Protocol ID:00103 / Autism

A Double Blind Randomized Placebo Controlled Study of CM-AT for the Treatment of Autism in Children With All Levels of Fecal Chymotrypsin

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STUDY SYNOPSIS

Title:	A Double Blind Randomized Placebo Controlled Study of CM-AT for the Treatment of Autism in Children With All Levels of Fecal Chymotrypsin
Protocol Number:	00103
Development Phase:	III
Number of Study Centers:	Approximately 35 clinical sites in the United States
Number of Subjects:	Approximately three-hundred (300) patients will be randomized
Estimated Study Length:	Approximately 36 months, contingent upon meeting accrual targets
Duration of Treatment and Study Participation:	12 weeks, following a 2-week blinded drug run-in period.
Patient Population:	The study population will consist of children, both males and females, between 3 and 8 years of age inclusive at the time of consent, who are diagnosed with Autistic Disorder (AD) by DSM-IV-TR and ADI-R, and are screened by the SCQ.
Test Product, Dose, and Mode of Administration:	CM-AT (pancreatic enzyme concentrate encapsulated in hydrogenated soybean oil) 900mg 3x daily sprinkled over food. To be taken with a meal or large snack.
Study Methodology:	This is a Phase III multi-center, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of CM-AT in pediatric patients with autism at all levels of fecal chymotrypsin.
Study Design:	In this Phase III multi-center, randomized, double-blind, placebo-controlled study, all study participants must have an initial ABC-I score of $\geq$ 11 and a diagnosis of Autistic Disorder as demonstrated by the DSM-IV-TR and by the ADI-R. Subjects will also be screened using the SCQ and must achieve a score of $\geq$ 15 to be considered eligible. Those subjects who qualify will be given a two week blinded drug run-in. Subjects will then be evaluated for compliance and re-evaluated for level of Irritability with the ABC-I scale. If their score on the ABC-I scale has increased by 30% or more or decreased by 30% or more, or is <9, they will be discontinued from the study. If all entry criteria are met, the subject will be randomized at the Visit 1/Baseline visit.
Study Rationale:	Sponsor studies have demonstrated the clinical potential of CM-AT formulations in treating core and non-core autism symptoms in subjects with autism ages 3-8 with low fecal chymotrypsin (FCT) levels when dosed at a level of 900mg 3x daily. This study will further quantify the changes in the target population as measured by standardized behavioral and quality of life tests, physiological measures, as well as characterize the efficacy and safety of the product. The study will further delineate the efficacy in a population that is biomarker negative (>12.6U/g of fecal chymotrypsin) who have autism. The data from this study will help determine safety and efficacy of CM-AT in pediatric patients with autism of both biomarkers positive and negative.

	This study will be undertaken in children whose Aberrant Behavior Checklist: subscale for Irritability / Agitation (ABC-I) $\geq$11 is at Screening/Enrollment. This number represents those who fall above approximately 0.5 std deviations from the mean seen in the Sponsor's 00101 study.
Safety:	Fecal globin levels, the presence of occult blood, α_1-antitrypsin, and weight loss will be used to monitor the safety and tolerability of CM-AT. • The presence of fecal globin may indicate bleeding in the large intestine, while a positive occult blood may indicate bleeding along the entire gastrointestinal tract. • An increase in α_1-antitrypsin may signal an immunologic response of the colonic mucosa, leading to potential formation of colonic strictures. • Weight loss may be indicative of malabsorption. • All of the above markers may be linked due to gastrointestinal irritation, but have not specifically been noted thus far in the Sponsor's experience with enzyme therapies. • Parental input at the standard visits, diary entries, and other assessments will also be used to monitor safety. • Of 468 children with autism given pancreatic enzymes in early Sponsor studies, and in the Phase III clinical studies (00101 & 00102), in which 180 were initially enrolled, and 140 continued into Open-Label, the drug appeared to be safe and well-tolerated with no related SAE experienced in either study the duration of which has been greater than 288 weeks. Primarily, AEs appeared to be GI in nature.
Rating Instruments:	ABC, SRS-2 (Preschool or School Age), PedsQL Inventory – Family Impact Module, CGI (S), CGI (I). Other measures: DSM-IV, SCQ and ADI-R.
Study Objectives:	Endpoint (outcome) measurements for treatment with CM-AT versus placebo in biomarker negative and positive subjects will be analyzed as described in Statistical Considerations. **PRIMARY ENDPOINT MEASUREMENTS** • Aberrant Behavior Checklist: subscale of Irritability/Agitation (ABC-I) at FCT levels $\leq$ 12.6 **SECONDARY ENDPOINT MEASUREMENTS** • Aberrant Behavior Checklist: subscale of Lethargy/Social Withdrawal (ABC-L) at FCT levels $\leq$ 12.6 **EXPLORATORY ENDPOINT MEASUREMENTS** • Behavioral changes: o Aberrant Behavior Checklist: subscale of Irritability/Agitation (ABC-I) at FCT levels > 12.6 o Aberrant Behavior Checklist: subscale of Lethargy/Social Withdrawal (ABC-L) at FCT levels > 12.6 o Aberrant Behavior Checklist: subscale of Hyperactivity (ABC-H) at FCT levels $\leq$ 12.6 o Aberrant Behavior Checklist: subscale of Total (ABC-T) at FCT levels $\leq$ 12.6

	○ Aberrant Behavior Checklist: subscale of Stereotypy (ABC-S) at FCT levels ≤ 12.6 ○ Aberrant Behavior Checklist: subscale of Inappropriate Speech (ABC-IS) at FCT levels ≤ 12.6 ○ Aberrant Behavior Checklist: subscale of Irritability/Agitation (ABC-I) at all FCT levels ○ Aberrant Behavior Checklist: subscale of Lethargy/Social Withdrawal (ABC-L) at all FCT levels ○ Aberrant Behavior Checklist: subscale of Hyperactivity (ABC-H) at all FCT levels ○ Aberrant Behavior Checklist: subscale of Total (ABC-T) at all FCT levels ○ Aberrant Behavior Checklist: subscale of Stereotypy (ABC-S) at all FCT levels ○ Aberrant Behavior Checklist: subscale of Inappropriate Speech (ABC-IS) at all FCT levels ○ Pediatric Quality of Life Inventory (PedsQL) ○ CGI-I, CGI-S ○ SRS-2 • GI health: ○ Stool Test Panel ○ Weight gain/loss **SAFETY ENDPOINT MEASUREMENTS** • Adverse Events • Negative change in weight, if clinically inappropriate based upon standard scales • Incidence and/or change in clinical laboratory results for the following: ○ Fecal globin / Fecal occult blood ○ Stool pH ○ Presence or continued growth of pathogens, as indicated by stool panel antigen/toxin tests ○ Elevated α1-antitrypsin levels ○ Change in bowel habits due to colitis
Inclusion Criteria:	1. Age between 3 and 8 years, inclusive at the time of consent 2. If the child is 7 years of age or older, understand and sign a written assent form or give witnessed verbal assent, 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

Exclusion Criteria:	Subjects who meet any of the following criteria will be excluded from study participation: 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 use of 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 or abnormality f. Blood dyscrasia g. Ongoing gastrointestinal disease (e.g., Crohn's Disease, Celiac Disease. Not intended to exclude gastrointestinal issues, such as constipation or diarrhea not associated with another GI disease diagnosis.) h. Endocrine disorder (e.g., hypothyroidism, diabetes) i. Pancreatic disease (endocrine or exocrine) j. Previous diagnosis with or hospitalization for significant co-morbid psychiatric conditions such as depression, bipolar or other psychiatric disease (Not intended to exclude ADHD, anxiety associated with autism or obsessive-compulsive disorder) k. Any diagnosis of sleep or wakefulness disorder, such as narcolepsy, hypo or hypersomnia. 7. Evidence or history of severe, moderate or uncontrolled systemic disease, or history of metabolic disorders (e.g., amino acid deficiencies, hypoketosis) 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, omegas, or other supplement containing these products (does not require a washout) 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 (Allowable as part of a multivitamin. Folate not to exceed 400 mcg, B12 not to exceed 12 mcg). No injectables allowed of either.

	g. Chelating agents / chelation therapy h. Any other investigational drug or therapy, oncology drug, anti-helminthic, or anti-yeast drug i. Off-label medications 10. Asthma, when medication (oral, inhaled, or injectable) is given on a daily basis or is necessary >3 times per week. 11. Ongoing dietary restriction for allergy or other reasons except nut allergies (lactose-free allowable) 12. Inability to ingest the study drug 13. Inability to follow the prescribed dosing schedule 14. Subjects who are likely to experience significant changes in their ongoing psychosocial or medical treatments for autism over the course of the trial (e.g., initiation of new behavioral therapy, initiation of new medication or alternative treatment). Minor changes in ongoing treatment (e.g., missed therapy sessions due to holiday/vacation; planned break in therapy due to school holidays) will not be considered significant. 15. Use of any stimulant medication or other medication given for ADHD must be discontinued 5 days prior to entering the study (Vayarin requires a 30-day washout) 16. Subjects taking an SSRI must be on a stable dose for a minimum of 30 days prior to entering the study. 17. History of premature birth < 35 weeks gestation 18. Prior history of stroke in utero, or other intrauterine insult
Additional Inclusion Criteria at Visit 1/Baseline for Randomization:	The subject must meet the following additional inclusion criteria upon returning for Visit 1/Baseline in order to be randomized: 1. The subject must have demonstrated IP compliance that is ≥50% during the 2-week blinded drug run-in period 2. Upon retest at Visit 1/Baseline, the subject's score on the ABC-I must have increased or decreased by less than 30%, and also must be ≥9 3. Subjects must continue to meet all inclusion/exclusion criteria

Statistical Considerations:	The sample size is based on (a) the primary efficacy variable of the change from baseline to week 12 for the Aberrant Behavior Checklist (ABC) subscale for Irritability; (b) the primary analysis set of low-level fecal chymotrypsin (FCT) ≤ 12.6 Units/gram randomized subjects; and (c) a 1:1 randomization scheme. Assuming a mean ± standard deviation decrease in ABC Irritability from baseline to week 12 of 3.7 ± 7 for CM-AT and 0.6 ± 5 for Placebo, a sample size of 82 evaluable low-level subjects per treatment group yields 90% power to declare a statistically significant difference between treatments at a two-sided 0.05 level of significance. Assuming 15% premature withdrawal, 97 low-level subjects will be randomized. In order to achieve 97 randomized low- level subjects per group, a total of 162 subjects per group will be randomized (based on previous data indicating 60% of autistic children are low-level). Primary analyses (assessing CM-AT vs. Placebo difference) on change from baseline to week 12 will be estimated from a Mixed Model Repeated Measures (MMRM) across all visits assuming the unstructured within-subject correlation structure. Included in the model will be the main effects of randomized treatment group, visit, baseline ABC irritability, study center and the treatment-by-visit interaction effect. Analyses with and without imputation for missing data will be performed. If statistical significance, in favor of CM-AT, is shown on the primary efficacy endpoint in the primary analysis set of low-level randomized patients (FCT ≤ 12.6 Units/gram), the study will be considered to be a success statistically. The secondary efficacy variable is change from baseline to week 12 in ABC Lethargy/ Social Withdrawal (ABC-L) of low-level randomized patients (FCT ≤ 12.6 Units/gram). As an exploratory analysis, the MMRM analyses will be repeated on the ABC-I and ABC-L for the non-low-level FCT randomized patients (FCT > 12.6 Units/gram) As an additional exploratory analysis, the above MMRM analyses will be repeated on the ABC-I and ABC-L on all randomized patients in a similar manner as for the low-level randomized patients. For safety, fecal globin levels, the presence of occult blood, α_1-antitrypsin, and weight loss will be used to monitor the safety and tolerability of CM-AT. These safety measures will be presented descriptively by treatment group. No formal statistical comparisons will be carried out.