	87.6	23.2	21	84.4	18.1			
	EOS	17	102.0	24.4	18	88.4	23.3	20	84.5	19.0	3.13	2 57.5	0.051[#]
BMI (kg/m^2)	Base	21	33.6	8.0	18	30.0	6.7	21	28.9	7.3			
	EOS	17	34.6	8.5	18	30.2	6.5	20	29.1	7.7	2.80	2 57.4	0.07

BMI, body mass index; EOS, end of study.

* In the follow-up pair-wise comparisons, participants randomized to MK-0777 3 mg BID had a significant decrease in standing diastolic blood pressure compared to those randomized to placebo (mean difference (±SE): -3.57 ± 1.41 mmHg; t = 2.54; df = 55.8; $p = 0.01$).

[#] In the follow-up pair-wise comparisons, there were significant group differences between placebo and the MK-0777 3 mg BID group (mean difference (±SE): 1.12 ± 0.55 kg; t = 2.04; df = 57.9; $p < 0.05$) and the MK-0777 8 mg BID group (mean difference (±SE): 1.23 ± 0.54 kg; t = 2.30; df = 60.0; $p = 0.025$).

Table S7. Laboratory Means at Baseline and Taper Visit

		Placebo			3 mg MK-0777			8 mg MK-0777			ANCOVA Test for Treatment Effect		
Measure	**Visit**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**F**	**df**	***p* value**
GGT	Base	21	39.81	33.13	18	33.56	15.35	20	33.90	21.73			
GGT	Taper	17	44.82	37.62	16	33.94	18.05	19	31.89	25.54	0.77	2, 48	0.47
LDH	Base	21	163.29	34.12	18	174.56	60.56	20	155.10	26.91			
LDH	Taper	17	160.41	31.38	18	175.00	42.97	19	169.95	39.19	0.92	2, 50	0.40
AST (SGOT)	Base	21	20.95	7.74	18	38.50	56.18	20	23.85	10.86			
AST (SGOT)	Taper	17	22.65	7.94	18	24.61	8.41	19	24.21	10.61	0.15	2, 50	0.86
ALT (SGPT)	Base	21	28.14	11.55	18	35.17	30.25	20	26.85	16.63			
ALT (SGPT)	Taper	17	32.00	18.14	18	26.61	13.28	19	27.11	22.27	0.93	2, 50	0.40
Alk_Phosphatase	Base	21	81.86	16.83	18	82.83	22.65	20	76.90	24.55			
Alk_Phosphatase	Taper	17	84.00	19.77	18	81.72	23.73	19	75.00	26.88	0.14	2, 50	0.87
Tot_Bilirubin	Base	21	0.51	0.17	18	0.52	0.25	20	0.50	0.26			
Tot_Bilirubin	Taper	17	0.51	0.26	18	0.54	0.43	19	0.55	0.35	0.07	2, 50	0.93
Total_Protein	Base	21	7.34	0.47	18	7.32	0.39	20	7.32	0.41			
Total_Protein	Taper	17	7.38	0.43	18	7.41	0.43	19	7.25	0.55	0.97	2, 50	0.39
Albumin	Base	21	4.38	0.29	18	4.37	0.31	20	4.32	0.26			
Albumin	Taper	17	4.35	0.32	18	4.41	0.38	19	4.35	0.24	0.13	2, 50	0.88
Globulin	Base	21	2.96	0.50	17	2.95	0.38	20	2.99	0.44			
Globulin	Taper	17	3.03	0.50	17	2.99	0.42	19	2.89	0.50	1.33	2, 49	0.28
Glucose	Base	21	98.05	13.15	18	98.22	15.42	20	98.90	23.17			
Glucose	Taper	17	100.71	21.27	18	107.61	37.58	19	99.42	23.63	0.67	2, 50	0.52
BUN	Base	21	13.52	4.29	18	12.89	4.01	20	12.70	3.80			
BUN	Taper	17	13.24	5.38	18	13.44	5.86	19	12.79	3.61	0.21	2, 50	0.81
Creatinine	Base	21	1.02	0.21	18	0.96	0.30	19	0.89	0.20			
Creatinine	Taper	17	1.01	0.18	18	0.97	0.31	19	1.02	0.58	1.25	2, 49	0.30
Sodium	Base	21	140.29	2.08	18	139.61	3.48	20	140.35	2.30			
Sodium	Taper	17	139.82	1.88	18	139.39	2.83	19	139.05	2.55	0.88	2, 50	0.42
Potassium	Base	21	4.11	0.34	18	4.14	0.37	20	4.22	0.32			
Potassium	Taper	17	4.08	0.22	18	4.08	0.36	19	4.18	0.32	0.21	2, 50	0.81
Chloride	Base	21	103.14	2.83	18	103.28	4.91	20	103.75	3.40			
Chloride	Taper	17	103.29	2.82	18	103.00	4.58	19	102.68	3.59	0.64	2, 50	0.53
CO2	Base	21	24.50	3.09	18	24.02	2.69	20	24.02	4.36			
CO2	Taper	17	23.36	2.95	18	23.33	3.72	19	24.38	3.29	1.89	2, 50	0.16
Cholesterol	Base	21	182.00	39.04	18	169.61	34.48	20	185.55	37.07			
Cholesterol	Taper	17	181.47	37.77	18	175.17	41.40	19	171.95	34.72	1.26	2, 50	0.29

Supplemental Methods and Materials

Slit-lamp eye examination results

Five people who participated in Merck sponsored studies of MK-0777 for the treatment of generalized anxiety disorder were observed to have cataracts on post-study slit-lamp eye examinations. There were no pre-study evaluations, which precluded any assessment of whether the observed cataracts were due to study participation. Regardless, in order to maximize the safety of our study participants, we excluded potential participants with a history of posterior subcapsular cataracts or age-inconsistent nuclear or cortical cataracts, or uveitis. The reason for excluding potential participants with uveitis is that uveitis is a risk factor for the development of cataracts.

A slit-lamp eye examination was conducted at Screening, end of the Treatment Phase, and 6 and 12 months after completion of the Treatment Phase. The Lens Opacities Classification System III (1) was used to grade cataracts and the grading scale developed by Gwon and colleagues (2) was used for the evaluation of uveitis.

Fifty-five post-randomization slit lamp eye examinations were performed: 48 were conducted in participants who completed the study and 7 were conducted in participants who terminated prior to completion. These included 15/18 participants randomized to MK-0777 3 mg BID, 19/21 participants randomized to MK-0777 8 mg BID, and 21/21 participants randomized to placebo. Three participants (one MK-0777 3 mg BID, one MK-0777 8 mg BID, and one placebo), all of whom completed double-blind treatment, were found to have positive findings on their follow-up examination. All reported findings were minimal to mild increases in nuclear color grade or nuclear opalescence grade. None of the participants developed posterior subcapsular cataracts nor did any exhibit any evidence of uveitis.

In summary, there was no evidence of increased incidence of clinically relevant cataracts or uveitis.

1. Chylack LT Jr, Wolfe JK, Singer DM, Leske C, Bullimore MA, Baily IL, *et al.* (1993): The Lens Opacities Classification System III. *Arch Ophthalmol* 111: 831-836.
2. Gwon A, Mantras C, Gruber L, Cunanan C (1993): Concanavalin A-induced posterior subcapsular cataract: a new model of cataractogenesis. *Invest Ophthalmol Vis Sci* 34: 3483-3488.