RESEARCH ARTICLE

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Donepezil for Treatment of Cognitive Dysfunction in Children With Down Syndrome Aged 10–17

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The objective of this 10-week, randomized, double-blind, placebo-controlled multicenter study was to assess the efficacy and safety of donepezil for the treatment of cognitive dysfunction exhibited by children with Down syndrome (DS). Intervention comprised donepezil (2.5–10 mg/day) in children (aged 10–17 years) with DS of mild-to-moderate severity. The primary measures were the Vineland-II Adaptive Behavior Scales (VABS-II) Parent/Caregiver Rating Form (PCRF) the sum of nine subdomain standardized scores and standard safety measures. Secondary measures included the VABS-II/PCRF scores on the following domains and their respective individual subdomains: Communication (receptive, expressive, and written); Daily Living Skills (personal, domestic, and community); Socialization (interpersonal relationships, play and leisure time, and coping skills), and scores on the Test of Verbal Expression and Reasoning, a subject-performance-based measure of expressive language. At baseline, 129 participants were assigned treatment with donepezil or placebo. During the double-blind phase, VABS II/PCRF sum of the nine subdomain standardized scores, called v-scores, improved significantly from baseline in both groups ($P < 0.0001$), with no significant between-group differences. This trial failed to demonstrate any benefit for donepezil versus placebo in children and adolescents with DS, although donepezil appeared to be well tolerated.

Key words: Down syndrome; cognition; children; donepezil

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INTRODUCTION

Cognitive dysfunction (manifested by below-average IQs, delayed learning and adaptive functioning, and impaired language development) in children with Down syndrome (DS) is a significant unmet therapeutic challenge.

Amyloid precursor protein, which is overproduced in DS, causes degeneration of basal forebrain cholinergic neurons [Salehi et al., 2006]. Other studies link these deficits to a central cholinergic deficit or dysfunction [Kiss et al., 1989; Allen et al., 2000]. In the murine trisomy 16 (TS16) fetal model for DS acetylcholine-positive

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cells are 60–70% less than in littermate controls, without differences between populations in acetylcholinesterase (AChE) and the number of cholinergic neurons is also lower in TS16 fetuses [Kiss et al., 1989; Fiedler et al., 1994]. Cholinergic dysfunction is also observed in immortalized cell lines derived from the TS16 fetal cortex [Allen et al., 2000]. Limited evidence of cholinergic deficit is also available from postmortem studies of infants and children with DS [Casanova et al., 1985; Kish et al., 1989; Florez et al., 1990], while clinical evidence suggests that peripheral cholinergic dysfunction may be centrally mediated in children and young adults with DS [Fernhall and Otterstetter, 2003; Tasdemir et al., 2004; Heffernan et al., 2005].

Two small, open-label trials of cholinesterase inhibitors (ChEIs) have been conducted in children [Heller et al., 2004, 2006a, 2006b; Spiridigliozzi et al., 2007] and one large, double-blind, placebo-controlled trial has been conducted in young adults (aged 18–35) [Kishnani et al., 2009] with DS. These suggested a treatment benefit, measured using the Vineland Adaptive Behavior Scales (VABS) [Sparrow et al., 1984]. Language function, particularly expressive language function, also showed consistent improvement, notable because the expressive language skills of children and adolescents with DS lag behind those of children and adolescents with normal development or other developmental disabilities [Heller et al., 2003]. The studies in children were limited by their size and open-label design. The young adult data suggested that practice/learning effects and floor/ceiling effects limited interpretation, however, the positive findings of the young adult study prompted this study in children.

This randomized, double-blind, placebo-controlled trial was designed to evaluate the efficacy and safety of donepezil in the treatment of cognitive dysfunction exhibited by children with DS. It was hypothesized that a short-term study (dosing over 10 weeks with all participants on a maximum dose for at least 4 weeks) would be sufficient to demonstrate efficacy. The trial was in a relatively large sample of children with DS, is the first of its kind, and attempted to address the limitations of previous studies.

METHODS

This 10-week, multicenter, randomized, double-blind, placebo-controlled phase 2 study (Clinical Trials Registry NCT00754052) aimed to establish proof of concept of the efficacy of donepezil on the cognitive dysfunction exhibited by children and adolescents with DS and to evaluate the safety of donepezil in this population.

The study was approved by the institutional review board of each institution at which participants were enrolled. Written informed consent or verbal assent was obtained from each participant and written informed consent was obtained from the caregiver, who provided patient data.

Randomization of 150 participants was planned to ensure 128 completers, assuming 15% would discontinue. Randomization was stopped at 129 because only 3% had discontinued. Eligible participants were living in the community with a reliable parent or caregiver who agreed to complete the VABS-II Parent/Caregiver Rating Form (PCRF) at all visits and to assure administration of study medication. Participants were male or female, aged 10–17 years at baseline, weighed $\geq$20 kg, were ambulatory or ambulatory-aided, and had a diagnosis of DS documented by chromosome analysis showing free trisomy 21. Robertsonian translocation and mosaic forms of DS were not allowed. Eligibility criteria included a VABS-II/PCRF Adaptive Behavior Composite score $>$55 at screening, consistent with mild-to-moderate intellectual disability. Participants had to be in general good health with no medical conditions that were both clinically significant and unstable and no clinically significant abnormal screening laboratory values. Participants with diabetes, thyroid disease, or a history of seizure disorders were allowed to enroll provided that they were stable on treatment. Female participants of child-bearing potential had to practice an effective method of birth control and were required to have a negative serum pregnancy test at screening, with urine pregnancy tests monitored at remaining study visits.

A current, *primary* psychiatric diagnosis other than DS was not allowed; however, since many children with DS have secondary psychiatric diagnoses, these children were not automatically excluded. Use of psychoactive medications was allowed provided they were not strongly anticholinergic and the dose and usage was stable for $>$3 months prior to screening and during the study. Initiation of, or an increased dose of, psychoactive medication during the study was prohibited and when such medication was required as a rescue medication, the participant was discontinued. Prior ChEI use was allowed if the participant had not been treated in the past 3 months and if treatment was not stopped for lack of tolerability or efficacy or for the sole purpose of enrolling in this study.

Prior to screening, the nature, purpose, and details of the study were explained to each participant and his/her responsible parent or caregiver. Participants and caregivers were informed that they could refuse to enter the study or withdraw from it at any time.

Participants were randomly assigned to treatment with either donepezil or placebo administered as matching liquid formulations of 5 mg/5 ml. The initial dose was 2.5 mg/day (2.5 ml/day), with dose escalations of 2.5 mg/day (2.5 ml/day) increments every 2 weeks (assuming achievement of steady-state levels) to a maximum of 10 mg/day (10 ml/day), according to the participant's weight and the investigator's judgment. However, dose adjustments were permitted for tolerability. Maximum dosing was 2.5 mg/day for participants weighing from $\geq$20 to $<$25 kg, 5 mg/day for participants from 25 to $<$50 kg, and 10 mg/day for participants $\geq$50 kg. The intent was to achieve maximum doses from 0.1 to 0.2 mg/kg/day for at least 4 weeks.

Efficacy and safety evaluations were conducted at baseline and at weeks 4 and 10. The primary efficacy measures were the VABS-II/PCRF Communication, Daily Living Skills, and Socialization domains [Sparrow et al., 2006]. Each domain contains three subdomains, for a total of nine subdomains: receptive, expressive, written; personal, domestic, and community; and interpersonal relationships, play and leisure time, and coping skills, respectively. For each subdomain, raw scores are converted to standardized scores, called v-scores, based on age and a national sample of normal children [mean = 15, standard deviation (SD) = 3]. For each domain, v-scores are summed and converted to standardized domain scores (mean = 100, SD = 15). Standardized domain scores are then summed to form an adaptive behavior composite score, which is converted to a final standardized composite score

(mean = 100; SD = 15). The primary efficacy end point was the mean change from baseline to week 10 in the sum of the VABS-II/PCRF nine subdomain v-scores using the last observation carried forward (LOCF) method to replace missing data. Secondary efficacy variables included additional analyses of the VABS-II/PCRF and a subject-performance-based measure of expressive language function, the Test of Verbal Expression and Reasoning (TOVER) [Heller et al., 2006c]. Safety evaluations included adverse events/serious adverse events (AEs/SAEs), vital signs, physical and neurological examinations, electrocardiograms, and standard laboratory evaluations (hematology, chemistry, urinalysis). Pharmacokinetic (PK; plasma donepezil) and pharmacodynamic [PD; red blood cell acetylcholinesterase inhibition (RBC AChEI)] measures were also obtained.

Statistical Methods

No published data existed from which to reliably estimate treatment effect size for the VABS-II/PCRF. Therefore, a clinically meaningful standard of improvement of 0.5–1 SD on at least one subdomain v-score was used. Assuming a mean difference of 2.0 (and a SD = 4.0) between the two groups' change from baseline in the sum of the nine v-scores, a sample of 64 participants per group (with baseline and at least one postbaseline assessment) would provide approximately 80% statistical power at a two-sided 0.05 alpha level overall.

The primary analysis was performed on the primary efficacy end point using an analysis of covariance model including factors for treatment, final targeted dose (mg/kg), age group (10–13 vs. 14–17 years), and baseline efficacy variable score as covariates. Final targeted dose (mg/kg) is a continuous variable and was defined as the maximum dosing for the participant's weight (as described above) divided by the weight at screening. The primary analysis set for efficacy was the intent-to-treat (ITT) population. All statistical tests were run at an overall 0.05 level of significance and were two-tailed. No multiple comparison adjustments were made for secondary analyses. Safety variables were summarized by descriptive statistics.

RESULTS

One hundred twenty-nine participants were randomized to study medication, constituting the safety population (64 donepezil, 65 placebo); 127 participants (62 donepezil, 65 placebo) provided postbaseline data, constituting the efficacy ITT population (Fig. 1). Four participants (3.1%) in the donepezil group discontinued prior to completing 10 weeks of treatment; only one discontinued due to an AE.

No remarkable differences in demographic and baseline characteristics of the ITT population were observed between the two groups (Table I). Screening and baseline cognitive assessment scores, VABS-II/PCRF nine subdomain sum scores at baseline,

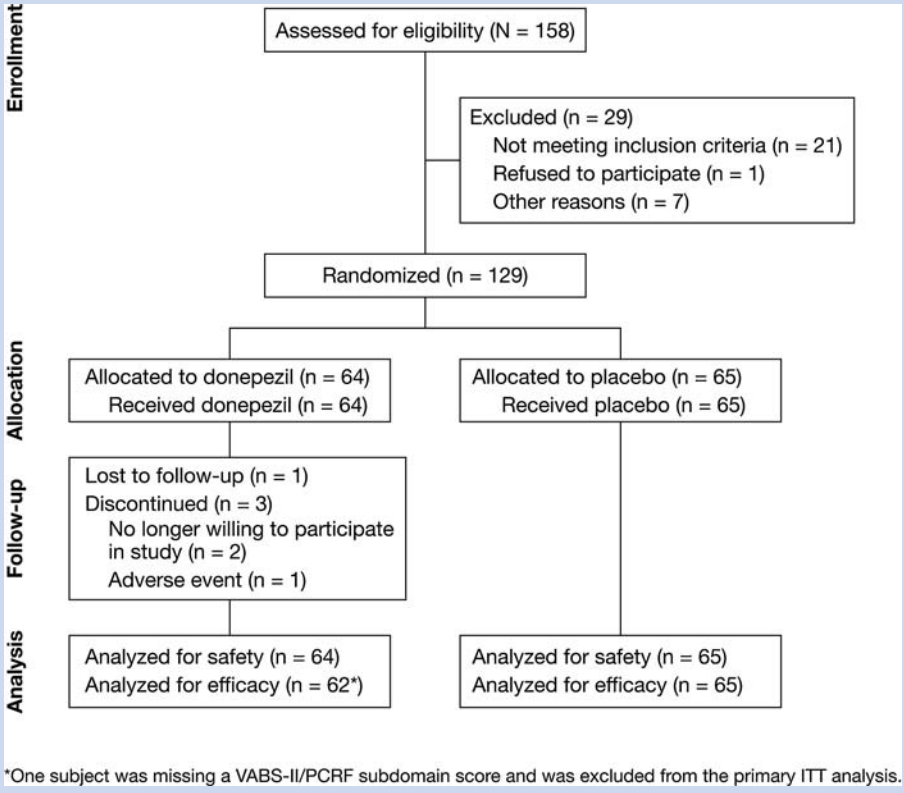

FIG. 1. Subject disposition.

TABLE I. Demographic and Baseline Characteristics: Intent-to-Treat Population

	Treatment group					
	Donepezil			Placebo		
Demographic characteristic	**Male n = 36**	**Female n = 26**	**Total N = 62**	**Male n = 30**	**Female n = 35**	**Total N = 65**
Age group, years, n (%)						
10–13	23 (63.9)	17 (65.4)	40 (64.5)	19 (63.3)	19 (54.3)	38 (58.5)
14–17	13 (36.1)	9 (34.6)	22 (35.5)	11 (36.7)	16 (45.7)	27 (41.5)
Mean (SD)	12.9 (2.3)	13.1 (2.5)	13.0 (2.4)	12.8 (1.9)	13.1 (2.2)	13.0 (2.1)
Range	10–17	10–17	10–17	10–16	10–17	10–17
Race, [n [%]]						
White	34 (94.4)	19 (73.1)	53 (85.5)	26 (86.7)	31 (88.6)	57 (87.7)
Black	0	3 (11.5)	3 (4.8)	0	3 (8.6)	3 (4.6)
Asian	0	0	0	3 (10.0)	1 (2.9)	4 (6.2)
Other	2 (5.6)	4 (15.4)	6 (9.7)	1 (3.3)	0	1 (1.6)
Weight [kg, n [%]]						
Mean (SD)	50.9 (17.3)	49.6 (16.4)	50.4 (16.8)	48.0 (14.1)	52.8 (14.0)	50.6 (14.2)
Range	27.9–99.5	24.5–89.5	24.5–99.5	20.5–73.4	20.1–84.2	20.1–84.2
Body mass index, kg/m^2, n (%)						
Mean (SD)	23.5 (5.2)	24.6 (6.2)	23.9 (5.6)	22.4 (4.5)	26.4 (5.5)	24.6 (5.4)
Range	16.9–37.7	14.1–40.3	14.1–40.3	14.7–31.4	16.0–37.4	14.7–37.4

SD, standard deviation.

and TOVER scores at baseline were similar for both groups (Table II).

Improvements from baseline for the sum of the VABS-II/PCRF nine subdomain v-scores at week 10 LOCF (primary end point) were not significantly different between groups (Table III). For the TOVER, both groups improved approximately two points and were not significantly different (Table III).

Secondary efficacy analyses, specified a priori, included VABS-II/PCRF raw scores and v-scores for subdomains and domains, and standardized scores for domains and adaptive behavior composite scores, observed cases (OC) analyses at weeks 4 and 10, and a variety of responder analyses. None of these analyses identified meaningful differences between groups. For example, analysis of VABS-II/PCRF sum of the nine subdomain v-scores, change from baseline to week 4 OC and week 10 OC, showed mean score increases in both groups from baseline to week 4 and further increases at week 10. The change in placebo mean scores was statistically significant at week 4 ITT-OC ($P = 0.023$) and the changes in mean scores in both groups were statistically significant at week 10 ITT-OC ($P < 0.0001$). At neither time point was the least squares (LS) mean change difference between the two groups statistically significant. For the VABS-II/PCRF v-score for each of the nine subdomains, change from baseline to week 4 ITT-OC, baseline to week 10 ITT-OC, and baseline to week 10 ITT–LOCF in both treatment groups, all mean scores, except personal at week 4, increased, with greater increases at week 10 than at week 4. For 22 of the 54 comparisons to baseline, the *P*-value was <0.05. All mean increases were <1.0. The LS mean change treatment difference favored donepezil for the written, personal, domestic, and play and leisure time subdomains; placebo was favored in the receptive, expressive,

TABLE II. Baseline Cognitive Assessment Scores: Intent-to-Treat Population

	Treatment group	
Assessment	**Donepezil (n = 62)**	**Placebo (n = 65)**
VABS-II/PCRF ABCSS[a]		
N	62	65
Mean (SD)	67.4 (8.7)	67.2 (7.4)
Range	53–92	51–88
VABS-II/PCRF ABCSS[b]		
n	62	65
Mean (SD)	66.7 (8.0)	67.9 (8.2)
Range	53–89	51–87
VABS-II/PCRF[b,c]		
Sum of 9 v-scores		
n	61	65
Mean (SD)	83.1 (15.5)	85.7 (15.8)
LS mean (SE)	81.9 (2.0)	85.0 (1.9)
Range	50–122	52–118
TOVER[b]		
n	62	64
Mean (SD)	20.7 (12.2)	21.6 (11.4)
LS mean (SE)	21.3 (1.5)	21.9 (1.5)
Range	0–52	0–53

[a]Performed at screening.
[b]Performed at baseline.
[c]If a subdomain score was missing, the record was not used for this analysis. VABS-II/PCRF ABCSS, Vineland Adaptive Behavior Scales, Second Edition, Parent/Caregiver Rating Form Adaptive Behavior Composite Standard Score; LS, least squares; SD, standard deviation; SE, standard error of the mean; VABS-II/PCRF, Vineland Adaptive Behavior Scales, Second Edition, Parent/Caregiver Rating Form, sum of nine subdomain v-scores; TOVER, Test of Verbal Expression and Reasoning.

TABLE III. Main Primary and Secondary Efficacy Variables: VABS-II/PCRF, Sum of Nine Subdomain v-Scores, and TOVER, Total score, Change From Baseline to Week 10: ITT-LOCF Population

	VABS-II/PCRF			TOVER		
	Treatment group			Treatment group		
Visit	Donepezil	Placebo	*P*-value[a]	Donepezil	Placebo	*P*-value[a]
Baseline						
n	61	65		62	64	
Mean (SD)	83.1 (15.5)	85.7 (15.8)		20.7 (12.2)	21.6 (11.4)	
LS mean (SE)	81.9 (2.0)	85.0 (1.9)	0.253	21.3 (1.5)	21.9 (1.5)	0.791
Range	52–122	52–118		0–52	0–53	
Week 10 LOCF						
n	61	65		62	64	
Mean change (SD)	4.74 (9.2)	4.22 (8.5)		2.4 (6.0)	2.1 (5.5)	
LS mean change (SE)	4.43 (1.15)	4.42 (1.10)	0.999	2.3 (0.8)	2.0 (0.7)	0.796
Range	−28 to 40	−18 to 33		−8 to 19	−9 to 16	
P-value[b]	0.000	0.000		0.003	0.004	

If a subdomain score was missing, the record was not used for this analysis.

[a]Treatment difference. For baseline treatment differences, an analysis of variance model was used, with treatment and age group (10–13 and 14–17 years) as factors. For postbaseline treatment differences, an analysis of covariance model was used, with treatment and age group as factors and target dose (2.5 mg/day for those 20 to <25 kg, 5 mg/day for those 25 to <50 kg, and 10 mg/day for those ≥50 kg) divided by the subject's actual weight (kg) at screening and baseline v-score sum as covariates. ITT, intent to treat; LOCF, last observation carried forward; LS, least squares; OC, observe cases; SD, standard deviation; SE, standard error of the mean; TOVER, Test of Verbal Expression and Reasoning; VABS-II/PCRF, Vineland Adaptive Behavior Scales, Second Edition, Parent/Caregiver Rating Form, sum of nine subdomain v-scores.

[b]From a paired *t*-test (v-score sum or TOVER score at postbaseline visit minus baseline) for each treatment group.

community, interpersonal relationships, and coping skills subdomains. The week 10 OC domestic subdomain LS mean change treatment difference favored donepezil ($P = 0.047$). None of the other treatment difference comparisons showed P-values < 0.05.

Safety Results

The median duration of treatment was similar between groups (donepezil: 69.0 days, placebo: 70.0 days). In the safety population, the majority of participants in both groups (donepezil: 55; placebo: 63) received study drug for 61–90 days.

The mean average daily dose was 5.0 mg in the donepezil group and 5.6 mg in the placebo group. Mean compliance was similar and high (>90%) in both groups.

Table IV lists the AEs occurring in >2% (or >2 participants) regardless of investigator-judged relationship to study drug in both groups. The most common AEs (>5% or >3 participants) judged by the investigator to be drug-related in the donepezil group were diarrhea (12.5%) and vomiting (6.3%), and in the placebo group, diarrhea (12.3%; data not shown). More donepezil-treated participants (48.4%) than placebo-treated participants (30.8%) experienced AEs considered related to study drug.

The majority of AEs were mild in both treatment groups. No severe AEs or deaths were reported. One participant in the placebo group had two SAEs: a single hospitalization for gastroenteritis and dehydration. Both were moderately severe, were assessed as not related to study drug, and resolved.

One donepezil-treated participant discontinued due to treatment-emergent AEs during the study. This participant developed mild increased urinary frequency, which resolved.

Evaluation of changes in vital signs, physical and neurological examinations, clinical laboratory tests, and electrocardiograms did not find any cause for safety concerns.

Pharmacokinetic/Pharmacodynamic Results

Plasma donepezil levels were available for 57/60 donepezil participants who completed week 10; mean level was 32.23 ng/ml (SD = 18.85; range = 1.15–89.70). The relationship between dose and plasma level was generally linear, although the correlation P-value was 0.11, possibly influenced by some outliers (Fig. 2A). Only 31 participants provided adequate samples for PD analysis. Nonetheless, correlation between plasma level and percent RBC AChEI was robust ($P = 0.000$; Fig. 2B). Percent inhibition appeared to plateau at ≈75%. Neither plasma concentration nor percent RBC AChEI showed a significant correlation with change from baseline in the VABS-II/PCRF sum of the nine subdomain v-scores ($P = 0.35$ and 0.22, respectively).

DISCUSSION

In prior trials duration of therapy has ranged from 16 weeks (open-label pediatric) to 24 weeks (12-week double-blind followed by 12-week open-label extension, young adults aged 18–35 years). The variety of evidence and the significant unmet medical need for children with DS, led us to investigate benefits of donepezil on central cholinergic function in children. It was hypothesized that a short-term study (dosing over 10 weeks with all participants on a maximum dose for at least 4 weeks) would be sufficient to demonstrate efficacy. In retrospect this was a major limitation in the study design.

TABLE IV. Treatment-Emergent Adverse Events by Preferred Term Reported by ≥2% of Subjects, All Causalities: Safety Population

	Treatment group	
Any adverse event	**Donepezil n = 64, n (%)**	**Placebo n = 65, n (%)**
Diarrhea	11 (17.2)	10 (15.4)
Vomiting	8 (12.5)	2 (3.1)
Upper respiratory tract infection	6 (9.4)	5 (7.7)
Headache	5 (7.8)	2 (3.1)
Nausea	5 (7.8)	2 (3.1)
Cough	4 (6.3)	1 (1.5)
Pharyngitis	3 (4.7)	1 (1.5)
Rash	3 (4.7)	2 (3.1)
Abdominal pain upper	2 (3.1)	1 (1.5)
Fecal incontinence	2 (3.1)	0
Bronchitis	2 (3.1)	0
Gastroenteritis viral	2 (3.1)	1 (1.5)
Lethargy	2 (3.1)	0
Pyrexia	2 (3.1)	2 (3.1)
Rhinitis allergic	2 (3.1)	0
Somnolence	2 (3.1)	0
Viral infection	2 (3.1)	0
Decreased appetite	1 (1.6)	3 (4.6)
Ear infection	1 (1.6)	3 (4.6)
Fatigue	1 (1.6)	2 (3.1)
Nasal congestion	1 (1.6)	2 (3.1)
Sinusitis	1 (1.6)	3 (4.6)
Constipation	0	2 (3.1)
Gastroenteritis	0	2 (3.1)
Insomnia	0	2 (3.1)
Nasopharyngitis	0	4 (6.2)

If the same subject in a given treatment group had more than one occurrence of the same preferred term event category, only the most severe occurrence was used. Subjects were counted only once per treatment group in each row. MedDRA, Medical Dictionary for Regulatory Activities v11.0 coding was applied.

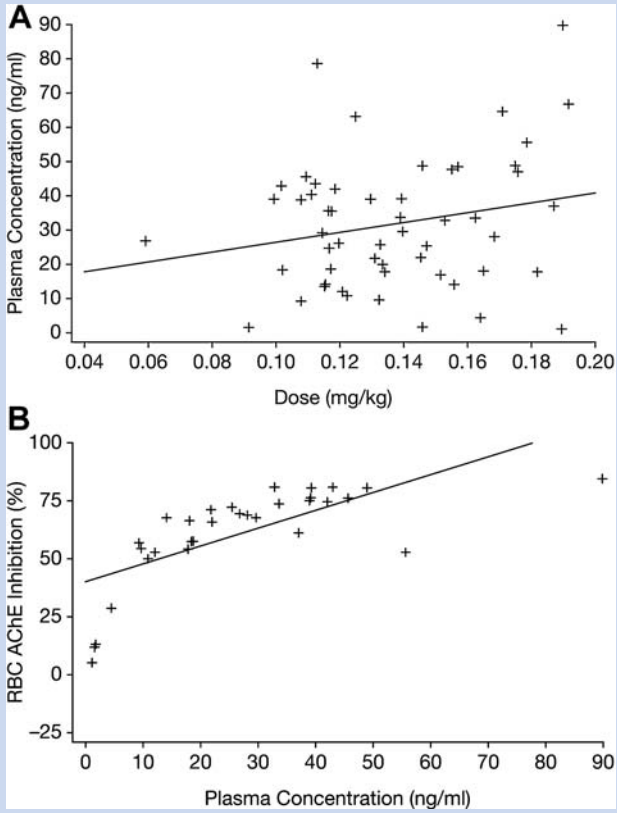

FIG. 2. Scatterplots of dose (mg/kg) versus donepezil plasma concentration (ng/ml) at week 10 (Panel A) and donepezil plasma concentration (ng/ml) versus percent red blood cell acetylcholinesterase (RBC AChE) inhibition at week 10 (Panel B).

This study failed to demonstrate any benefit for donepezil versus placebo in children and adolescents with DS. For the VABS-II/PCRF and the TOVER, mean scores for both treatment groups increased from baseline over the course of the study and placebo improvement was very similar to donepezil improvement. Within each group, these increases were usually statistically significant, but differences between treatments were small and not significant. Donepezil appeared to be safe and well tolerated.

This is the first and only large-scale, randomized, double-blind, placebo-controlled study of a pharmacological treatment for children and adolescents with DS. Prior studies included a similarly sized double-blind, placebo-controlled study of donepezil in young adults with DS and two small open-label studies in children, one with donepezil and one with rivastigmine. The young adult study results suggested that subject-performance-based measures in this population were influenced by practice and learning effects as well as ceiling and floor effects. In the young adult study, donepezil showed a significantly different improvement in VABS from baseline over placebo. However, it is noteworthy that the young adult study used the VABS first edition and all parents and caregivers were interviewed by a trained examiner who scored their responses to each item. On the VABS second edition used in this study, items were scored based on parent and caregiver responses to a questionnaire that they completed on their own.

The young adult study results guided the design of this study, anticipating that the VABS-II/PCRF would show a similar response to the parent-interview version of the VABS used in the young adult study. The VABS-II/PCRF was also selected to provide age-standardized scores starting at the subdomain level. The use of age standardized scores minimizes floor effects and the use of multiple V-scores could allow a better understanding of treatment effects. The open-label studies in children suggested that language function might be particularly responsive to AChEI treatment. Thus, the TOVER was added as a subject-performance-based measure to this study to supplement the parent/caregiver-reported VABS-II/PCRF.

Our expectations for the performance of the VABS-II/PCRF proved incorrect. While the donepezil group did show an increasing improvement from baseline over the 10 weeks of the study, consistent with titration to a target maximum dose over the course of the study, the placebo group showed virtually identical improvement. The TOVER results were very similar. Consequently, the results of this study did not show that donepezil benefits children with DS in

the 10-week time frame. However, it may be that the results were inconclusive because of limitations of the study design (10 weeks and four evaluations).

Plasma samples for the top 20 placebo responders were checked for donepezil levels to ensure that a drug distribution error had not occurred. These results confirmed that the placebo response was not due to a drug distribution error.

The PK and PD results showed that the target dosing for this study was appropriate, achieving levels of plasma donepezil and RBC AChE inhibition consistent with efficacy in Alzheimer disease trials. The reason for the lack of a significant correlation between these results and the efficacy measures is unclear, although a possibility would be that higher drug levels are required to achieve response in pediatric patients.

Donepezil is metabolized by the P450 cythochrome isoenzymes 2D6 and 3A4 in the liver. The metabolism of these enzymes is known to be affected by many medications. Psychoactive medications often share the same metabolic pathway despite the different neurotransmitter system targeted, so the variability in the PK/PD results might be explained partially by the metabolic impact of other medications permitted.

Secondary analyses of the VABS-II/PCRF, including the a priori-defined responder analyses, generally favored donepezil, but there was no pattern of statistical significance that would challenge the primary outcome. Of note, different subdomains improved in the two groups; whether this was just by chance is not clear.

This study raises important questions about the design of future studies in this population. The VABS-II/PCRF did not show floor or ceiling effects. However, it was completed four times over 12 weeks (screening, baseline, week 4, and week 10), whereas in the young adult study, the VABS was completed only at baseline and week 12. Perhaps with the more frequent observations, parents paid more attention to behaviors and rated them higher once they took more time to observe them. In the young adult study, the VABS was administered as a semi-structured interview, while in this study the VABS-II was simply read and completed by the parent or caregiver. The VABS-II manual shows a high correlation between the semi-structured interview version and the PCRF version; however, the standardization was completed with respondents who had no investment in the test outcome. The VABS-II manual suggests that the interview format be completed if there is any concern about respondent bias. For this study, the process of completing a skills analysis that identifies the limitations of their child with an intellectual disability may have introduced bias. In light of the gains observed in both groups, the parents may have overestimated their child's skill levels.

The TOVER results, being subject-performance-based, might be attributed to practice/learning effects since there are not multiple versions of the instrument and children may become more comfortable with the procedure and the interviewer over time.

The lack of a treatment effect raises the question of whether other assessments of cognitive function should be used as efficacy measures. While there are hundreds of options available, few have been shown to detect a cholinergic effect in this population. In addition to measure selection, it is equally important to address the factors that elicit optimal performance from individuals with DS [Heller et al., 2004]. This population is particularly sensitive to the interaction between examiner and study participant. Performance improves as the study participant becomes more comfortable with the examiner and the test environment. Thus, without study design modification, the possible practice/learning effects detected in this study may occur in other clinical trials utilizing repeated measures regardless of the measure.

Ultimately, a non-interactive measure such as a biomarker, perhaps functional magnetic resonance imaging, may be one way to separate a true treatment response from a robust placebo response. Alternatively, a study examining long-term treatment effects may be another approach to identifying a true treatment response.

From these results, no recommendation can be made for the use of donepezil to treat cognitive dysfunction in children and adolescents with DS. While donepezil was generally safe and well tolerated, the performance gains observed in the donepezil and placebo groups were virtually identical. These results raise questions about the potential benefits of donepezil. Specifically: a) were potential benefits inhibited by the short study length? b) did the repeated exposure to the measures inflate test scores? c) were the actually benefits of donepezil masked by the robust response of the placebo group? and d) is there no benefit of donepezil to these children and adolescents? The answers to these questions await further study.

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