Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Clinical Trial Sites

Site Name	Site Type
University of Arizona Medical Center	University
Children's Specialized Hospital	Hospital
Children's Specialized Hospital (Egg Harbor)	Stand-Alone
SAARC - Southwest Autism Research Center Resource Center	Stand-Alone
University of Texas, Houston UT BBSB	University
Pediatric Research, University of Toledo	University
MIND Institute, University of California, Davis	University
Cleveland Clinic Autism Center Children's Hospital for Rehabilitation	Hospital
Duke University Center for Autism and Brain Development	University
Detroit Clinic Research Center	Stand-Alone
APG Research LLC	Stand-Alone
Advent Health Medical Group Pediatrics at Orange County	Pediatric Office
PRIME-Psychiatric Research Inst. Of Montefiore Einstein Autism & Obsessive Compulsive Spectrum Program	Hospital
LSU Health Sciences Center, Dept. of Psychopharmacology Research	University
Lovelace Scientific Resources, The Mind Network, Univ. of New Mexico	University
Omega Medical Research	Stand-Alone
UCSF (Univ. of California, SF) PRONTO (Program for Research on Neurodevelopmental and Translational Outcomes)	University
Carilion Clinic, Virgina Tech, Carilion School of Medicine	University
The Focus Center	Stand-Alone
Vanderbilt University Behavioral Health	University
NRC Research Institute	Stand-Alone
Pediatric Clinical Research Unit, Arkansas Children's Hospital	Hospital
Yale Child Study Center, Center for Translational Developmental Neuroscience	University
Richmond Behavioral Associates	Stand-Alone
Lake Charles Clinical Trials	Stand-Alone
IMMUNOe Research Centers	Stand-Alone
CRCNJ	Stand-Alone
NeuroScience, Inc.	Stand-Alone
Research Institute at Deaconess Clinic	Hospital
Segal Institute for Clinical Research, Charleston Outpatient Clinic	Stand-Alone
Univ. of Virginia, Center for Psychopharmacology in Youth	University
Segal Institute for Clinical Research	Stand-Alone

eTable 2. Inclusion/Exclusion Criteria

Inclusion Criteria:	1. Age between 3 and 8 years, inclusive 2. If the child is 7 years of age or older, understand and sign a written assent form, if mental capacity allows 3. The parent or guardian of the subject must be able to understand and sign a written informed consent document, a waiver of assent document (in some cases), and be able to read English 4. Meets the current Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR) diagnostic criteria for autistic disorder (AD), screened by the SCQ and confirmed by the ADI-R. 5. Aberrant Behavior Checklist: subscale of Irritability/Agitation (ABC-I) score ≥11.0 at enrollment.
Exclusion Criteria:	1. Patient weighing < 13kg 2. Allergy to porcine products 3. Previous sensitization or allergy to trypsin, pancreatin, or pancrelipase 4. History of severe head trauma, as defined by loss of consciousness or hospitalization, skull fracture or stroke. 5. Seizure within the last year prior to enrollment, or the need for seizure medications either at present or in the past. 6. Diagnosed with any of the following: a. HIV-positive b. Cancer (regardless of remission state) c. Cerebral palsy d. Muscular dystrophy e. Known genetic disorder f. Blood dyscrasia g. Ongoing gastrointestinal disease h. Endocrine disorder (e.g., hypothyroidism, diabetes) i. Pancreatic disease (endocrine or exocrine) j. Depression/bi-polar or other psychiatric disease 7. Evidence of severe, moderate or uncontrolled systemic disease 8. Any co-morbid condition which in the Investigator's or Medical Director's opinion makes it undesirable for the subject to participate in the trial or would jeopardize compliance with the protocol. 9. Supplementation with any of the following within 30 days of entering the study: a. Any enzyme product or a product containing pancreatic/digestive enzymes of plant or animal origin b. Pancreatin, thyroid, or adrenal extracts, either synthetic plant or animal-based c. Essential fatty acids/omega/ or other supplement containing product d. Amino acids, or amino acid containing products e. Any secretin product including transdermal, oral, or injectable f. Vitamin B12/folate either oral or injectable g. Chelating agents / chelation therapy h. Any other investigational drug or therapy/oncology drug/anti-helmenthic / anti-yeast drug i. Off-label medications

eTable 3. Participant Demographics

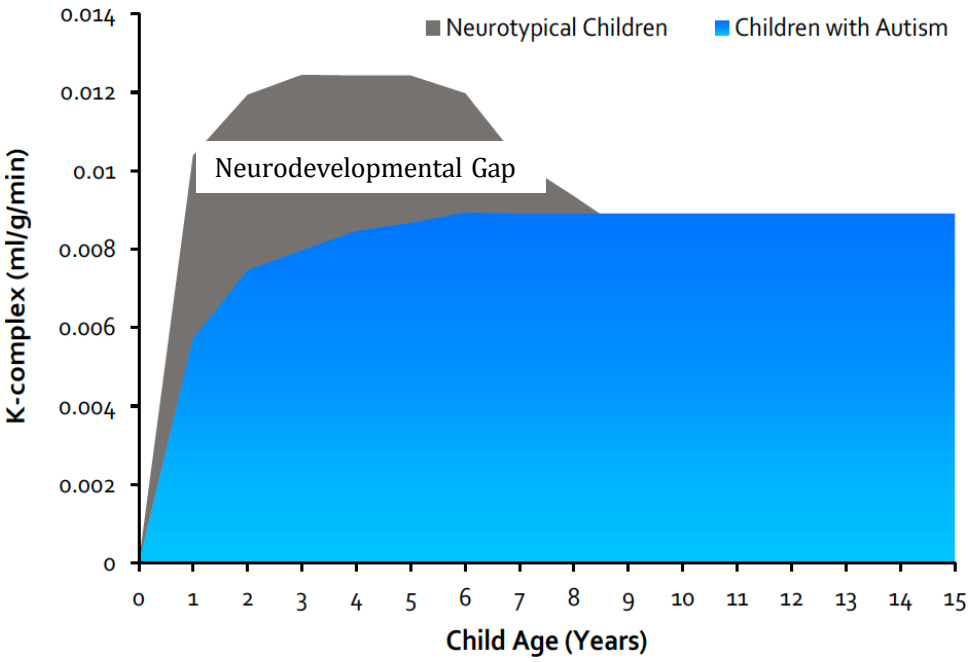
Demographics in Age 3 to 6 Years (ITT Population)

	Age 3 to 6 Years		Age 3 to 6 Years with Moderate to Severe ASD[1]	
	CM-AT (N=92)	Placebo (N=98)	CM-AT (N=29)	Placebo (N=40)
Age (years)				
N	92	98	29	40
Mean	4.5	4.5	4.7	4.4
Standard deviation	0.8	0.8	0.7	0.8
Median	4.6	4.7	4.7	4.5
Minimum, Maximum	3.0, 5.9	3.0, 5.9	3.5, 5.7	3.0, 5.9
Gender, n (%)				
Male	71 (77.2)	79 (80.6)	20 (69.0)	30 (75.0)
Female	21 (22.8)	19 (19.4)	9 (31.0)	10 (25.0)
Race, n (%)				
White	61 (66.3)	70 (71.4)	16 (55.2)	28 (70.0)
Asian	12 (13.0)	10 (10.2)	6 (20.7)	3 (7.5)
Black or African American	10 (10.9)	8 (8.2)	3 (10.3)	5 (12.5)
Multiple	7 (7.6)	6 (6.1)	3 (10.3)	4 (10.0)
Other	2 (2.2)	3 (3.1)	1 (3.4)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Ethnicity n (%)				
Not Hispanic or Latino	71(77.2)	80(81.6)		
Hispanic or Latino	20 (21.7)	18(18.4)		

eTable 4. Autism Diagnostic Interview Revised (ADI-R): Subscale Scores at Baseline

ADI-R Subscale		Baseline	
		Drug	Placebo
A	Social Interaction	21.7	22.2
B	Communication Verbal	15.0	15.1
B	Communication Non-Verbal	10.5	10.8
C	Restricted, Repetitive and Stereotyped Patterns of Behavior	6.9	7.2
D	Abnormality of Development Evident at or before 36 Months	4.1	4.2

eFigure. Neurodevelopmental Gap in Brain Synthesis Capacity in Autistic Children Compared With Non-Autistic Children



eTable 5. Participant Disposition

Subject Disposition in Age 3 to 6 Years (ITT Population)

	Age 3 to 6 Years		Age 3 to 6 Years with Moderate to Severe ASD (1)	
	CM-AT (N=92) n (%)	Placebo (N=98) n (%)	CM-AT (N=29) n (%)	Placebo (N=40) n (%)
Completed Study	71 (77.2)	80 (81.6)	24 (82.8)	34 (85.0)
Discontinued Study	21 (22.8)	18 (18.4)	5 (17.2)	6 (15.0)
Primary Reason for Early Discontinuation				
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Noncompliance	8 (8.7)	1 (1.0)	2 (6.9)	0 (0.0)
Protocol violation			0 (0.0)	1 (2.5)
Withdrawal of consent	5 (5.4)	6 (6.1)	2 (6.9)	2 (5.0)
Lost to Follow-up			1 (3.4)	1 (2.5)
Other			0 (0.0)	1 (2.5)

[1]Defined as a baseline CGI-S score ≥4 and ABC-I ≥18.

eTable 6. Fecal Chymotrypsin Data

Group	FCT @ Baseline	FCT @ Week 12	Change
CM-AT	7.46	10.94	3.47
Placebo	7.69	8.69	1.00
p Value <			.0383

eTable 7. Responder Analysis (30%)

	CM-AT		Placebo	
	N	**%**	**N**	**%**
All Responders	77	100%	67	100%
≥ 30% Response	61	79%	42	62%

e Table 8.

CGI: Severity

	CGI-S Screening	CGI-S Wk 12	CGI-S Change
CM-AT	3.53	3.26	-0.37
Placebo	3.50	3.42	-0.19

eTable 9.

CGI: Improvement

Group	Wk2	Wk6	Wk12
CM-AT	2.61	2.32	2.08
PLACEBO	2.67	2.38	2.28

eTable 10.

CGI: Improvement—Most Severe (ABC-I ≥18, CGI-S≥4)

Group	Wk2	Wk6	Wk12
CM-AT	2.47	2.17	1.81
PLACEBO	2.70	2.18	2.02