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Efficacy and safety of memantine in children with autism spectrum disorder: Results from three phase 2 multicenter studies

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Abstract

Three phase 2 trials were conducted to assess the efficacy and long-term safety of weight-based memantine extended release (ER) treatment in children with autism spectrum disorder. MEM-MD-91, a 50-week open-label trial, identified memantine extended-release treatment responders for enrollment into MEM-MD-68, a 12-week randomized, double-blind, placebo-controlled withdrawal trial. MEM-MD-69 was an open-label extension trial in which participants from MEM-MD-68, MEM-MD-91, and open-label trial MEM-MD-67 were treated ⩽48 weeks with memantine extended release. In MEM-MD-91, 517 (59.6%) participants were confirmed Social Responsiveness Scale responders at week 12; mean Social Responsiveness Scale total raw scores improved two to three times a minimal clinically important difference of 10 points. In MEM-MD-68, there was no difference between memantine and placebo on the primary efficacy parameter, the proportion of patients with a loss of therapeutic response (defined as ⩾10-point increase from baseline in Social Responsiveness Scale total raw score). MEM-MD-69 exploratory analyses revealed mean standard deviation improvement in Social Responsiveness Scale total raw score of 32.4 (26.4) from baseline of the first lead-in study. No new safety concerns were evident. While the a priori–defined efficacy results of the double-blind trial were not achieved, the considerable improvements in mean Social Responsiveness Scale scores from baseline in the open-label trials were presumed to be clinically important.

Keywords

Asperger's disorder, autism spectrum disorders, clinical trial, medication, memantine, pervasive developmental disorder-not otherwise specified, randomized withdrawal, school-age children, Social Responsiveness Scale

Introduction

In the United States, approved pharmacological interventions for autism spectrum disorder (ASD) are limited to risperidone and aripiprazole, both of which are indicated by the US Food and Drug Administration (FDA) for the treatment of irritability associated with ASD (Janssen Pharmaceuticals, Inc., 2014; Otsuka Pharmaceutical Co., Ltd., 2016), but not for the core symptoms of impaired social communication and interaction, stereotyped behaviors, and restricted interests (*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), 2013).

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The molecular mechanisms of ASD are not fully understood but may involve altered glutamatergic signaling. Glutamate acts on *N*-methyl-D-aspartate (NMDA) receptors in the areas of the brain important for learning and memory (Parsons, Stoffler, & Danysz, 2007). As altered changes in glutamatergic signaling have been observed in pediatric individuals with ASD (Choudhury, Lahiri, & Rajamma, 2012; Rojas, 2014; Spencer et al., 2014), interventions that modulate glutamate receptors may therefore be of therapeutic benefit.

Results from several clinical studies suggest that modulation of the glutamatergic NMDA receptor may provide clinical benefits for the symptoms of ASD. Treatment with immediate-release (IR) memantine—a low-to-moderate affinity, uncompetitive NMDA receptor antagonist—has been shown to improve both communication and social interactions in several trials conducted in individuals with ASD and pervasive developmental disorder not-otherwise specified (PDD-NOS) (Chez et al., 2007; Ghaleiha et al., 2013; Owley et al., 2006).

Extended-release (ER) memantine monotherapy was investigated in children with autistic disorder, Asperger's disorder, or PDD-NOS as part of a phase 2 clinical development program designated under the US FDA Pediatric Written Request (PWR). In a 12-week, randomized, double-blind, placebo-controlled trial (MEM-MD-57A, NCT00872898; conducted May 2009 through August 2012) in which memantine-ER was administered over a limited, weight-based dose range (3–15 mg/day), there was a trend toward improvement on the primary efficacy measure of caregiver/parent ratings on the Social Responsiveness Scale (SRS) of ~10 points from baseline in both treatment groups, but no significant between-group differences were observed between memantine-ER and placebo at study end (Aman et al., 2016). Following the 12-week double-blind study, participants were eligible to enroll in a long-term (48 week) safety and tolerability extension study (MEM-MD-67, conducted November 2009 through February 2013; NCT01999894) examining open-label memantine-ER (Aman et al., 2016). Like the double-blind phase, SRS scores with memantine-ER continued to improve by ~6 points over the 48-week open-label extension period, regardless of prior treatment.

In addition to trials MEM-MD-57A and MEM-MD-67 described above, three clinical trials also included under the PWR (MEM-MD-91, MEM-MD-68, and MEM-MD-69) further examined the safety, tolerability, and efficacy of memantine ER in individuals with autistic disorder, Asperger's disorder, or PDD-NOS. Like MEM-MD-57A and MEM-MD-67, memantine-ER was administered over a limited, weight-based dose range (3–15 mg/day). In MEM-MD-91, a 50-week open-label study, participants who responded to memantine-ER were identified and further evaluated in a 12-week double-blind, placebo-controlled, and randomized withdrawal study (MEM-MD-68). Participants from both MEM-MD-91 and MEM-MD-68 were then eligible to enroll in MEM-MD-69, an open-label extension study to evaluate the long-term (up to 48 weeks) safety and tolerability of memantine-ER for ASD. Findings from these three studies of memantine-ER in ASD participants are reported here.

Methods

Studies and procedures

The three phase 2 studies described in this article (MEM-MD-91, NCT01592786; MEM-MD-68, NCT01592747; MEM-MD-69, NCT01592773) were conducted between June 2012 and August 2014 at multiple global centers in pediatric outpatients with autistic disorder, Asperger's disorder, or PDD-NOS as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; DSM-IV-TR, 2000). Each study was conducted in full compliance with FDA guidelines for good clinical practice and in accordance with the ethical principles of the Declaration of Helsinki and the Code of Federal Regulations (CFR) (21CFR312.120). Outside the United States, MEM-MD-91 was carried out in full compliance with the guidelines of the Independent Ethics Committees (IECs) and national health authorities of Australia, Belgium, Canada, Colombia, Estonia, France, Hungary, Iceland, Italy, New Zealand, Poland, Republic of Korea, Serbia, Singapore, South Africa, Spain, and Ukraine. MEM-MD-68 was carried out in full compliance with the guidelines of the IECs and national health authorities of Belgium, Colombia, Estonia, France, Hungary, Iceland, Italy, New Zealand, Poland, South Korea, Serbia, South Africa, Spain, and Ukraine. MEM-MD-69 was carried out in full compliance with the guidelines of the IECs and national health authorities of Belgium, Canada, Colombia, Estonia, France, Hungary, Iceland, Italy, New Zealand, Poland, Republic of Korea, Serbia, South Africa, Spain, and Ukraine. The study protocols and amendments, informed consent forms, and information sheets were approved by the IECs at each study center in conformance with US CFR, Title 21, Part 56, the European Union Clinical Trial Directive 2001/20/EC (if applicable), and local regulations.

An independent Data and Safety Monitoring Board (DSMB) reviewed safety data at defined intervals throughout each study. Before the conduct of any study procedure, participants provided written informed assent (when developmentally appropriate), and the study participant's parent, legal guardian, or legally authorized representative provided voluntary and written informed consent (in compliance with 21 CFR Parts 50 and 312) and Health Insurance Portability and Accountability Act (HIPAA) authorization (United States).

The objective of each trial and the details regarding study design, enrollment criteria, and efficacy and safety outcomes are described in Table 1. In MEM-MD-91,

Table 1. Phase 2 trial designs and objectives.

	MEM-MD-91 (NCT01592786)	MEM-MD-68 (NCT01592747)	MEM-MD-69 (NCT01592773)
Objective(s)	• To assess safety and tolerability of memantine ER • To identify memantine responders for enrollment into MEM-MD-68	• To evaluate the safety, tolerability, and efficacy of memantine ER versus placebo in patients previously on stable memantine therapy[a]	• To assess the long-term safety and tolerability of memantine ER
Design	Open-label	Randomized, double-blind, placebo-controlled, withdrawal	Open-label extension
Study sites	118 sites in 18 countries	92 sites in 15 countries	106 sites in 16 countries
Duration (FPFV/LPLV)	Up to 50 weeks (1 June 2012/9 July 2013)	12 weeks (10 September 2012/11 September 2013)	48 weeks (18 October 2010/31 January 2014)
Dosing	Memantine ER[b] • Group A: ⩾60 kg; max: 15 mg/day • Group B: 40–59 kg; max: 9 mg/day • Group C: 20–39 kg; max: 6 mg/day • Group D: <20 kg; max: 3 mg/day	Randomized 1:1:1 to memantine ER • Full-dose arm[c] • Reduced dose arm[d] ○ 15 mg/day reduced to 6 mg/day ○ 9 mg/day reduced to 3 mg/day ○ 6 mg/day reduced to 3 mg/day ○ 3 mg/day reduced to 3 mg every other day • Placebo[e]	Memantine ER[b] • Group A: ⩾60 kg; max: 15 mg/day • Group B: 40–59 kg; max: 9 mg/day • Group C: 20–39 kg; max: 6 mg/day • Group D: <20 kg; max: 3 mg/day
Titration	6 weeks	None	6 weeks
Primary efficacy variable	None (all efficacy analyses were exploratory)	SRS: Proportion of participants with LTR[f]	None
Secondary variables	None	• Time to first LTR • CCC-2 change from BL in 10 subscales at week 12	None
Exploratory/ additional variables	• SRS: change from BL in total raw score and subscales • SRS responder[g] • Confirmed SRS responder[h] • CCC-2: change from BL in subscales • CGI-S subscales • CGI-I subscales • ABC-C: change from BL in subscales	• CGI: change from BL in CGI-S subscales (week 12) • CGI-I subscales at week 12 • ABC-C: change from BL in subscales (week 12) • SRS: change from BL in subscales (awareness, cognition, communications, motivation, and autistic mannerisms) at week 12 • SRS: change from BL in total raw score (week 12)	• SRS: change from BL in total raw score • CGI-S: change from BL in subscales (overall severity, social interaction, communication, integrated social interaction and communications, stereotyped behaviors and restricted interests, associated maladaptive behaviors, and daily function) • ABC: change from BL in subscales (irritability, lethargy, stereotypy, hyperactivity, and inappropriate speech) • CCC-2 subscales
Safety evaluations	• Vital signs, adverse events, menarcheal status, and pregnancy • Suicidality assessment and cognitive testing • Physical exams and electrocardiograms • Clinical laboratory determinations using blood and urine samples		

ABC-C: Aberrant Behavior Checklist–Community Version; AUC: area under the curve; BL: baseline; CCC-2: Children's Communication Checklist, Second Edition; CGI: Clinical Global Impressions; ER: extended-release; FPFV: first patient first visit; LPLV: last patient last visit; LTR: loss of therapeutic response; NOAEL: no observed adverse effect level; SRS: Social Responsiveness Scale; CGI-I: Clinical Global Impression–Improvement scale; CGI-S: Clinical Global Impression–Severity scale.

[a]Only those participants who met the pre-defined responder criterion, defined as ⩾10-point improvement (reduction in score) on the SRS relative to the total raw score at two consecutive visits separated by at least 2 weeks.

[b]Participants were divided into four weight-base dose groups; dose limits were selected to ensure an AUC exposure below the predefined limit of 2100 ng·h/mL, which represents a 10-fold lower exposure than the one observed at the NOAEL in juvenile rats (15 mg/kg/day).

[c]Same weight-based dose from MEM-MD-91 was continued.

[d]Weight-based dose from MEM-MD-91 was reduced by ⩾50% at randomization in response to a request from the Food and Drug Administration (FDA) (i.e. participants who were receiving up to 15, 9, and 6, or 3 mg/day in MEM-MD-91 were reduced to 6 mg/day, 3 mg/day, 3 mg/day, and 3 mg every other day, respectively).

[e]Switched at randomization.

[f]LTR was defined as a ⩾10-point increase in SRS total raw score at any double-blind visit compared with the score at randomization.

[g]Defined as a patient with ⩾10-point improvement in SRS total raw score from baseline.

[h]Defined as a patient with ⩾12 weeks of exposure to investigational product who met the SRS responder criterion at two consecutive visits separated by ⩾2 weeks (only the scores from the last two SRS assessments were used for the determination of a confirmed responder).

participants who completed ⩾12 weeks of treatment and met the defined responder criterion at two consecutive visits separated by at least 2 weeks (i.e. confirmed responder) were eligible to transition to randomized trial MEM-MD-68. The responder criterion was defined as a ⩾10-point improvement (reduction in score) on the SRS total raw score from baseline (i.e. the last available measurement before the first dose of study medication). While the 10-point threshold was not based on empirically derived criteria for a minimal clinically important difference (MCID), the cutoff was recommended based on clinically meaningful observations (Dr John N Constantino, personal communication, October 2011) and was further discussed with the FDA.

MEM-MD-68 utilized a randomized withdrawal design in which participants from MEM-MD-91 who had ⩾12 weeks of memantine exposure and achieved confirmed responder status were equally randomized to one of three treatment arms: a full-dose memantine arm, a reduced-dose memantine arm, and placebo (Table 1). This randomized-withdrawal study was designed per FDA Guidance for Industry E11 Clinical Investigation of Medicinal Products in the Pediatric Population. Participants who completed MEM-MD-68 or who discontinued due to loss of therapeutic response (LTR)—defined as a ⩾10-point increase in SRS total raw score at any double-blind visit versus SRS score at randomization—were eligible to enroll into the long-term open-label safety study, MEM-MD-69. In addition to enrolling participants who either completed or met the LTR criterion in MEM-MD-68, participants who completed open-label study MEM-MD-67 (Aman et al., 2016) or MEM-MD-91 could enroll in MEM-MD-69.

The study sponsor (Forest Research Institute (FRI), Jersey City, NJ; currently Allergan plc) made an administrative decision to terminate MEM-MD-69 prematurely based on results from the previously initiated double-blind controlled studies MEM-MD-57A and MEM-MD-68. While no new safety concerns were evident, FRI (in collaboration with the Copernicus Group Institutional Review Board (IRB)) believed the decision to be ethically sound, eliminating further exposure and burden to trial participants and families/caregivers. Therefore, the exploratory efficacy parameters of trial MEM-MD-69 were not fully evaluated.

Participants

All participants met DSM-IV-TR diagnostic criteria for autistic disorder, Asperger's disorder, or PDD-NOS based on both the Autism Diagnostic Observation Schedule (ADOS; modules 2 or 3) and the Autism Diagnostic Interview–Revised (ADI-R). Participants are referred to as they were classified at the time the studies were conducted (i.e. DSM-IV-TR terminology in which autistic disorder, Asperger's disorder, and PDD-NOS were defined separately from the current spectrum known as ASD).

Participants were male and female outpatients 6–12 years of age with SRS total raw score > 44 (girls) or >53 (boys), IQ score ⩾50 on the Kaufman Brief Intelligence Test, Version 2 (or other standardized IQ test), verbal fluency of ⩾3-word phrases, Aberrant Behavior Checklist irritability subscale (ABC-I) score < 17, no significant risk of suicidality (based on investigator judgment, ABC-I, the suicidal ideation section of the Children's Columbia-Suicide Severity Rating Scale at screening, or any suicidal behavior), and normal physical examination, laboratory tests, electrocardiogram (ECG), and vital signs.

Patients were excluded for the following: having any primary psychiatric (Axis I) diagnosis other than autistic disorder, Asperger's disorder, or PDD-NOS; meeting DSM-IV-TR criteria for bipolar I disorder, psychotic disorder not otherwise specified, posttraumatic stress disorder, schizophrenia, or major depressive disorder within the past 6 months; having a medical history of neurological disease including, but not limited to, movement disorder, Tourette syndrome, tuberous sclerosis, fragile X syndrome, velocardiofacial syndrome, chromosome 15q duplication syndrome, Angelman syndrome, active epilepsy/seizure disorder (defined as seizure activity within 5 years of screening (visit 0) except simple febrile seizures), known abnormal computed tomography/magnetic resonance imaging of the brain or a structural lesion of the brain; medical conditions that might interfere with the conduct of the study, confound interpretation of the study results, or endanger the patient's well-being, including evidence or history of malignancy or any significant hematologic, endocrine, cardiovascular (including any rhythm disorder), respiratory, renal, hepatic, or gastrointestinal disease; and use of memantine or participation in an investigational study of memantine within 90 days of screening.

Use of the following concomitant medications was not allowed within five half-lives or 4 weeks of screening, whichever was shorter: NMDA antagonists (e.g. amantadine, ketamine, and dextromethorphan), general anesthetics, antianginal agents, antiarrhythmics, anticoagulants, systemic antifungal agents, antineoplastics, the antiviral agents Symmetrel and Endantadine, diuretics, hormone suppressants, H_2 blockers, hypoglycemic agents, hypolipidemics, insulin, and systemic steroids. Chronic and episodic use of analgesics (nonnarcotic only), antiacne medications (topical only, excluding isotretinoin), antihistamines, topical antifungal agents, anti-inflammatory drugs (excepting indomethacin and systemic corticosteroids), antipsoriatic treatments (except acitretin), anxiolytics, H_2 blockers/proton pump inhibitors (only if stable for at least 6 months prior to lead-in study), laxatives (if taken before lead-in study), migraine treatment, muscle relaxants, sedatives/hypnotics, steroids (topical, inhalant, intranasal), vitamins, and herbal remedies was allowed.

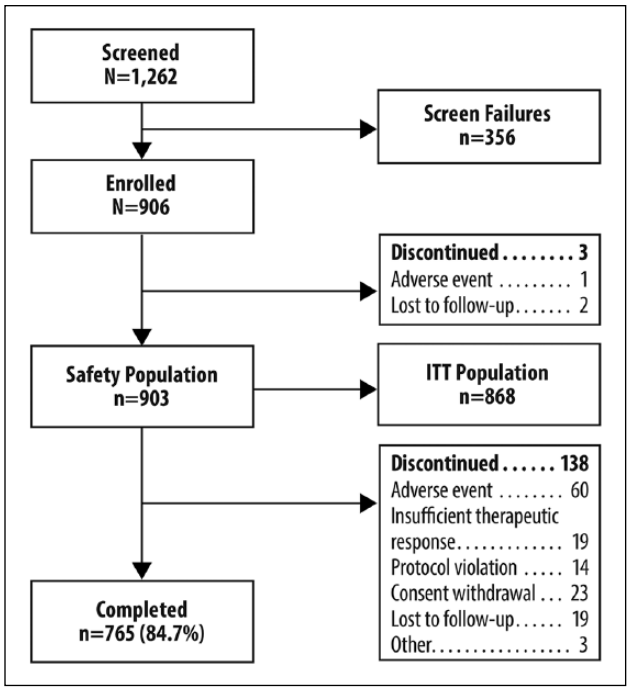

Figure 1. Trial MEM-MD-91 Study Flow.
ITT: intention-to-treat.

Only episodic use of local anesthetics, antacids, antibiotics, antidiarrheal preparations, antinauseants (phosphoric acid preparations only), antiviral agents (only Zovirax, Valtrex, and Famvir), cough/cold preparation (except dextromethorphan), and vaccines was allowed. Chronic use of the following drugs was allowed: anorectics, anticonvulsants (excluding topiramate, zonisamide, and lamotrigine), antidepressants, antiobesity agents (Xenical and Alli only), antipsychotics, reproductive hormones, thyroid hormone replacement therapy (only if stable for at least 6 months prior to lead-in study), antihypertensives, psychotropic drugs not otherwise specified, and stimulants. The dose of drugs with central nervous system activity must have been stable for at least 30 days prior to screening and were to remain stable throughout the study. Dose increases for concomitant medications were prohibited during the study, but dose reductions were allowed upon consultation with the Sponsor Study Physician. There were no dietary restrictions.

Participant disposition and baseline characteristics

In open-label trial MEM-MD-91, a total of 1262 children were screened, 906 enrolled, and 903 received ⩾1 weight-based open-label memantine-ER dose. A total of 868 participants had ⩾1 post-visit SRS total raw score and were included in the intention-to-treat (ITT) population (Figure 1); 765 (84.7%) completed the trial. Similar percentages of participants with autistic disorder (83.3%), Asperger's disorder (88.1%), and PDD-NOS (86.6%) completed the study. Baseline demographics were similar between ASD subtypes (Supplemental Material 1). SRS total raw scores at baseline were similar between autistic disorder and PDD-NOS subgroups, but numerically higher in those with Asperger's disorder (Supplemental Material 1). Mean (standard deviation (SD)) treatment duration was similar between weight-based treatment groups (Table 2) and slightly shorter among those with autistic disorder (92.3 (38.6) days) versus either Asperger's disorder (98.8 (45.4) days), or PDD-NOS (99.5 (45.3) days). A total of 84.3% of participants were taking concomitant medications and supplements, most commonly (⩾10.0%) multivitamins (14.7%), ibuprofen (13.0%), paracetamol (11.7%), risperidone (10.2%), and loratadine (10.1%).

In MEM-MD-68, participants must have had ⩾12 weeks of open-label treatment and met the confirmed responder criterion in study MEM-MD-91 to participate in this 12-week, randomized, double-blind, placebo-controlled withdrawal study. Of 479 (92.6%) confirmed responders from lead-in study MEM-MD-91 who were randomized, 477 received ⩾1 dose of double-blind study medication, and 471 participants had ⩾1 post-baseline SRS total raw score assessment and were included in the ITT population (Figure 2). A total of 160 participants were randomized to placebo, 158 to their full memantine dose received during MEM-MD-91 and 161 to a reduced memantine dose (at least 50% reduction). Overall, 30.1% completed the study and 65.8% discontinued due to LTR (Supplemental Material 2). Mean duration of exposure was comparable across treatment groups (Table 2), and 80.9% of participants were taking concomitant medications and supplements, most commonly (⩾10.0%) melatonin (16.4%), multivitamin (13.4%), and loratadine (10.1%). Baseline demographics were comparable among the ASD subtypes (Supplemental Material 1) and across treatment groups (Supplemental Material 2). While mean SRS total raw scores were similar across ASD subtypes (Supplemental Material 1) and between treatment groups (Supplemental Material 2), the overall mean SRS total raw score at baseline for the ITT population (69.4 ± 25.2 SD) was approximately 40 points lower than baseline of lead-in study MEM-MD-91 (109.8 ± 24.0 SD; ITT), as expected given the design and sequence of the trials.

In open-label trial MEM-MD-69, 749 participants were screened and 747 received ⩾1 dose of study medication (safety population). A total of 81 (10.8%) completed the study by the time of early termination (31 January 2014; see Studies and procedures). As a result of early study termination, 582 participants discontinued (Figure 3) and thus full evaluations of efficacy outcomes were not performed. Baseline demographics were generally comparable across ASD subtypes (Supplemental Material 1), and 83.8% of participants were taking concomitant medications and

Table 2. Summary of results.

		MEM-MD-91 (NCT01592786)	MEM-MD-68 (NCT01592747)			MEM-MD-69 (NCT01592773)
			PBO[a]	Full[b]	Reduced[c]	
Treatment duration, mean ± SD, days (safety population)		95.1 ± 41.9	42.7 ± 29.9	44.1 ± 30.8	46.3 ± 30.9	203.0 ± 74.9
MD-91/69	Group A: ⩾60 kg; max 15 mg/day	92.4 ± 41.8	N/A			–
MD-91/69	Group B: 40–59 kg; max 9 mg/day	96.4 ± 46.2	N/A			–
MD-91/69	Group C: 20–39 kg; max 6 mg/day	94.9 ± 40.1	N/A			–
MD-91/69	Group D: < 20 kg; max 3 mg/day	94.8 ± 50.2	N/A			–
Final daily dose, mean ± SD, mg/day (safety population)						
MD-91/69	Group A: ⩾60 kg; max 15 mg/day	14.1 ± 2.7 (n = 70)	N/A			14.7 ± 1.2 (n = 63)
MD-91/69	Group B: 40–59 kg; max 9 mg/day	8.6 ± 1.3 (n = 227)	N/A			9.1 ± 2.0 (n = 188)
MD-91/69	Group C: 20–39 kg; max 6 mg/day	5.8 ± 0.8 (n = 589)	N/A			6.2 ± 1.2 (n = 482)
MD-91/69	Group D: < 20 kg; max 3 mg/day	3.0 ± 0.0 (n = 17)	N/A			3.9 ± 1.4 (n = 14)
	Full-dose memantine ER[d]	N/A	7.3 ± 2.52			N/A
	Reduced dose memantine ER[e]	N/A	3.3 ± 1.0 (n = 160)			N/A
MD-68	Group A: 15 mg/day reduced to 6 mg/day	N/A	6.0 ± 0.0 (n = 20)			N/A
MD-68	Group B: 9 mg/day reduced to 3 mg/day	N/A	3.0 ± 0.0 (n = 35)			N/A
MD-68	Group C: 6 mg/day reduced to 3 mg/day	N/A	3.0 ± 0.2 (n = 102)			N/A
MD-68	Group D: 3 mg/day reduced to 3 mg every other day	N/A	1.5 ± 0.0 (n = 3)			N/A
SRS total raw score change from baseline, mean ± SD (OC, ITT)		−28.2 ± 25.2	PBO[a,d,e]	Full[b,d,e]	Reduced[c,d,e]	−32.4 ± 26.4
Autistic disorder		−27.1 ± 25.2	−12.2 (10.9)	−10.2 (14.2)	−13.5 (17.2)	–
Asperger's disorder		−30.8 ± 27.1	−8.0 (10.0)	−25.7 (18.4)	−13.6 (14.9)	–
PDD-NOS		−29.8 ± 22.6	−10.3 (22.8)	−18.6 (22.7)	−15.5 (26.1)	–
Proportion of participant with LTR (ITT), % (n/N)			PBO[a]	Full[b]	Reduced[c]	
Autistic disorder		N/A	73.0 (73/100)	64.3 (63/98)	66.7 (66/99)	N/A
Asperger's disorder		N/A	60.0 (18/30)	73.1 (19/26)	70.0 (21/30)	N/A
PDD-NOS		N/A	64.3 (18/28)	69.0 (20/29)	67.7 (21/31)	N/A
SRS mean change from baseline among confirmed responders (week 12), mean ± SD (OC, ITT)						
MD-91	Group A: ⩾60 kg; max 15 mg/day	−30.7 ± 23.0	N/A			N/A
MD-91	Group B: 40–59 kg; max 9 mg/day	−25.7 ± 25.9	N/A			N/A
MD-91	Group C: 20–39 kg; max 6 mg/day	−27.5 ± 27.2	N/A			N/A
MD-91	Group D: < 20 kg; max 3 mg/day	−23.6 ± 23.5	N/A			N/A

(Continued)

Table 2. (Continued)

	MEM-MD-91 (NCT01592786)	MEM-MD-68 (NCT01592747)			MEM-MD-69 (NCT01592773)
		PBO[a]	Full[b]	Reduced[c]	
SRS total score—all participants (ITT) at study end	OC	PBO[a] (LOCF)	Full[b] (LOCF)	Reduced[c] (LOCF)	OC
Mean (SD)	79.2 (28.2)	83.4 (28.5)	88.6 (32.6)	82.3 (31.3)	69.6 (26.9)
25th percentile	59.0	64.0	69.0	58.0	50.0
50th percentile	78.0	82.0	89.0	83.0	70.0
75th percentile	99.5	104.0	109.0	103.5	88.0

ITT: intention-to-treat; N/A: not applicable, PDD-NOS: pervasive developmental disorder-not otherwise specified; OC: observed cases; SD: standard deviation; SRS: Social Responsiveness Scale; ER: extended release; LTR: loss of therapeutic response; LOCF: last observation carried-forward; "–" indicates data unavailable (not collected or not analyzed), PBO: placebo.
Treatment duration was calculated as the number of days from the date of the first dose of double-blind investigational product to the date of the last dose of double-blind investigational product (inclusive).
[a]Switched at randomization.
[b]Same weight-based memantine-ER dose from MEM-MD-91 was continued.
[c]Weight-based memantine dose from MEM-MD-91 was reduced by ⩾50% at randomization; 15, 9, 6, and 3 mg/day in MEM-MD-91 were reduced to 6 mg/day, 3 mg/day, 3 mg/day, and 3 mg every other day, respectively.
[d]Change from baseline of this study, before first dose of double-blind treatment.
[e]Change from baseline at week 12.

supplements, most commonly (⩾10.0%) melatonin (17.0%), multivitamin (15.9%), ibuprofen (11.4%), risperidone (10.6%), and paracetamol (10.3%). Mean SRS total raw score at visit 1 (extension baseline) was 86.7 ± 29.5 (safety population), which was approximately 21 points lower than baseline of the lead-in study (108.4 ± 24.5). SRS total raw scores were numerically greater among those with Asperger's disorder versus either autistic disorder or PDD-NOS (Supplemental Material 1). Mean (SD) duration of memantine treatment during this extension study was 203 (74.9) days (Table 2); mean treatment duration from the first dose of memantine in the lead-in studies was 325.3 (96.2) days.

Dosing

Dosing schemes are described in Table 1. Briefly, open-label memantine-ER was administered by weight in trials MEM-MED-91 and MEM-MD-69, and participants were divided into four weight groups: group A, ⩾60 kg; group B, 40–59 kg; group C, 20–39 kg; and group D, <20 kg. The maximum daily dosage of memantine allowed in each group was 15, 9, 6, and 3 mg/day in groups A, B, C, and D, respectively. As pediatric patients are expected to gain weight during the course of development, study participants could be reassigned to the next higher weight group during the course of the study (per prespecified criteria) to maintain drug exposure levels that were considered therapeutically equivalent if a participant's weight deviated significantly over time.

In the double-blind study (MEM-MD-68), participants were randomized 1:1:1 to memantine-ER full-dose, memantine-ER reduced dose (to assess dose response per FDA request), or placebo. Participants randomized to the full-dose arm received the same weight-based open-label memantine dose received in MEM-MD-91. In the reduced-dose arm, the weight-based memantine dose received in MEM-MD-91 was reduced by ⩾50%. As such, the maximum memantine dosages allowed in the reduced-dose arm were 6 mg/day, 3 mg/day, 3 mg/day, and 3 mg every other day for participants previously assigned to groups A, B, C, and D in MEM-MD-91. Participants randomized to placebo were switched from their weight-based open-label memantine dose to placebo at randomization. Premier, Inc. provided Interactive Web Response System (IWRS) services for randomization and investigational-product dispensing for all countries.

Efficacy assessments

All studies utilized the SRS (Constantino et al., 2003; Constantino & Gruber, 2012), the Children's Communication Checklist, Second Edition (CCC-2) (Bishop, 2006), the CGI (Guy, 1976), and the Aberrant Behavior Checklist–Community Version (ABC-C) (Aman, Singh, Stewart, & Field, 1985).

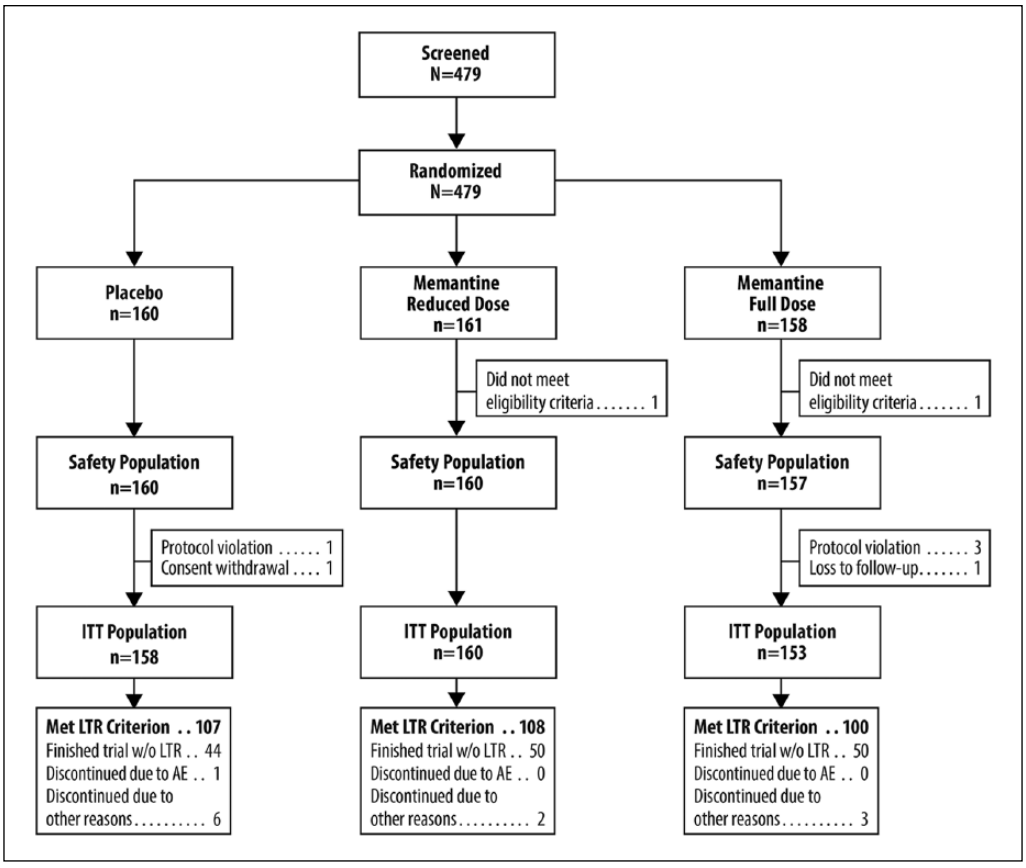

Figure 2. Trial MEM-MD-68 Study Flow.
ITT: intention-to-treat, LTR: loss of therapeutic response.

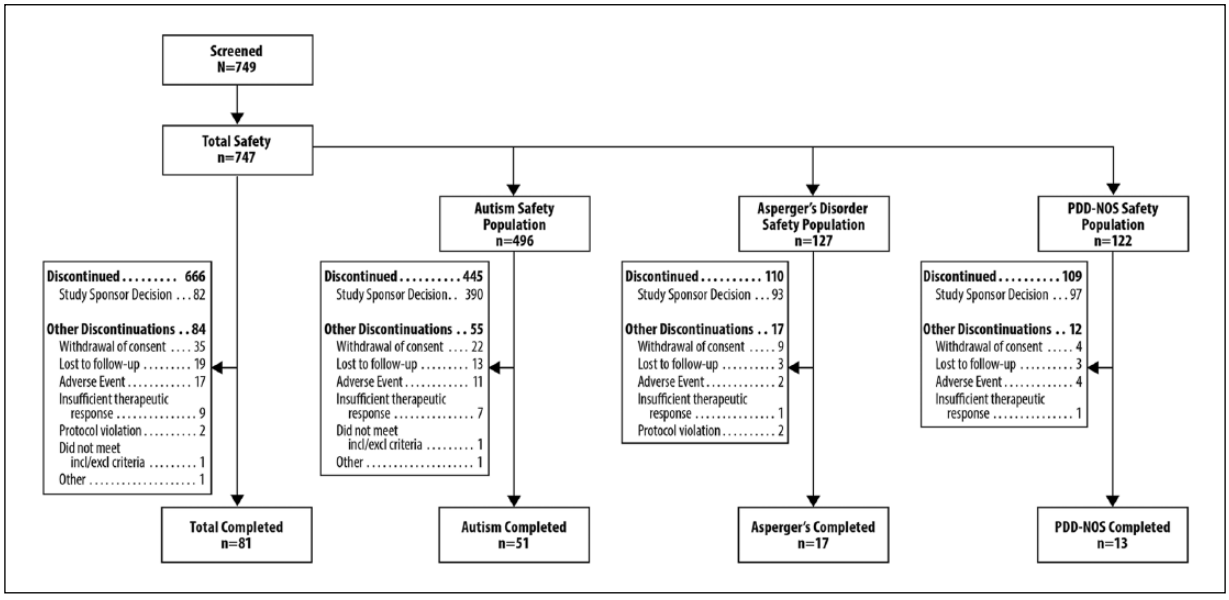

Figure 3. Trial MEM-MD-91 Study Flow.

The SRS is a 65-item caregiver-rated assessment consisting of five subscales to assess social abilities: social awareness, social cognition, social communication, social motivation, and autistic mannerisms. Each item is rated from 0 to 3 in a Likert-type response format with higher scores indicating greater social impairment.

The SRS measures the severity of social communication deficits as they occur in natural environments. The SRS is a sensitive measure (i.e. it strongly correlates with *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criterion scores) (Constantino et al., 2003) and has been found to have good internal consistency reliability and test–retest reliability in younger and older individuals (Pine, Luby, Abbacchi, & Constantino, 2006). The SRS has been used as a primary measure of response to intervention in several other clinical trials (Aman et al., 2016; Constantino et al., 2003; Parker et al., 2017; Yatawara, Einfeld, Hickie, Davenport, & Guastella, 2016).

The CCC-2 is a validated, norm-referenced, and caregiver-rated scale evaluating difficulties children may have that can affect communication (items 1–50) and strengths that children may have when communicating with others (items 51–70). The 10 subscales assess speech, syntax, semantics, coherence, initiation, scripted language, context, nonverbal communication, social relations, and interests; rated by an informant. The total of 70 items (seven per subscale) is rated from 0 to 3 with higher scores indicating greater impairment.

The Clinical Global Impression (CGI) scale compares pre-treatment ratings of severity (Clinical Global Impression–Severity scale (CGI-S)) with ratings of improvement after start of therapy (Clinical Global Impression–Improvement scale (CGI-I)). Using the same methodology as specified in the original CGI (Guy, 1976), the CGI rater was a clinician who provided a global impression of severity (CGI-S) based on overall severity, as well as on each of the domains of social interaction, communication, integrated social interaction and communication, stereotyped behaviors and restricted interests, associated maladaptive behaviors, and daily function. The ratings for each CGI-S evaluation range from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The CGI-I was similarly conducted on overall improvement, as well as the domains of social interaction, communication, integrated social interaction and communication, stereotyped behaviors and restricted interests, associated maladaptive behaviors, and daily function. The ratings for CGI-I range from 1 (marked improvement) to 7 (marked worsening).

The ABC-C is a 58-item questionnaire with five subsections to assess behavioral symptoms of irritability, social withdrawal, stereotypy, hyperactivity/noncompliance, and inappropriate/repetitive speech. Items were rated by an informant and based on behavior observed over the prior 2-week period with higher scores indicating greater impairment.

Safety measures

Safety outcomes included adverse events (AEs), vital signs, laboratory tests, ECG, suicidality, and physical examination.

Statistical analyses

For MEM-MD-91, efficacy analyses were exploratory and based on the ITT population (all who received ⩾1 open-label memantine-ER dose and had ⩾1 follow-up assessment that included a valid SRS during treatment). For MEM-MD-68, efficacy analyses were based on the ITT population, defined as all who received ⩾1 dose of double-blind study medication (memantine-ER or placebo) and had ⩾1 post-baseline SRS total raw score in the double-blind period. For MEM-MD-69, exploratory efficacy analyses were based on all participants who received ⩾1 dose of open-label memantine-ER and had ⩾1 post-baseline assessment.

For MEM-MD-68, the primary efficacy parameter—proportion of participants with LTR on the SRS by study end—was analyzed using the Cochran–Mantel–Haenszel test, controlling for ASD subtype. The secondary endpoint, time-to-first LTR, was analyzed using Kaplan–Meier estimates; between-group comparisons for time-to-first LTR were performed using the log-rank test stratified by ASD subtype; hazard ratio and 95% confidence interval (CI) were estimated using a Cox model with treatment group and ASD subtypes as explanatory variables. Change from baseline to week 12 for each CCC–2 subscale (secondary endpoint) was performed using an analysis of covariance model with treatment group and ASD subtype as factors and baseline score as covariate, using the last observation carried-forward (LOCF) approach. At least 450 participants (150/treatment arm) were planned to detect a clinically meaningful difference in LTR with 85% power using a two-sided Chi-square test at 5% significance level. This sample size was considered convincingly large to detect a clinically meaningful difference in LTR, as agreed upon with the FDA (8 May 2013).

For MEM-MD-91 and MEM-MD-69, exploratory efficacy measures were evaluated using descriptive statistics for all continuous variables (SRS total raw score and subscales, ABC subscales, and CCC-2 subscales) and frequency distributions (number and percentage) for categorical variables (CGI-severity (CGI-S) and CGI-I subscales) by weight group using an observed case approach. No covariate-adjusted analyses were conducted. Plots of cumulative distribution function change from baseline in SRS total raw score at the end of each study were performed by ASD subtype. The baseline for each MEM-MD-69 efficacy parameter was baseline of the first lead-in study. To provide a sufficient number of responders for enrollment in MEM-MD-68, approximately 800–900 participants would be enrolled in MEM-MD-91.

Safety parameters were summarized by means of descriptive statistics for the safety population, defined as all randomized participants who received ⩾1 dose of double-blind treatment (MEM-MD-68) or ⩾1 dose of open-label memantine-ER (MEM-MD-91, MEM-MD-69).

Table 3. Treatment emergent adverse events ⩾3% in any treatment group (safety population).

Incidence of TEAEs, n (%)[a]	MEM-MD-91 (NCT01592786)	MEM-MD-68 (NCT01592747)			MEM-MD-69 (NCT01592773)
		PBO[b]	Full[c]	Reduced[d]	
Participants with ⩾1 TEAE	*578 (64.0)*	50 (31.3)	54 (34.4)	52 (32.5)	*424 (56.8)*
Headache	72 (8.0)	3 (1.9)	2 (1.3)	2 (1.3)	41 (5.5)
Nasopharyngitis	57 (6.3)	2 (1.3)	3 (1.9)	2 (1.3)	55 (7.4)
Pyrexia	52 (5.8)	2 (1.3)	2 (1.3)	3 (1.9)	47 (6.3)
Irritability	49 (5.4)	8 (5.0)	4 (2.5)	5 (3.1)	17 (2.3)
Cough	42 (4.7)	2 (1.3)	3 (1.9)	3 (1.9)	23 (3.1)
Vomiting	41 (4.5)	3 (1.9)	0	6 (3.8)	51 (6.8)
Upper respiratory tract infection	34 (3.8)	0	3 (1.9)	1 (0.6)	37 (5.0)
Gastroenteritis viral	32 (3.5)	0	3 (1.9)	3 (1.9)	29 (3.9)
Psychomotor hyperactivity	27 (3.0)	2 (1.3)	1 (0.6)	1 (0.6)	4 (0.5)
Agitation	23 (2.5)	2 (1.3)	2 (1.3)	5 (3.1)	9 (1.2)
Anxiety	15 (1.7)	5 (3.1)	0	1 (0.6)	16 (2.1)

Italic font is used to set apart all participants with a TEAE from those with the specified TEAEs. TEAE: treatment-emergent adverse event, PBO: placebo.
[a]Reported by ⩾3% in any treatment group across all three studies.
[b]Switched at randomization.
[c]Same weight-based memantine extended-release (ER) dose from MEM-MD-91 was continued.
[d]Weight-based memantine dose from MEM-MD-91 was reduced by ⩾50% at randomization; 15, 9, 6, and 3 mg/day in MEM-MD-91 were reduced to 6 mg/day, 3 mg/day, 3 mg/day and 3 mg every other day, respectively.

Descriptive statistics are presented for continuous variables (change from baseline in SRS total raw score and subscales, change from baseline in ABC subscales, and change from baseline in CCC-2 subscales) and frequency distributions are presented for categorical variables. In MEM-MD-68, between-group comparability was tested using a two-way analysis of variance with treatment group and ASD subtype as factors for categorical variables and the Cochran-Mantel-Haenszel test controlling for ASD subtype for categorical variables.

Results

Because of the design and sequence of the three studies, SRS scores at baseline were substantially higher in the lead-in open-label study (MEM-MD-91) than in the double-blind withdrawal study (MEM-MD-68), which is selected for stabilized responders from MEM-MD-91. Baseline scores were intermediate in the open-label follow-on study (MEM-MD-69), possibly reflecting regression to the mean among the participants in MEM-MD-68. Mean age and other baseline characteristics were comparable between trials (Supplemental Material 1). The proportion of participants diagnosed with autistic disorder was approximately two-thirds of the population with the remainder split nearly equally between Asperger's disorder and PDD-NOS (Supplemental Material 1).

Trial MEM-MD-91

Confirmed responders. At week 9 (first post-baseline SRS assessment), 543 (62.6%) responded to treatment and 517 (59.6%) were confirmed SRS responders. The percentage of confirmed responders was similar between autistic disorder (57.4%) and Asperger's disorder (60.9 %) and numerically greater in PDD-NOS (66.7%). Mean (SD) time to confirmed response was 95.9 (21.0) days for autistic disorder, 98.3 (22.9) days for Asperger's disorder, and 102 (30.5) days for PDD-NOS.

Safety. A total of 64% of participants had ⩾1 treatment-emergent adverse event (TEAE) (34.3% mild, 27.7% moderate, and 2.0% severe intensity) with similar incidences across ASD subtypes; the most commonly reported TEAEs (>5.0%) were headache, nasopharyngitis, pyrexia, and irritability (Table 3). AEs leading to premature discontinuation occurred in 60 (6.6%) participants, with a slightly higher percentage among those with autistic disorder (7.8%) than with Asperger's disorder (4.4%) or PDD-NOS (4.4%). Serious adverse events (SAEs) occurred in 6 (0.7%) participants: abnormal behavior (n=2), accidental exposure (single incident of accidental ingestion of study drug, reported by the investigator as an SAE), constipation, disinhibition, and gastroenteritis (n=1 each). Three participants discontinued; of the three that continued, memantine was reduced only in the participant who experienced gastroenteritis.

Exploratory efficacy. Mean improvements in SRS total raw scores two to three times the 10-point minimum used to confirm treatment responders were observed from baseline to the end of the study for the ITT population and for each ASD subtype; similar results were observed among confirmed responders at week 12 (Table 2). At study end, the

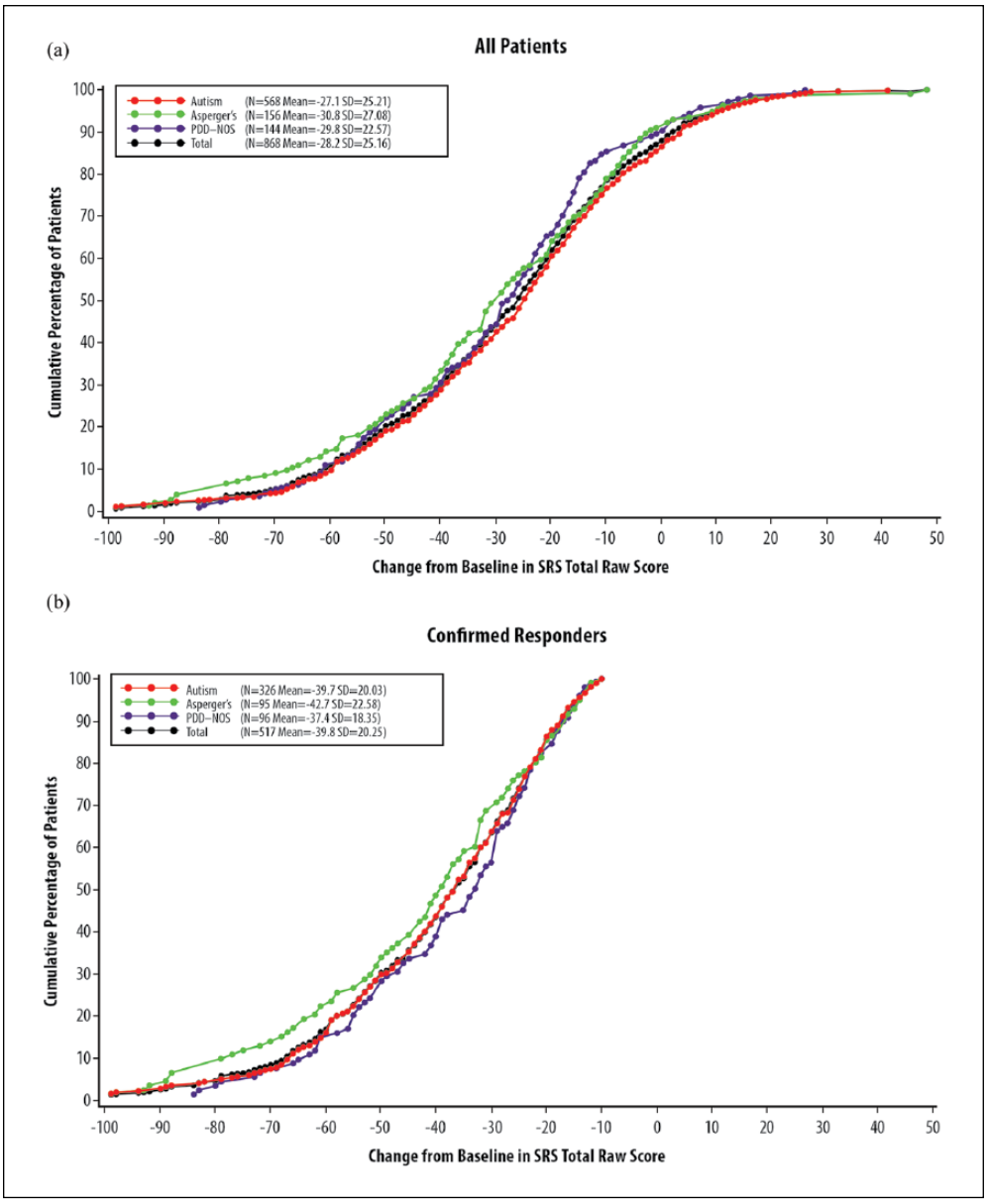

Figure 4. Cumulative percentage of patients achieving a 10-point minimum improvement in SRS total raw score from baseline among a) all patients, and b) confirmed responders (Open-label Trial MEM-MD-91).
CDF: cumulative distribution function, PDD-NOS: pervasive developmental disorder-not otherwise specified, SRS: social responsiveness scale.

mean (SD) SRS total raw score for all participants was 79.2 (28.2); the 25th, 50th, and 75th percentiles were 59.0, 78.0, and 99.5 (Table 2). Among confirmed responders, mean (SD) SRS total raw score at study end was 70.2 (25.3) with 25th, 50th, and 75th percentiles of 53.0, 68.0, and 87.0.

The cumulative percentages of participants achieving a −10 to −80 point change from baseline in SRS total raw score at week 12 was slightly greater among those with Asperger's disorder and PDD-NOS versus autistic disorder (Figure 4(a)). Approximately 75% of all participants achieved ⩾10-point improvement in SRS total raw score (Figure 4(a)). Among confirmed responders, the cumulative percentage of participants achieving an SRS total raw score change from baseline of approximately −30 to −90 points at week 12 was greatest among those with Asperger's disorder and autism versus PDD-NOS (Figure 4(b)).

At the end of the 50-week study, treatment with memantine-ER conferred greater numerical mean improvements from baseline on the ABC subscales, the CCC-2 subscales, the CGI-S, and the CGI-I (Supplemental Material 3).

MEM-MD-68

Primary efficacy variable. A similar proportion of participants in each treatment group experienced LTR during the 12-week treatment period: 69.0% placebo, 66.7%

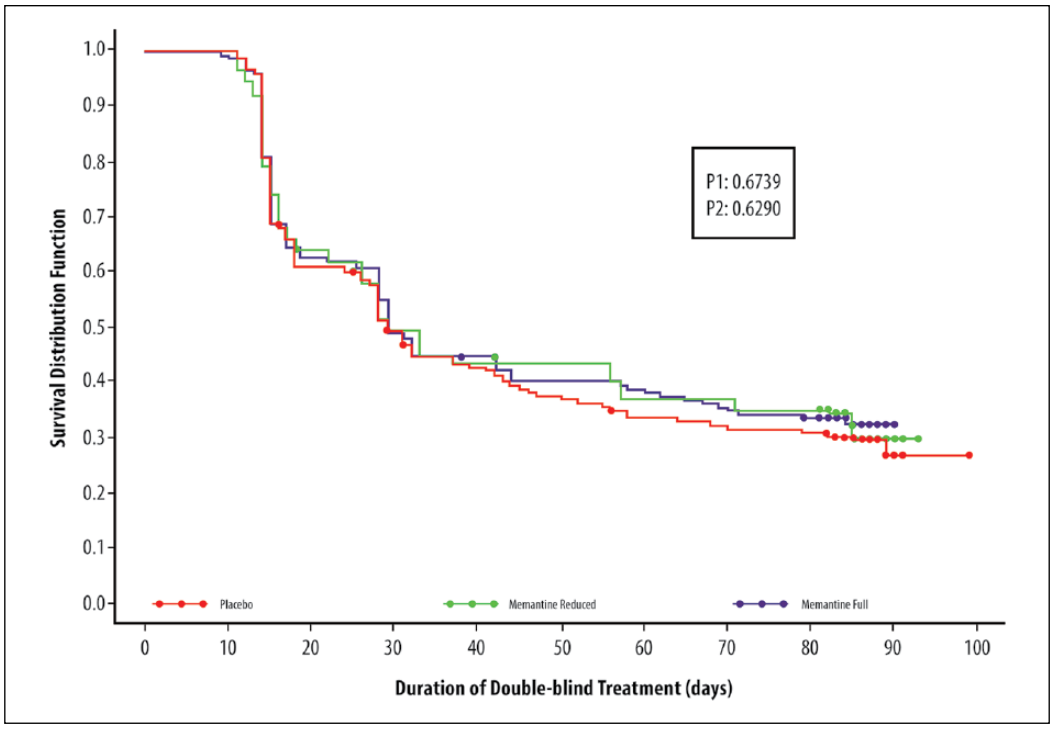

Figure 5. Survival distribution for LTR by treatment group (Double-blind, Placebo-controlled trial MEM-MD-68).
P1 is the *P* value for the treatment comparison between memantine full-dose and placebo based on log-rank test stratified by Autism Spectrum Disorder subtype.
P2 is the *P* value for the treatment comparison between memantine reduced-dose and placebo based on log-rank test stratified by Autism Spectrum Disorder subtype.

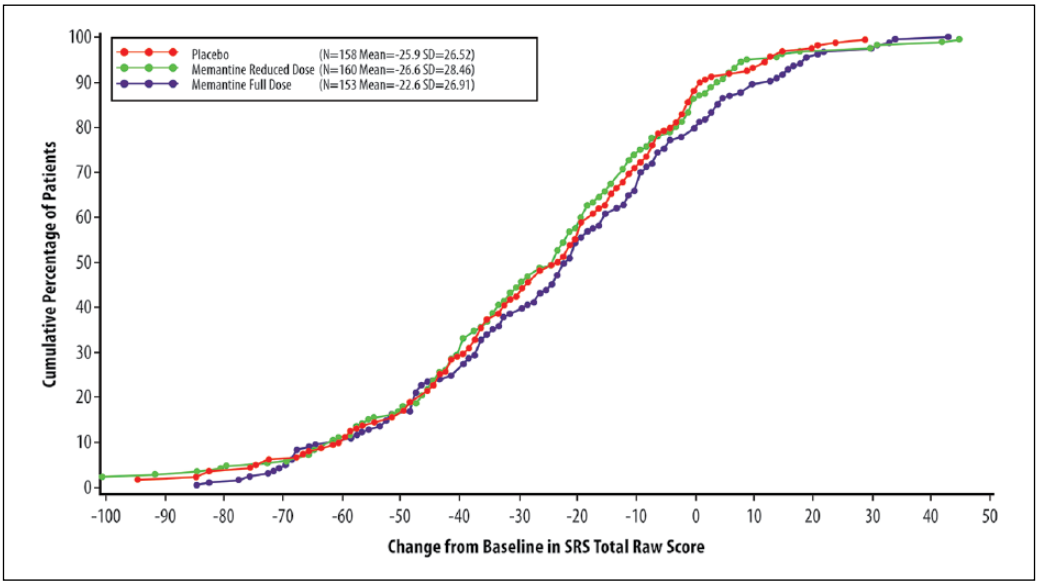

Figure 6. Cumulative percentages of patients achieving a given change from baseline in SRS total raw score (Double-blind, Placebo-controlled trial MEM-MD-68).
CDF: cumulative distribution function, SRS: social responsiveness scale.

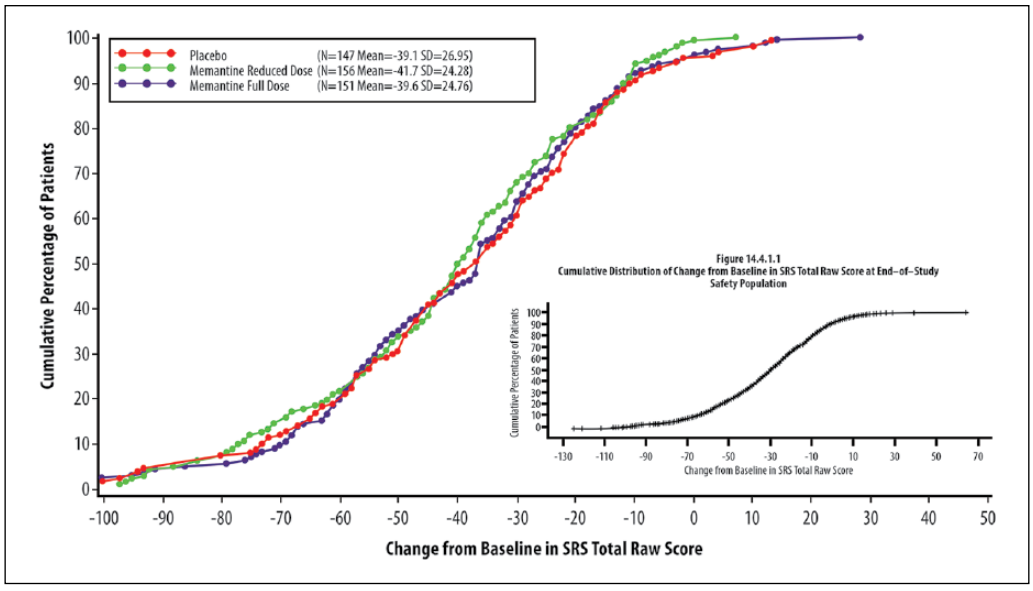

Figure 7. Cumulative percentages of patients achieving a given change from baseline in SRS total raw score by treatment group and overall (inset) (Open-label Trial MEM-MD-69).
CDF: cumulative distribution function, SRS: social responsiveness scale.

full-dose, and 67.5% reduced-dose memantine (ITT). Odds ratios for LTR versus placebo were 1.1 (95% CI: 0.7, 1.8; p = .66) for the full-dose group, and 1.1 (95% CI: 0.7, 1.7; p = .78) for the reduced-dose group. A numerically greater proportion of placebo-treated participants with autistic disorder experienced LTR (73.0%) versus full-dose (64.3%) and reduced dose (66.7%), indicating a trend in favor of memantine ER for this ASD subtype. The opposite numerical trend was observed for Asperger's disorder: 60.0% placebo, 73.1% full-dose, and 70.0% reduced dose. In PDD-NOS participants, the proportions of participants experiencing LTR were comparable between dose groups (Table 2).

Secondary efficacy variables. The median time to first LTR was 29 days (95% CI: 28, 42) for the placebo group, and 30 days (95% CI: 28, 44) and 33 days (95% CI: 28, 56) for the memantine full-dose and reduced-dose groups, respectively. Regardless of treatment group, approximately 33% of participants met LTR criterion by the first visit (~2 weeks; Figure 5). There were no significant changes from baseline to week 12 on any CCC-2 subscale between the placebo and memantine treatment groups (LOCF).

Additional efficacy assessments. At week 12, no clinically meaningful changes from baseline were observed between treatment groups on the additional efficacy variables, CGI-I and CGI-S, ABC-C, or SRS subscales and SRS total raw score. Mean (SD) changes from baseline at week 12 in SRS total raw scores ranged from −8.0 (10.0) in the placebo-treated Asperger's group to −25.7 (18.4) in the full-dose Asperger's group (Table 2). At week 12, the 25th, 50th, and 75th percentiles for mean SRS total raw scores were generally comparable between treatment groups (Table 2).

Overall, there were negligible differences between treatment groups in the cumulative percentage of participants achieving improvement in SRS total raw scores by study end; however, there appeared to be a trend toward smaller cumulative percentages of participants in the memantine full-dose group versus either the placebo or reduced-dose memantine groups in which a worsening of +10 to +20 points on SRS total score from baseline was observed (Figure 6).

Safety. The percentages of participants with TEAEs were similar across treatment groups, with 31.3%, 34.4%, and 32.5% of the placebo and full- and reduced-dose memantine groups, respectively, reporting at least one TEAE. The most common TEAEs were irritability, vomiting, agitation, and anxiety (Table 3). Most TEAEs were mild to moderate in intensity. A total of six participants reported a severe TEAE: two with reduced memantine and four with placebo. One participant in the placebo group (Asperger's disorder) discontinued the study due to an AE (irritability), and one participant in the reduced-memantine group reported an on-therapy SAE (furuncle of the nasal bridge) that was unrelated to study drug.

MEM-MD-69

Safety. A total of 56.8% of participants reported ⩾1 TEAE (31.6% mild, 22.9% moderate, and 2.3% severe). The most commonly reported TEAEs (>5.0%) were nasopharyngitis, vomiting, pyrexia, and headache (Table 3). A total of 17 participants discontinued due to an AE:

aggression (0.5%), abnormal behavior (0.4%), anxiety (0.4%), irritability (0.3%), and weight increased (0.3%). Eight (1.1%) participants reported a total of 11 on-therapy SAEs (all n = 1): abdominal pain (periumbilical), abdominal pain (right lower quadrant), abnormal behavior, appendicitis, dehydration, dysphoria, foreign body, homicidal ideation, rectal prolapse, suicidal ideation, and vomiting. Three participants (all with Asperger's disorder) experienced a behavior-related SAE: dysphoria (treatment related), homicidal and suicidal ideation (not treatment related), and abnormal behavior (not treatment related).

Exploratory efficacy. By the end of the study, there was a mean ± SD decrease (improvement) in SRS total raw score of 32.4 ± 26.4 from baseline of the first lead-in study (N = 747; safety population and observed cases). Mean (SD) SRS total raw score at study end was 69.6 (26.9), with 25th, 50th, and 75th percentiles of 50.0, 70.0, and 88.0 for all participants who enrolled in MEM-MD-69 after MEM-MD-68 (Table 3; N = 458; safety population, observed cases). The percentage of participants achieving ⩾10-point improvement in SRS total raw scores was comparable regardless of intervention (Figure 7), and ~90% of participants overall demonstrated improvement (Figure 7 inset).

Efficacy among confirmed responders. Among MEM-MD-91 confirmed responders who were subsequently enrolled into MEM-MD-68 and then into MEM-MD-69 (N = 464, ITT), mean (SD) change from MEM-MD-91 baseline in SRS total raw score at week 48 (n = 106) was −50.0 (26.3). Mean (SD) changes from baseline by prior treatment groups were −53.9 (23.7), −51.4 (24.5), and −45.9 (29.4) for the placebo (n = 31), memantine full-dose (n = 34), and memantine reduced-dose (n = 41), respectively.

Compared with baseline, fewer participants had an overall CGI-S rating of severely ill (1.3% vs 7.8%), markedly ill (9.4% vs 32.0%), or moderately ill (37.9% vs 48.1%) at study end. Numerical improvements from baseline were observed for the ABC subscales at study end with the greatest mean (SD) change from baseline noted in hyperactivity (−5.9 (8.6), and the least change observed for inappropriate speech (−1.2 (2.6)).

Discussion

Discovering effective interventions for child neurodevelopmental disorders remains an ambitious and important endeavor, as early intervention in both psychiatric and behavioral disorders (including ASD, attention deficit hyperactivity disorder (ADHD), depression, and anxiety) may alter long-term prognoses (Grabb & Gobburu, 2017). Despite the growing efforts of the scientific community to develop and empirically test new interventions for ASD and related disorders, an effective therapy to treat or cure the core ASD symptoms remains elusive.

Conducting clinical trials in children is fraught with many operational, physiological, and ethical challenges (Kern, 2009). Clinical trials in children with ASD may be particularly challenging given the heterogeneity of the disorder, including the range of symptom severity and multifaceted presentation in each individual. The potential for overestimated response rates on both clinician and caregiver-rated scales—driven by observer/rater biases, the psychometric properties of existing measures, and their sensitivity to change, beliefs of parents, and their enthusiasm for effective interventions (Masi, Lampit, Glozier, Hickie, & Guastella, 2015)—can complicate the interpretation of clinical trial results in this patient population. Although many clinical trials in ASD and other neurodevelopmental disorders are unsuccessful for numerous reasons, the findings from such trials should neither be completely dismissed nor presumed to be invalid (Jeste & Geschwind, 2016). The statistically insignificant findings of the double-blind, placebo-controlled trial of memantine ER in ASD individuals presented here are no exception.

Like the previously reported double-blind trial MEM-MD-57A in which a high placebo-response was observed (Aman et al., 2016), there was a strong placebo response in MEM-MD-68 withdrawal study that may have obscured a therapeutic effect of memantine. A clinically significant improvement of ⩾10 points from baseline in SRS total raw scores was evident in both the full- and reduced-dose memantine groups; however, most placebo-treated groups also reported clinically meaningful improvements (excepting placebo-treated participants in the Asperger's group). As participants in MEM-MD-68 had a very high response rate at the end of the open-label lead-in trial (all were confirmed responders), this enriched population may be particularly susceptible to placebo effects and/or high expectations among caregivers, *suggesting a need for a higher threshold for the responder criterion or a larger change on the SRS (>10-point increase in score) to define LTR.*

Although a change of 10 points or more on the SRS total raw score is considered a potentially significant improvement, the determination of an MCID of the SRS has not been formally examined in individuals with autism. In the absence of this determination, relating the results of the present investigation to the SD of the distribution of standardization sample and to the standard error of measurement (SEM) can be helpful in interpreting the results. Based on the SRS manual, the SD of parent report for the entire standardization sample (N = 1011) was 24.6 with a mean of 31.2 and an SEM of 6.29. Therefore, the findings reported here are unlikely to change while using either the SD or the SEM as threshold for change on the SRS.

While high expectations may have contributed to higher SRS scores in the placebo group, regression to the mean may have contributed to lower scores. As SRS scores were particularly high in this enriched population, regression to the mean over prolonged treatment likely occurred, as has

been shown in other trials conducted in children (Milich, Roberts, Loney, & Caputo, 1980; Werry, Sprague, & Cohen, 1975). Furthermore, the nocebo effect—that individuals may have perceived a loss of efficacy in the double-blind study and thus assumed they were receiving placebo, leading to further losses of therapeutic benefit—may have occurred. Thus, the LTR criterion used in these trials may simply not have been an appropriate measure in this patient population known to have a high placebo response rate. Indeed, these results suggest the need to perhaps refine the definition of LTR so that possible treatment effects would not be obscured. For instance, including a requirement that participant scores revert to baseline prior to the first dose of double-blind drug, or that a ⩾50% reduction in SRS improvement must occur, could add to the sensitivity of the LTR criterion. The results presented here underscore the need to develop an MCID for the SRS and SRS subscales to fully characterize response to treatment, as has been done for instruments in other therapeutic areas.

The large, mean improvements in SRS scores from baseline to end of open-label treatment (at levels that were three to four times the theorized clinically meaningful improvement level of 10 points) may be further evidence that caregivers had an expectation of success and falsely created treatment responders. If memantine was effective for a subgroup of participants (even though the characteristics of those individuals may not yet be known), these trial results may support the notion that altered glutamatergic signaling is at least partly underlying the poorly understood molecular mechanisms of ASD; perhaps greater success could have been achieved with a higher, flexible-dose range. Although the maximal weight-based dose groups were identified in Part 1 of the MEM-MD-57A trial (N = 12), a previous pilot study of memantine found that memantine doses 10–20 mg/day were well tolerated in pediatric ADHD participants with the 20 mg/day dose conferring greater improvement on efficacy measures than the 10 mg/day dose (Findling et al., 2007). This suggests that the memantine doses used in these ASD studies were possibly inadequate for most trial participants, despite results from a population pharmacokinetic study that suggested the appropriateness of the weight-based memantine ER dosing (Carrothers, Periclou, Khariton, & Ghahramani, 2014). Furthermore, as the concomitant medication profile was consistent across the three trials, a lack of treatment effect may have been masked by concomitant medications or interactions with concomitant medications. Although this scenario is probably unlikely, limiting the use of concomitant medications should be considered when designing future ASD clinical trials.

Despite not achieving a priori endpoints, the double-blind, controlled trial (MEM-MD-68) along with its open-label lead-in study (MEM-MD-91) and the long-term open-label safety study (MEM-MD-69) were successful in many ways. One of the successes of these phase 2 trials was the recruitment of a very wide and diverse study population using a broad array of recruitment strategies (Spera et al., 2014); however, the publicity surrounding this program may have contributed to unrealistic expectations. Such variability in baseline conditions has been previously recognized as possibly contributing to the uncertainty of the outcomes in these trials and other studies of neuropsychiatric disorders (Benedetti, Carlino, & Piedimonte, 2016).

As the manner in which ASD clinical trials are conducted has evolved over the years, the results from this trial program will hopefully inform future decisions when considering the design of large trials of pharmacotherapies in ASD individuals. Future studies may consider possible instrument-specific effects and an MCID, as well as potential caregiver biases and expectations suggested by these results. While the SRS was an appropriate tool at the time these trials were conducted, additional validated scales may better identify effective interventions for ASD.

In conclusion, treatment with memantine-ER in the double-blind, placebo-controlled trial failed to achieve the primary and exploratory efficacy endpoints, as a similar percentage of memantine- and placebo-treated patients experienced LTR and no clinically meaningful changes from baseline were observed between treatment groups on the CGI-I and CGI-S, ABC-C, or SRS subscales and SRS total raw score. Among participants in the initial open-label study, there was a considerable decrease in mean SRS scores from baseline, a change that was presumed to be a clinically important improvement. The reasons for the large improvement are unclear.

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Supplemental material

Supplemental material for this article is available online.

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