**AWARD NUMBER:** W81XWH-17-1-0253

**TITLE:** Cannabidivarin (CBDV) Versus Placebo in Children with Autism Spectrum Disorder (ASD)

**PRINCIPAL INVESTIGATOR:** Eric Hollander, MD

**CONTRACTING ORGANIZATION:** ALBERT EINSTEIN COLLEGE OF MEDICINE, INC

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# REPORT DOCUMENTATION PAGE

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**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**

The CDC currently estimates 1 in 44 children have Autism Spectrum Disorder (ASD). Children with ASD have problems with social communication, irritability, repetitive behaviors, impulsivity, temper tantrums, and a high caregiver burden. The only medications approved by the FDA for symptoms of ASD are aripiprazole and risperidone. Both of these are used to reduce irritability but have short-term and long-term side effects. This double-blind randomized placebo-controlled study will test the efficacy and safety of a new medication, cannabidivarin (CBDV), to treat autism in children ages 5-18. CBDV is non-psychoactive, is derived from the cannabis plant, but has effects opposite to THC. Approximately 100 patients will be enrolled at Montefiore and NYU sites during the duration of the study. The study lasts up to 16 weeks, and during this time, patients will undergo 9 study visits. Mood, social and cognitive functions will be assessed by the means of research questionnaires. All adverse effects will be reported. We will assess the effects of CBDV versus placebo on irritability and social functions in patients with ASD.

In year 3 of the project we have adapted study protocol to the COVID-19 pandemic situation making 5 out of 9 visits of study participants remote, and received acknowledgement from ORP HRPO that these changes do not require HRPO approval prior to implementation. During year 4 of this project, we continued our efforts in screening and enrolling patients both at AECOM-MMC site and NYU site and obtained No cost Extension (NCE) to conduct a study from the Department of Defense. During year 5 of this project, we continued our efforts in screening and enrolling patients both at AECOM-MMC site and NYU site and applied for second No cost Extension (NCE) to conduct a study from the Department of Defense.

Study is ongoing. Prior to COVID-19 pandemic onset, we have projected a total of 100 patients enrolled by end of Q4 year 5, at the two sites, including AECOM/MMC and NYU (consisting of 16 subjects to be enrolled at year 2, i.e. 8 subjects at each site; 34 subjects to be enrolled at year 3, i.e. 17 subjects at each site; 34 subjects to be enrolled at year 4, i.e. 17 subjects at each site; 8 subjects to enrolled at quarter 1 of year 5, i.e. 4 subjects at each site and 8 subjects to be enrolled at quarter 2 of year 5, i.e. 4 subjects at each site). Total number of subjects screened at AECOM/MMC site is 45 to date. Therefore 45 subjects were screened, 23 subjects have completed the study, 6 are active, 10 are screen failures, 5 have dropped out from the study and 1 is waiting to be randomized. Total number of subjects enrolled at NYU site is 9 (out of 50 projected for NYU site). Therefore 9 subjects were enrolled, 0 subjects are currently active, and 3 subjects completed the study. NYU site has been activated as of 10/23/2019. On 04/13/2022 Dr. Hollander confirmed to the DOD GOR, Dr. Tschiffely that NYU is no longer enrolling subjects under the DOD award.

We will be submitting a new CDMRP DOD grant proposal on 08/18/2022 (LOI invited to full application on 06/21/2022) to complete an additional 50 subjects in the same protocol with addition of immune, metabolomics and endocannabinoid measures to better understand the mechanism of action of CBDV in childhood ASD.

**15. SUBJECT TERMS**

NONE LISTED

| **16. SECURITY CLASSIFICATION OF:** | | | **17. LIMITATION OF ABSTRACT** | **18. NUMBER OF PAGES** | **19a. NAME OF RESPONSIBLE PERSON** |
|---|---|---|---|---|---|
| | | | | | USAMRDC |
| **a. REPORT** | **b. ABSTRACT** | **c. THIS PAGE** | UU | **30** | **19b. TELEPHONE NUMBER** *(include area code)* |
| U | **U** | | | | |

**Standard Form 298 (Rev. 8-98)**
**Prescribed by ANSI Std. Z39.18**

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**1.INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope ofthe research.*

The CDC currently estimates 1 in 44 children have Autism Spectrum Disorder (ASD). Children with ASD have problems with social communication, irritability, repetitive behaviors, impulsivity, temper tantrums, and a high caregiver burden. The only medications approved by the FDA for symptoms of ASD are aripiprazole and risperidone. Both of these are used to reduce irritability but have short-term and long-term side effects. This double-blind randomized placebo-controlled study will test the efficacy and safety of a new medication, cannabidivarin (CBDV),to treat autism in children ages 5-18. CBDV is non-psychoactive, is derived from the cannabis plant, but has effects opposite to THC. Approximately 100 patients will be enrolled at Montefiore and NYU sites during the duration of the study. The study lasts up to 16 weeks, and during this time, patients will complete 9 study visits (due to COVID-19 Pandemic 5 out of 9 visits of study participants are remote). Mood, social and cognitive functions will be assessed by the means of research questionnaires. All adverse effects will be reported. We will assess the effects of CBDV versus placebo on irritability and social functions in patients with ASD.

**2. KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Cannabidivarin, Autism spectrum Disorders, irritability, cannabinoids, autism, repetitive behaviors

**3. ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

**What were the major goals of the project?**

*List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion*

| | Timeline | AECOM/Monte | NYU |
|---|---|---|---|
| **Major Task 1: Preparatory Stage** | Months | | |
| **Subtask 1: Prepare and Submit Regulatory Documents** | | | |
| Coordinate with Sites and GW Pharma for clinical trial agreements (CTAs) submission | 1-4 | 100%, 11/16/2018 | 100%, 08/09/2019 |
| Coordinate with Sites and GW Pharma for nondisclosure agreements (NDAs). | 1-4 | 06/03/2016 | 06/03/2016 |
| Coordination with GW Pharma and other sites for the continued work on the submission or re-submission of an Investigational New Drug (IND) application to the U.S. Food and Drug Administration. The Investigators plan to submit the IND application prior to study start so that approval is underway when the funding period begins. | 1-4 | IND application submitted on 01/19/2018. IND may proceed status granted on 04/02/2018. Annual IND report receipt acknowledged on 07/31/2019, 09/29/2020 and 09/15/2021. | Same status as at AECOM/ MMC |
| Refine eligibility criteria, exclusion criteria, screening protocol | 1-4 | 100% | 100% |
| Finalize consent form & human subjects protocol | 1-4 | 100% | 100% |
| Finalize recruitment materials | 1-4 | 100% | 100% |
| Coordinate with Sites for the US Army Medical Research and Material Command Office of Research Protections (ORP) and the Human Research Protection Office (HRPO) Submission | 1-4 | 100% | 100% |
| Coordinate with Sites for IRB protocol submission | 1-4 | 100% | 100% |
| Coordinate with Sites for CTSA sponsored Clinical Research Center (CRC) approval | 1-4 | 100% | 100% |

| | | | |
|---|---|---|---|
| Submit amendments, adverse events and protocol deviations as needed | As needed | As needed | As needed |
| Coordinate with Sites for annual IRB report for continuing review | Annually | Reapproved on 10/6/2021. | Reapproved on 03/01/2022. |
| *Milestone Achieved: Local IRB approval at AECOM/Monte and NYU* | 4 | 05/15/2018 | 05/02/2018 |
| *Milestone Achieved: HRPO and ORP approval for protocol* | 4 | 05/25/2018 | 2/5/2019 |
| **Subtask 2: Training of Study Staff** | | | |
| Coordinate with Sites for Coordinator training | 4-6 | 100%, 06/01/2018 | 100%, 06/01/2018 |
| Coordinate with Sites for training Raters until 100% concordance | 4-6 | 100%, 06/01/2018 | 100% 06/01/2018 |
| Complete Regulatory Binders | 4-6 | 100% | 100% |
| Create Manual of Operations | 4-6 | 100% | 100% |
| *Milestone Achieved: Research staff trained and Regulatory procedures set up* | 4-6 | 06/01/2018 | 06/01/18 |
| **Subtask 3: Facilitate Communication Between Sites and Staff** | | | |
| Coordinate with Sites bi-weekly meetings to review study goals, recruitment and enrollment | 1-48 | 100% | 100% |
| *Milestone Achieved: Bi-weekly meetings completed throughout study* | 1-48 | Study is ongoing | Study is ongoing |
| **Subtask 4: Assessments and Surveys Preparation** | | | |
| Finalize assessment measurements | 4-6 | 100% | 100% |
| Order all assessments and distribute across sites | 4-6 | 100% | 100% |
| Prepare Patient Study Binders including surveys and source documents | 4-6 | 100% | 100% |
| *Milestone Achieved: All study materials prepared for patient enrollment* | 4-6 | 100% | 100% |
| **Subtask 5: Receipt of Study Drug** | | | |
| Develop protocol with pharmacy for storage and dispensing of study drug/placebo and randomization protocol | 1-4 | 08/01/2018 | 08/01/2018 |
| Work with GW Pharma to ship study drug and placebo to sites | 6 | Drug shipped by GW to the US depot on 2/5/19; received at the US depot on 02/15/19; received at AECOM/MMC on 03/20/19. | Drug shipped by GW to the US depot on 2/5/19; received at the US depot on 02/15/19. NYU site received the drug supply on 11/19/2019 |
| *Milestone Achieved: Receipt of Study Drug and Placebo* | 6 | Achieved | Achieved |
| **Subtask 6: Data Management Preparation** | | | |
| Coordinate with Sites for flow chart for study steps, data collection and database requirements | 4-6 | 100% | 100% |
| Develop and Maintain Electronic Database at AECOM | 4-48 | 100%, maintenance is ongoing | 100%, maintenance is ongoing |
| *Milestone Achieved: Electronic database prepared and maintained throughout study* | 4-48 | Study is ongoing | Study is ongoing |
| **Major Task : Participant Recruitment and Enrollment** | | | |
| Subtask 1: Begin Subject Recruitment | | | |

| | | | |
|---|---|---|---|
| Contact patients in site databases | 6-42 | 100% | 100% |
| Advertise using internet and radio advertisements and study flyers | 6-42 | 99%, study is ongoing | 99%, study is ongoing |
| *Milestone Achieved: All patients in databases contacted* | 6 | 100%, ongoing | 100%, ongoing |
| *Milestone Achieved: 1st Advertisements are placed* | 6 | 100%, study is ongoing | 100%, study is ongoing |
| Subtask 2: Conduct Study | | | |
| Consent and screen potential patients and review I/E criteria (n=100) | 6-42 | Ongoing | Ongoing |
| Evaluate and assign eligible participants to one of the two randomized groups | 6-42 | Ongoing | Ongoing |
| Participants complete assigned condition over 12 weeks | 6-42 | Ongoing | Ongoing |
| Assess all participants at the appropriate study visits | 6-42 | Ongoing | Ongoing |
| *Milestone Achieved: Study Begins* | 6 | April 12 2019 | October 23 2019 |
| *Milestone Achieved: 1st Patient Consented and Enrolled* | 6 | April 12 2019 | January 14 2020 |
| *Milestone Achieved: Last Patient Consented and Enrolled* | 42 | Ongoing | Ongoing |

**What was accomplished under these goals?**
***Major Task 1: Preparatory Stage.***

**Subtask 1: Prepare and Submit Regulatory Documents.**

*Coordinate with Sites and GW Pharma for Clinical Trial Agreements (CTA) Submission.*

We regularly discussed all contract-related issues with Dr. Dhanonjoy C. Saha, Director of Office of Grant Support at AECOM/MMC. Furthermore, we conducted a series of conference calls for CTA negotiation and revisions with Deirdre Flaherty, Head of Pipeline Programs at GW Pharma, which occurred on 9/11/17, 10/20/17 and 10/23/17.

On 01/22/2018 we conducted a meeting between Dr. Eric Hollander (AECOM/MMC), Dr. Vera Nezgovorova (AECOM/MMC), Deirdre Flaherty (GW Pharma) and James Ryan (GW Pharma Contract Specialist) to finalize terms of statistical support for the project and discuss study drug dispense questions. Same day, a revised draft of the CTA was received for review by Dr. Dhanonjoy C. Saha, Director of Office of Grant support at AECOM/MMC. On 02/07/2018 we conducted a meeting with Attorney Laura Wilson-Youngblood, Assistant Counsel at AECOM/MMC, to review the terms before she could proceed for further negotiation of final details with GW Pharma.

On 03/16/18 a call between Attorney Laura Wilson-Youngblood, Assistant Counsel at AECOM/MMC, Deirdre Flaherty (GW Pharma), James Ryan (GW Pharma Contract Specialist), Dr. Eric Hollander (AECOM/MMC) and Dr. Vera Nezgovorova (AECOM/MMC) occurred to further negotiate details of the CTA with GW Pharma with an emphasis on Steering Committee charter development. It was decided that AECOM/MMC will proceed with CTA signature with GW Pharma, and a subcontract will be than issued between AECOM/MMC and NYU to document the terms of collaboration for this study. Subcontract between AECOM/MMC and NYU is currently being finalized.

Following that call, CTA updated by GW Pharma was reviewed by Einstein legal team, which included Lara Jean Ancona, Esq., Partner at Garfunkel Wild firm. Feedback on breaking the blind for the analyses; rights and liabilities of GW Pharma and feedback on publications committee has been incorporated. CTA and Steering Committee Charter were submitted for GW Pharma review on 03/30/18. To further address final terms of the agreement, a call between Dr. Volker Knappertz (Chief Medical Officer at GW Pharma), Deirdre Flaherty (GW Pharma) and Dr. Eric Hollander (AECOM/MMC) occurred on 05/03/18, where key points of the CTA were reviewed prior to its execution by legal teams on both sides. On 05/10/2018 Einstein legal team, comprising Attorney Laura Wilson-Youngblood, Assistant Counsel at AECOM/MMC and Lara Jean Ancona, Esq., Partner at Garfunkel Wild firm, had a call with James Ryan (GW Pharma Contract Specialist) to finalize terms of the CTA. Revisions to the contract in regards to IP and data analysis provisions were incorporated by GW Pharma contract department and Einstein legal team and sent to GW Pharma contract division for approval on 06/13/2018. GW Pharma contract division completed review of the revised contract terms on 07/18/2018. Dr. Eric Hollander (AECOM/MMC), Dr. Orrin Devinsky (NYU) and Dr. Volker Knappelz (Chief Medical Officer at GW Pharma) had a call on 07/20/2018 to discuss IP provisions for the CTA finalization. Einstein legal team had a series of calls with Cynthia Clark, attorney from Greenwich Biosciences (US subsidiary of GW Pharmaceuticals) on 07/18/2018, 08/07/2018, 08/20/2018 and 08/28/2018 to discuss IP provisions. Following these calls a budget was prepared to reflect additional funds that would be provided by GW to cover the creation of a study specific EDC (Electronic data capture solution), additional staff and pharmacy support, and for safety labs requested by the FDA. Budget was prepared for AECOM/MMC and NYU sites and submitted on 09/12/2018. On September 26 2018 Dr. Eric Hollander (AECOM/MMC), Casara Jean Ferretti (AECOM/MMC), Dr. Vera Nezgovorova (AECOM/MCC) had a call with GW Pharma financial team to review the submitted budget. Additional follow-up communication, which included calls and emails in regards to budget justification were conducted bi-weekly during October 2018 between AECOM/MMC team and GW Pharma team. On 11/16/18 GW Pharma finalized approval of the additional funding support, and the CTA contract between AECOM/MMC and GW Pharma was signed by GW Pharma. An amended contract between AECOM/MMC and GW was executed on 03/20/2019. Subcontract between AECOM/MMC and NYU was signed on 08/09/2019. An additional amendment for the contract between AECOM/MMC to reflect data management costs supplementation by GW was signed on 01/16/2020. Amendment to the contract between AECOM/MMC and GW Pharma was signed on 03/24/2021. Research subaward agreement amendment between AECOM/MMC and NYU was signed on 04/06/2021**. Research subaward agreement with NYU site was terminated on 03/09/2022 by AECOM/MMC and NYU officials. On 04/13/2022 Dr. Hollander confirmed to the DOD GOR, Dr. Tschiffely that NYU is no longer enrolling subjects under the DOD award and submitted a request to GOR to rebudget funds from NYU to AECOM/MMC site.**

*Coordinate with Sites and GW Pharma for Nondisclosure Agreements (NDA).*

Two-way confidentiality agreement between Montefiore Medical Center and GW Pharma has been signed as of June 3 2016, and the copy of the executed CDA is on file.

*Coordinate with GW Pharma and other sites for the continued work on the submission or resubmission of an Investigational New Drug (IND) Application to the U.S. Food and Drug Administration.*

During current reporting period, we obtained a study May proceed letter from an Investigational New Drug (IND) Application to the U.S. Food and Drug Administration.

This work was preceded by a series of email communications and phone calls organized by Kevin Hong (AECOM/MMC)) and Karen Twigden (GW Pharma), which took place on 7/26/17, 7/28/17, 8/7/17, 8/10/17, and 8/16/17. Dr. Hollander and Kevin Hong organized and participated in a meeting with Dr. Orrin Devinsky, Latoya King, and Anjanette Burns at NYU to review logistic obstacles and regulatory challenges associated with IND submission. Following that meeting on 9/11/2017, Dr. Hollander and GW Pharma agreed to delay IND application submission. It was suggested to wait until release of Edition 6 of the Investigator's Brochure (IB), as it would include updated pharmacokinetics and dosage regimen data pertinent to the upcoming IND submission. Upon release of IB edition 6 by GW Pharmaceuticals in preparation of our IND submission, we conducted a series of meetings with Dr. Michelle Wellborn (GW Pharma consultant) and Deirdre Flaherty (GW Pharma), which occurred on 11/22/2017, 11/27/2017 and 01/17/2018. Investigational New Drug Application to the U.S. Food and Drug Administration was submitted by us on 01/19/2018. It was received into Neurology Division Office on 02/01/2018 with assigned IND # 138371. Study May Proceed letter from Department of Health and Human services, Food and Drug Administration, Division of Psychiatry Products, Office of Drug Evaluation I, Center for Drug Evaluation and Research was received on 04/02/18 with non-hold comments. These non-hold clinical and clinical pharmacology comments were incorporated in the study protocol. Annual IND report was submitted on 07/22/2019 and its receipt was acknowledged on 07/31/2019. Annual IND report was submitted on 09/21/2020, and its receipt was acknowledged on 09/29/2020. **Annual IND report was submitted on 09/15/2021, and its receipt was acknowledged on the same day.**

*BNE application submission.*

On 10/9/17, Dr. Eric Hollander and Kevin Hong consulted Dr. Sheryl Haut, Director of the Adult Epilepsy Program and Chief of Neurology Service at AECOM/MMC, who had worked with a Cannabidiol containing compound from GW Pharma in the past to inquire about unanticipated challenges for the study implementation and were advised on importance of tandem submission to the Institutional Review Board and to the New York State Department of Health, Bureau of Narcotic Enforcement (BNE) for the timely BNE inspection scheduling and application processing.
We submitted application to the New York State Department of Health, Bureau of Narcotic Enforcement (BNE) for Class 7 Individual Researcher and Class 9 Importer licenses approvals in tandem with our IRB submission. Our BNE application was received as of 11/7/2017. Soon after AECOM/MMC Investigational Drug Service Pharmacy received BNE inspection for GW Pharma safe, which was approved. On 01/16/2018 after submitting conditional IRB approval notice for AECOM/MMC site, we were advised by Michele Mulloy, Regulatory Compliance Section Manager, Bureau of Narcotic Enforcement (BNE), that we would need to provide final unconditional IRB approval letter and IND approval letter from the FDA prior to the BNE final review and approval. Following FDA study May Proceed letter receipt on 04/02/18, we received an IRB approval letter without IND clause, which satisfied Bureau of Narcotic Enforcement (BNE) requirements. Case number for BNE inspection was assigned. As we were moving forward with BNE inspection, we were advised that an independent safe designated only for Dr. Hollander study would be required as a condition for BNE approval. Reconditioned Amsec Plate Steel Safe Model 2230 (right swing) UL-TL-30 1 Group 1R radiological lock: SG560 UL group 1 lock, SGD550 dial w/ 10" spindle; SGR167 ring, SC, SPKL was successfully ordered and installed on 04/16/18. Inspector Johnson from the BNE completed site and safe inspection on 04/18/18. BNE review was completed on 04/25/18. Dr. Hollander received Class 7 Individual Researcher and Class 9 Importer licenses approvals on 05/11/2018. Renewal of BNE Class 7 license application to engage in a controlled substance activity was submitted by Dr. Hollander on 02/03/2020 and was approved on 03/13/2020. BNE Class 7 license is effective from April 25 2020 to April 25 2022. **On 06/13/2022 Dr. Hollander confirmed to Mr. Johnson from the BNE license audit team, that since the compound in the study is no longer scheduled, BNE license is no longer needed.**

*DEA application submission.*

We communicated with Terrance Woodworth (GW Pharma consultant) and were advised to submit DEA application upon submission of our IND application prior to the IND approval by the FDA. Thus on 02/09/2018 we submitted DEA Schedule I application, which included the following items:
-DEA application form 225
-Certification that an IND application was submitted
-PI signed and dated CV
-Cover Letter
-Application Fee
-Copy of conditionally IRB approved study protocol
-IND acknowledgement letter
BNE approval and IND approval by the FDA are required for the subsequent DEA approval. IND approval by the FDA was received on 04/02/2018. However, in order to expedite DEA approval, we scheduled DEA Inspection on site. Inspector

Rivera completed DEA inspection at AECOM/MMC on 04/11/18. Additional DEA inspection to approve reconditioned Amsec Plate Steel Safe Model 2230 (right swing) UL-TL-30 1 Group 1R radiological lock: SG560 UL group 1 lock, SGD550 dial w/ 10" spindle; SGR167 ring, SC, SPKL was conducted by Inspector Rivera on 05/18/2018. DEA Schedule I license was received on June 26 2018. Upon DEA annual renewal requirements, it was renewed 09/05/2018 and 09/18/2019 and was valid through 10/31/2020. As of March 20, 2020, DEA formally notified GW/Greenwich Biosciences Inc. that they considered GW's products, including CBDV and GWP42006 to be non-controlled substances. Recently, DEA also published this information in the Federal Register. We also received a memo from GW/Greenwich Biosciences Inc. on June 8 2020, which was acknowledged by Einstein IRB, #1 East on 06/11/2020 with reference #065366.

Since the CBDV used in the study is no longer a controlled substance, there is no further need for Dr. Hollander to have the DEA Schedule I Researcher registration i.e. to extend his registration.

*Finalize consent form and human subjects protocol.*

After programmatic review and subsequent follow-up communications with Dr. Stan Niu, Science Officer at the Department of Defense, requested changes in the protocol have been incorporated. After a conference call on 10/20/17 between Dr. Eric Hollander (AECOM/MMC), Dr. Orrin Devinsky (NYU), Dr. Volker Knappertz (Chief Medical Office at GW Pharma), Deirdre Flaherty (GW Pharma), James Ryan (Contract specialist at GW Pharma), Dr. Vera Nezgovorova (AECOM/MMC), Kevin Hong (AECOM/MMC), Danya Schlussel (AECOM/MMC) and Dr. Bonnie Taylor (AECOM/MMC), language was added to eligibility criteria regarding parent consent and child assent; exclusion criteria were specified regarding history of drug abuse. As the protocol was finalized, Dr. Hollander deemed that these additions were not substantive, and that they would not affect study recruitment process or statistical power.

Following a meeting on 11/22/17 between Dr. Eric Hollander (AECOM/MMC), Dr. Orrin Devinsky (NYU), Deirdre Flaherty (GW Pharma), Dr. Terrance Woodworth (GW Pharma), Dr. Michelle Wellborn (GW Pharma), Dr. Kenneth Sommerville (GW Pharma) Dr. Vera Nezgovorova (AECOM/MMC), Danya Schlussel (AECOM/MMC) and Dr. Bonnie Taylor (AECOM/MMC), language was added to human subjects protocol to include safety assessments. It was concluded that Columbia Suicide Severity Rating Scale will be administered in the beginning of each study visit. Following this meeting schedule of events was updated to include safety labs. As an additional statistical analysis not affecting statistical power, age of subject was proposed to be a covariate. Appendix A on P450 Drug Interactions, Flockchart table and Appendix B on U91A9 or U9T2B7 potential interactions were added to the human subjects protocol. Informed consent was revised to include language specifying potentials benefits to the study participant. IDSMC (Independent Data Safety Monitoring Committee) charter was developed and its members were confirmed. As the protocol and informed consent were finalized, Dr. Hollander deemed that these additions were not substantive, and that they would not affect study recruitment process or statistical power.

The following changes were made to the study protocol and ICF following HRPO ORP comments received on 02/13/18, and were IRB approved on 03/28/18:

1. Protocol: Section L: As required by the Human Research Protections Office (HRPO)/U.S. Army Medical Research and Materiel Command (USAMRMC) the role and responsibilities of the Research Monitor have been modified and now include: May discuss the protocol with the investigators, interview subjects, and consult with others outside the study about the research; Shall have the authority to stop the protocol, remove subjects from the protocol, and take any necessary steps to protect the safety and well-being of subjects until the IRB can assess the Monitor's report; Shall have the responsibility to promptly report their observations and findings to the IRB or other designated official; Is required to review all unanticipated problems involving risks to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the research monitor must comment on the outcomes of the event or problem and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The research monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or research monitor to be possibly or definitely related to participation and report of events resulting in death must be promptly forwarded to the USAMRMC ORP HRPO.
2. Protocol: Section C7: As required by the Human Research Protections Office (HRPO)/U.S. Army Medical Research and Materiel Command (USAMRMC), the protocol must describe how participation in the research is intended to be beneficial to each subject participating in the study and the benefit(s) must apply to both the treatment and placebo groups. This section has been modified accordingly.
3. Consent Form: Page 7: The "Benefits" section of the ICF has been modified according to #2 above

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 12/13/2018 with reference #047991:**

Addition of Investigator Brochure Edition 7, September 18.

Amendment to the study protocol:
1. change of version of VABS-II scales to VABS-3
2. addition of MERS scale
3. per FDA non-hold comments:
a) Laboratory safety studies were added to Week 2 study visit to identify any abnormality occurring early in the study drug exposure.

b) As it was recommended to monitor blood levels during the titration phase as well, to ensure safe use of the background medications that are mainly metabolized by CYP2C19, CYP3A4, UGT1A9, or UGT2B7, we will monitor for plasma drug levels of VPA, Lamotrigine, Oxcarbazepine, Phenytoin and Clobazam if applicable to any patient. Other medications may be monitored on a patient by patient basis, if there are safety concerns suspected to be related to a drug-drug interaction.
c) language was added, that the exclusion of medications that are potent inhibitors or inducers of CYP2C9 is not required.
d) language was added, that study drug is administered with food consistently throughout the study.
e) protocol wording on section C1 (page 10) and H (page 25) was amended to indicate that only patients with ABC-I≥18 will be included rather that refer to 'stratified for marked irritability' and 'stratified for ABC-I≥18'.
f) the protocol text for 'Analysis in regard to ABC-SW' is amended to specify more clearly the planned analysis.
4. Addition of GW Pharmaceuticals as additional funding source.

Amendment to informed consent:
1. Change of VABS-II to VABS-3 scales (as new version of VABS appeared).
2. Addition of GW Pharmaceuticals as additional funding source.

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 03/27/2019 with reference # 051122:**

1. Adding second location for the CRC (1300 Morris park ave) at 1572 form.
2. Changes in the protocol:
a) removing line "module 4 will be used in this study" for ADOS-2 scale on page 17 of the protocol
b) removing Social Responsiveness Scale (SRS) from baseline assessments ( p. 20 of the protocol)
c) adding Dr. J. Battaglia as research monitor (p.26 of the protocol).

On 04/08/2019 first IDSMC meeting has occurred, and following that meeting was decided to add sesame oil allergy as an exclusion criterion to the study protocol on page 12.

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 04/16/2019 with reference # 051762:**
addition of sesame oil allergy as an exclusion criteria to the study protocol on page 12.

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 10/04/2019 with reference #056458:**
1. Addition of IB version 7.1. Summary of changes table is provided at page 79 of IB. Major updates included are final clinical data from a Phase 1 pharmacokinetic (PK) trial and a Phase 2 trial in focal seizures, pharmacology, absorption, distribution, metabolism and excretion (ADME), and toxicology studies. The cut-off for IB edition 7 was 31 July 2018 and included information from Development Core Safety Information (DCSI; cut-off 27 September 2018).
2. Changes in the study protocol:
 1) change in exclusion criteria 11 to reflect liver dysfunction manifested by > 2 X UNL values of AST or ALT
 2) liver function tests to be done at week 2 and week 8.
 3) addition of the MediData RAVE electronic data capture (EDC) system developed by Bioforum Data Masters.
3. Changes to ICF:
 1) addition of a new pager number
 2) use of finger prick technology for blood draw at week 2 and week 8
4. change to the assent:
 addition of word finger to the section "Will it hurt to be in the study".

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 10/17/2019 with reference #057064:**
We have added a line to the ICF saying patients will have the option of choosing either needle draw or finger prick for week 2 and week 8 lab work based on their comfort level/ preference

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 11/13/2019 with reference #057577.**
Changes on page 17, Section VI: Adding a line at the end of the paragraph to specify that the MERS will be completed only for subjects who display rigid behaviors.
Section VII b: Adding a line at the end of the paragraph to specify that the IQ test will be completed only if the subject is capable of doing so.
Following change was made in the ICF: the signature section on pg 9- i) Caregiver/ Legal Guardian is being changed to Parent/ Legal Guardian and, ii) Printed Name of Participant is being changed to Printed Name of Parent/ Legal Guardian.

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 01/29/2020 with reference #060025.**
Recruitment flyer and text for Montefiore e-screens, and Einstein update email text was approved to help facilitate recruitment efforts.

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 03/14/2020 with reference #060950, combined with # 059792.**
Addition of IB edition 8, issue date December 2019. Changes to the ICF based on request received from the study sponsor (02/24/2020) in reference to changes in the IB edition 8.
Summary of changes based on new information in the IB edition 8, which don't affect risk versus benefit relationship to the study protocol, and which included the following addition to the ICF (pp. 6-7):

*"Risks of Taking CBDV*
To date, 282 people (adult patients and healthy adult volunteers) have taken GWP42006 as a research participant in a GW-sponsored clinical trial. The side effects reported by people who have taken GWP42006 were generally mild to moderate in severity.
In a GW-sponsored trial which looked at convulsions in a type of epilepsy, the following common side effects were reported:

Very common side effects (affected more than 1 person in every 10)
- Diarrhea.
- Feeling sleepy.

Common side effects (affected 3 or more people in every 100)
- Feeling nauseous.
- Headache.
- Feeling dizzy.
- Stomach-ache/pain.
- Changes in blood tests that look at how the liver works.
- Changes in anticonvulsant drug levels in the blood.
- Low sodium levels in blood.
- Anemia (low iron levels in blood).
- Back pain.
- Feeling itchy
- Rash.
- Convulsions (only in people who have had convulsions before).

There may be other risks of CBDV that are currently unknown. If you are concerned, please contact your child's trial physician. As GWP42006 may affect the results of some blood tests, if your child needs a blood test please tell the tester that he/she is taking cannabidivarin as part of a clinical trial."

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 03/18/2020 with reference # 062721.**
Letter to enrolled subjects to inform them of changes approved in the amendment #059792. Due to COVID-19 situation, letter was approved to be sent via email.

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 04/11/2020 with reference #063312 and clarification # 063901 approved on 05/04/2020.**
Addition of dietary diary and body composition analysis via bioimpedance to the protocol and ICF at baseline and all subsequent visits. Addition of information on specimen and information banking to the ICF.
Addition of these measures (dietary diary and body composition analysis via bioimpedance) doesn't change risk versus benefit relationship for the study protocol.
Clarification #063901 specifies that amendment #063312 introduced changes are only applicable for Montefiore-Einstein site and not NYU site.

**Following acknowledgement approved by Einstein IRB#1, East on 06/11/2020 with reference #065366.**
Correspondence from GW Pharmaceuticals and their correspondence with DEA on the de-scheduling of CBDV.

**Following non-substantial changes to ensure participant safety and reduce participant burden during the COVID-19 pandemic were made and approved by Einstein IRB#1, East on 07/06/2020 with reference # 066128.**

1) Reducing the number of on-site visits. Screening, week 2, week 6, week 10 and week 14 visits will be done remotely.
2) Informed consent will be done remotely at the screening visit and in person at the baseline visit.
3) Physical and Neurological exam will be done at all on-site visits only.
4) IQ test will be done at the baseline visit.
5)ECG will be done at the baseline visit and at week 12.
6) ADOS-2 will be done at the baseline visit not at screening.
7) C-SSRS will be done at all visits except for screening.
8) Dietary Diary will be done at all visits except for screening.
9) Vital signs, weight and BMI will be done at all on-site visits only.
10) Pregnancy test at all visits except for week 10 and week 14.
11) AE monitoring at all visits except for screening and baseline
12) CBC with differential and basic metabolic panel at screening and all on site visits
13) Liver function enzymes and AED drug levels at all visits except for week 10 and week 14.
14) Menstrual Diary at all visits except for screening and week 14.
15) Medication dispensed only at baseline, week 4 and week 8.
16) ABC scale to be done at screening, baseline, week 4, week 8, week 12, and week 14.
17) RBS-R to be done at baseline, week 4, week 8, week 12, and week 14.
18) MERS scale to be done at baseline, week 4, week 8, week 12, and week 14.
19) PedsQL to be done at baseline, week 4, week 8, week 12, and week 14.
20) CGI-I to be done at week 4, week 8, week 12, and week 14.
21) CGI-S to be done at screening, baseline, week 4, week 8, week 12, and week 14.

All labs during remote visits will be done at a local Quest Diagnostics facility convenient to the participant's location.

**Following non-substantial changes to ensure participant safety and reduce participant burden during the COVID-19 pandemic were made and approved by Einstein IRB#1, East on 08/10/2020 with reference # 067116 and following formatting change was approved with reference #067785 on 08/17/2020.**

a) Including Quest Diagnostics in the IRB application as an external site Not Engaged in Research. All lab work for the study during remote visits will be done at a Quest Diagnostics location convenient to the participant. Also editing the informed consent process section of the application-- 25.2 and 25.4.
b) Revising the protocol to incorporate the changes below:

1) Added ABC sub-scales to be secondary measures
2) Added ADI-R as a substitute for ADOS-2 if ADOS-2 can't be performed due to site restriction (face mask)
3) Allow ADOS-2/ADI-R from within 12 months to be used to meet eligibility
4) Reduced the number of AED drug testing to baseline, weeks 4, 8, 12 only
5) Updated schedule of events
6) Revised languages in section C5 safety assessment to reflect the changes in schedule of events
7) Clarified language in section C8.2 secondary measures to reflect frequencies per schedule of events
8) Updated language in section C9.1 on consent
9) Updated language in section C9.2 to clarify remote and in-person visit details
10) Added section C 9.3 for special circumstances (ie COVID-19)

c) Revising the consent to reflect the changes mentioned above. The new Einstein IRB ICF template for Greater than Minimal Risk studies has been used for this version.

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 9/18/2020 with reference # 068273:**
Submission of revised assent form with removal of witness signature field and time field to match the current assent formatting standards.

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 10/30/2020 with reference # 070030:**

1) Submission of the Montefiore social media request form which will be used to post ads for our study on Montefiore's social media pages
2) Revision of the phone screening script to be consistent with the recent version of the protocol

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 12/07/2020 with reference # 070974:** addition of the second DSMC meeting minutes and blinded data tables.

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 02/04/2021 with reference # 073117:** Addition of recruitment materials in Montefiore/ Einstein social media advertising templates.

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 07/19/2021 with reference #078073:** Adding most recent IDSMC committee meeting minutes and blinded data tables.

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 10/28/2021 with reference # 081568:**

1. Clarified in exclusion criteria that only genetic conditions with direct association to ASD or ASD like symptoms would lead to exclusion
2. Clarified that pregnancy test will be performed at screening, baseline, weeks 2, 4, 6, 12 via urine or blood sample
3. Clarified CSSR-S will be completed for patients capable of answering the questionnaire in conjunction with safety questions for patients unable to complete CSSRS
4. Clarified drug testing will be done by blood if patient unable to provide urine
5. Clarified patient is to maintain menstrual diary throughout study period and it will be reviewed monthly in clinic for applicable patient
6. Reduced dietary diary to only occur at baseline, weeks 4, 8 and 12
7. Clarified patient scale RBR, and PedsQL at week 14 will be checked for completion at visit and if incomplete, will allow for clinician-administered at time of visit
8. Removed LFT lab at Week 6 (Quest)
9. Corresponding changes to schedule of events
10. General formatting and typographic correction
11. Added in special circumstances section G for patient with > 3 mo between screen lab and baseline, drug administration will occur after baseline lab result is cleared by study clinician and communicated to pt
12. Corresponding change to ICF

**Following non-substantial changes were made and approved by Einstein IRB#1, East on 01/24/2022 with reference # 083623:** addition of the third IDSMC meeting minutes and blinded data tables.

*Finalize recruitment materials.*

Drafting of recruitment materials, including flyers, advertisements, and referral solicitations was completed. Recruitment flyer and text for Montefiore e-screens, and Einstein update email was approved by Einstein IRB #1 on 01/29/2020 with reference # 060025 to help facilitate recruitment efforts.

*Coordinate with sites for the US Army Medical Research and Material Command Office of Research Protections (ORP) and the Human Research Protection Office (HRPO) Submission.*

HRPO received our initial submission on 10/31/17. The following items were included:
-HRPO Protocol Submission Form
-Principal Investigator CV, Independent Medical Monitor bio-sketch
-Documentation of Human Subjects Training for all the Investigators at the Einstein site
-Updated FDA Form 1572
-Informed Consent, Assent, HIPAA forms
-Letters of Support from Collaborating Institutions (NYU, GW Pharma)
-Updated Research Protocol
-Peer and Programmatic Review of Protocol
-Email Correspondence with Protocol Changes
-Study Instruments and Data Collection Forms. The following items were included:
-Aberrant Behavior Checklist (ABC) – Irritability, Social Withdrawal
-Repetitive Behavior Scale – Revised (RBS-R)
-Pediatric Quality of Life Inventory (PedsQL) Family Impact Module
-Vineland Adaptive Behavior Scale – II (VABS-II)
-Clinical Global Impression Scale – Improvement, Severity (CGI-I, CGI-S)

-IQ Test: Stanford-Binet Intelligence Scales, 5e
-Autism Diagnostic Observation Schedule – II (ADOS-II)
-Social Responsiveness Scale (SRS)

On 02/08/2018 upon request we submitted to Dr. Margaret Frederick additional items from AECOM/MMC site, and then our application was routed by her to the Approval Authority by COB for HRPO pre-review. Following items were included in this additional submission:

-Investigators Brochure Edition 6, GW Pharmaceuticals
-Einstein IRB conditional approval notice
-Conditionally IRB approved Research Protocol
-Conditionally IRB approved Informed Consent, Assent and informed consent feedback tool.
-IND acknowledgement letter
-CITI GCP certificate of Dr. A. Djukic (medical monitor)
- Human subject's protection training of Dr. A.Djukic (medical monitor)

On 02/13/18 we received following comments from HRPO:
A. Required Information/Documents.

1. Provide the final IRB submission package, approval memo, and stamped consent and assent forms when available.
2. Ensure that the IRB approval memo or other communication from the IRB states the risk category for the inclusion of children (either 45 CFR 46.404, 45 CFR 46.405, or 45 CFR 46.406).

B. Revisions to be made to the protocol.

1. The role and responsibilities of the Research Monitor, Dr. Djukic, must include the following.

a) May discuss the protocol with the investigators, interview subjects, and consult with others outside the study about the research.

b) Shall have the authority to stop the protocol, remove subjects from the protocol, and take any necessary steps to protect the safety and well-being of subjects until the IRB can assess the Monitor's report.

c) Shall have the responsibility to promptly report their observations and findings to the IRB or other designated official.

d) Is required to review all unanticipated problems involving risks to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the research monitor must comment on the outcomes of the event or problem and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The research monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator.

e) Reports for events determined by either the investigator or research monitor to be possibly or definitely related to participation and report of events resulting in death must be promptly forwarded to the USAMRMC ORP HRPO.

2. BENEFITS to subjects - The protocol states in Section C7 that "It may or may not directly benefit the subjects." The consent form states on page 7 that "There may or may not be a direct medical benefit to you from being in this research study." As this protocol involves an experiment where the primary purpose is to determine the effect of the intervention, the requirements under 10 USC 980 apply. Since the protocol requires the informed consent from a legally authorized representative or parent, the protocol must describe how participation in the research is intended to be beneficial to each subject participating in the study. This cannot include monetary compensation or possible benefit from the study drug, as the benefit is not yet known and not all subjects will receive the study drug. The benefit(s) must apply to both the treatment and placebo groups. The benefit(s) can take many forms. The protocol could possibly include providing education to the families on strategies to handle irritability or other symptoms of ASD, or providing feedback to the families on the results from the behavioral testing that may help them handle symptoms of ASD. These are just suggestions. The PI must revised Section C7 to describe the benefit(s) to the subjects.

C. Revisions to be made to the consent form (Version dated 9 February 2017).

1.BENEFITS to subjects - Once the protocol has been updated to describe the benefit to the subjects, the description of this benefit must be added to the consent form page 7.

They were addressed as summarized above and approved by HRPO for the IRB submission.
On 03/23/18 revised protocol and ICF were submitted to IRB and were approved on 03/28/18. After obtaining FDA study May Proceed letter on 04/02/18, we then submitted it to HRPO as well on 04/03/2018. On 04/13/18 we confirmed with Dr.

Gloria Lawrence, Dr. Margaret Frederick successor from ORP HRPO, that the only outstanding item for HRPO approval is unconditional IRB approval (pending BNE and DEA approval).

We submitted NYU IRB approval to HRPO ORP on 05/02/2018 as it was received.

On 05/16/2018 we submitted to ORP HRPO Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) Approval letter #035849. ORP HRPO approval for AECOM/MMC site HRPO Log Number A-20351.a was granted on 05/25/2018.
On 12/19/2018 Albert Einstein College of Medicine Continuing Review report (Log Number A-20351.a) was submitted to ORP HRPO. On 01/14/2019 ORP HRPO accepted Albert Einstein College of Medicine Continuing Review report and supporting documents.
ORP HRPO approval for NYU site HRPO Log Number A-20351.b was granted on 02/05/2019. NYU site Continuing review report was accepted by HRPO ORP on 04/01/2019 and on 04/16/2020.

On 05/02/2019 AECOM/MMC submitted following amendment to the study protocol to ORP HRPO (Log Number A-20351.a)
1) change in Independent Research Monitor name to Dr. Battaglia (his CV and GCP training are on file)
2) addition of exclusion criteria (allergy to sesame oil) on page 12 of the protocol.

On 11/13/2019 AECOM/MMC site submitted Continuing Review Report to ORP HRPO (Log Number A-20351.a).
On 01/27/2020 ORP HRPO accepted Albert Einstein College of Medicine Continuing Review report and supporting documents.

On 08/19/2020 AECOM/MMC site submitted following amendments to the study protocol to ORP HRPO (Log Number A-20351.a) and it was acknowledged on 08/21/2020. We further received a confirmation on 08/25/2020 that changes being made do not meet ORP HRPO criteria for substantive amendments and do not require HRPO approval prior to implementation.

On 10/29/2020 AECOM/MMC site submitted Continuing Review Report to ORP HRPO (Log Number A-20351.a).
On 11/4/2020 ORP HRPO accepted Albert Einstein College of Medicine Continuing Review report and supporting documents.

On 03/04/2021 NYU site submitted Continuing Review Report to ORP HRPO (Log Number A-20351.b).
On 03/24/2021 ORP HRPO accepted NYU Continuing Review Report (Log Number A-20351.b) and supporting documents.

**On 10/14/2021 AECOM/MMC site submitted Continuing Review Report to ORP HRPO (Log Number A-20351.a).**
**On 10/26/2021 ORP HRPO accepted Albert Einstein College of Medicine Continuing Review report and supporting documents.**
**On 05/11/2022 NYU site submitted Continuing Review Report to ORP HRPO (Log Number A-20351.b).**

*Coordinate with sites for IRB protocol submission.*
Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) received our initial IRB submission on 11/1/17. The following items were included: research protocol, parent consent/HIPAA forms, child assent form.

On 12/13/2017 Dr. Eric Hollander (AECOM/MMC) participated in Einstein IRB review meeting of the study protocol. Questions on frequency of Independent Data Safety Monitoring Committee (IDSMC) meetings, benefits to the child and psychoactive properties of CBDV have arisen, and were addressed during the meeting and in following the meeting correspondence.

On 01/08/2018 AECOM/MMC site received conditional IRB approval pending IND approval from the FDA, DEA license for schedule I substance, approval from Bureau of Narcotics, DEA approval to Pharmacy for additional storage space.

On 04/03/2018 AECOM/MMC site received conditional IRB approval pending approval from Bureau of Narcotics, DEA license for schedule I substance and DEA approval to Pharmacy for additional storage space.

On 05/11/2018 AECOM/MMC site received conditional IRB approval pending DEA license for schedule I substance and DEA approval to Pharmacy for additional storage space.

On 05/15/2018 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) Approval letter #035849.

DEA license for Schedule I substance and DEA approval to Pharmacy for additional storage space (letter from Clemencia Solorzano were submitted as amendment and acknowledged by Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East).

Progress report was submitted to Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) on 11/2/2018. Study protocol was reapproved on 11/12/2018 with reference # 046713.

On 12/13/2018 Albert Einstein College of Medicine Institutional Review Board (Einstein IRB#1, East) approved protocol amendment with reference # 047991. Non-substantial changes were made as outlined on pp.10.

On 03/27/2019 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval #051122 for the protocol amendment. Non-substantial changes were made as outlined on pp.11.

On 04/16/2019 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval #051762 for the protocol amendment. Non-substantial changes were made as outlined on pp.11.

On 10/04/2019 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval # 056458 for the protocol amendment. Non-substantial changes were made as outlined on pp.11.

On 10/17/2019 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval #057064 for the protocol amendment. Non-substantial changes were made as outlined on pp.11.

Progress report was submitted to Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) on 10/11/2019. Study protocol was reapproved on 10/28/2019 with reference # 057029.

On 11/13/2019 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval #057577 for the protocol amendment. Non-substantial changes were made as outlined on pp.11.

On 01/29/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval #060025 for the protocol amendment. Non-substantial changes were made as outlined on pp.12.

On 03/14/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval #060950 combined with #059792.Non-substantial changes were made as outlined on pp.12

On 03/18/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval #062721. Non-substantial changes were made as outlined on pp.12.

On 04/11/202 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #063312 and subsequent clarification # 063901 was approved on 05/04/2020. Non-substantial changes were made as outlined on pp.12.

On 06/11/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board acknowledgement with reference #065366. Non-substantial changes were made as outlined on pp.12.

On 07/06/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #066128. Non-substantial changes were made as outlined on pp.13.

On 08/10/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference # 067116 and formatting change was approved with reference #067785 on 08/17/2020. Non-substantial changes were made as outlined on pp.13.

On 08/19/2020 AECOM/MMC site submitted amendments to the study protocol to ORP HRPO (Log Number A-20351.a) and it was acknowledged on 08/21/2020. We further received a confirmation on 08/25/2020 that changes being made do not meet ORP HRPO criteria for substantive amendments and do not require HRPO approval prior to implementation.

Progress report was submitted to Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) on 09/16/2020 with reference # 068608. Study protocol was reapproved on 10/08/2020 with reference # 068608.

On 09/18/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #068273. Non-substantial changes were made as outlined on pp.13.

On 10/29/2020 AECOM/MMC site submitted Continuing Review Report to ORP HRPO (Log Number A-20351.a).
On 11/4/2020 ORP HRPO accepted Albert Einstein College of Medicine Continuing Review report and supporting documents.

On 10/30/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #070030. Non-substantial changes were made as outlined on pp.13.

On 12/07/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #070974. Non-substantial changes were made as outlined on pp.14.

On 02/04/2021 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #073177. Non-substantial changes were made as outlined on pp.14.

On 07/19/2021 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #078073. Non-substantial changes were made as outlined on pp.14.

**Progress report was submitted to Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) on 09/15/2021 with reference # 080502. Study protocol was reapproved on 10/06/2021 with reference # 080502.**

**On 10/28/2021 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #081568. Non-substantial changes were made as outlined on pp.14.**

**On 01/24/22 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #083623. Non-substantial changes were made as outlined on pp.14.**

Dr. Orrin Devinsky submitted to the New York University Langone Medical Center IRB #6 on 02/16/2018. His submission was delayed by the requirement to obtain IND # prior to the submission. AECOM/MMC site shared all IRB approved documents with NYU site to facilitate their submission, as we obtained IND#138371 as of 02/07/2018 in the mail. NYU site subsequently amended their IRB submission once HRPO comments were addressed by AECOM/MMC site and FDA study May Proceed letter was received on 04/02/2018. NYU site received IRB approval on 05/02/2018. This approval was submitted as amendment and acknowledged by Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East).
NYU site submitted Continuing review to their IRB on 03/15/2019 and received protocol reapproval on 03/20/2019.
NYU site submitted protocol amendments (same as Einstein site, outlined on p.7) on 04/19/19 and received approval on 05/14/2019. They subsequently submitted protocol amendments (same as Einstein site, outlined on p.7) and received approvals on 1/7/2020, 1/15/2020 and 2/4/2020.
NYU site Continuing Review #2 was submitted to their IRB on 3/5/2020 and received protocol reapproval on 3/17/2020.
Modification #12 for NYU site was on submitted 3/13/2020, and approved on 3/17/2020 (removal of personnel Kimberly Menzer, NP). Modification #13 for NYU site was submitted on 3/19/2020 and approved 3/27/2020 (addition of personnel Dana Price, MD). On 8/24/2020 NYU site submitted COVID-19 related amendment to their IRB which consisted in 1) updating protocol that some visits and procedures to be completed remotely by telephone or computer in order to decrease exposure risk during the COVID-19 pandemic. For these remote visits, any required labs will be collected at the subject's local Quest location; 2) updating main consent, 7-11 y.o. and 12-14 y.o. assents, and key information form to reflect protocol changes. NYU IRB approval for the COVID-19 related amendment was obtained on 9/30/2020.
NYU site Continuing Review #3 was submitted to their IRB on 02/19/2021 and received protocol reapproval on 03/09/2021.
**NYU site Continuing Review #4 was submitted to their IRB on 01/19/2022 and received reapproval on 03/01/2022.**
**On 05/11/2022 NYU site submitted Continuing Review Report to ORP HRPO (Log Number A-20351.b).**

*Coordinate with sites for CTSA-sponsored Clinical Research Center (CRC) approval.*

Application for Einstein-Montefiore CTSA-sponsored ICTR Clinical Research Center (CRC) was received on 11/10/2017. The following items were included: research protocol, parent consent form, child assent form, PI bio-sketch, study budget, projected use of CRC resources. We obtained ICTR approval notice on 11/28/2017 pending unconditional IRB approval. Following Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) Approval letter #035849 receipt on 05/15/2018 we submitted it to ICTR and conducted CRC initiation visit. Dr. Orrin Devinsky completed submission for NYU CTSA-sponsored CRC. His submission was delayed by the requirement to obtain IND # prior to the submission. NYU site IRB approval was granted on 05/02/2018.

*Submit amendments, adverse events, and protocol deviations as needed.*
All amendments, adverse events, and protocol deviations will be reported and documented as they arise.

*Coordinate with sites for annual IRB report for continuing review.*
As the study progressed, investigators and coordinators at AECOM/MMC, NYU, and GW Pharma communicated regularly in regard to initial IRB submissions and remain accountable for timely review of all regulatory activities relevant to annual IRB reporting. Progress report was submitted to Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) on 11/2/2018. Study protocol was reapproved on 11/12/2018 with reference # 046713. Progress report was submitted to Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) on 10/11/2019. Study protocol was reapproved on 10/28/2019 with reference # 057029. Progress report was submitted to Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) on 09/16/2020 with reference # 068608. Study protocol was reapproved on 10/08/2020 with reference # 068608. **Progress report was submitted to Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) on 09/15/2021 with reference # 080502. Study protocol was reapproved on 10/06/2021 with reference # 080502.**

NYU site submitted Continuing review#1 to their IRB on 03/15/2019 and received reapproval on 03/20/2019.
NYU site Continuing Review #2 was submitted to their IRB on 03/5/2020 and received reapproval on 03/17/2020.
NYU site Continuing Review #3 was submitted to their IRB on 02/19/2021 and received reapproval on 03/09/2021.
**NYU site Continuing Review #4 was submitted to their IRB on 01/19/2022 and received reapproval on 03/01/2022.**

**Subtask 2: Training of Study Staff**
Rater training was conducted on 06/01/2018. We completed regulatory binders and created manual of operations and IDSMC charter. Additional psychologist from NYU team, Dr. Michelle Lee, was trained on MERS scale on 09/20/2019.

**Subtask 3: Facilitate Communication between Sites and Staff**
We coordinate with NYU site weekly to review study goals and status of regulatory documents submission.
**On 04/13/2022 Dr. Hollander confirmed to the DOD GOR that NYU is no longer enrolling subjects under the DOD award and submitted a request to GOR to rebudget funds from NYU to AECOM/MMC site.**

**Subtask 4: Assessments and Surveys Preparation**
We finalized assessment measurements. We ordered study assessments and distributed them across sites.
We prepared patient study binders including surveys and source documents at AECOM/MMC site. NYU team did the same for NYU site.

**Subtask 5: Receipt of Study Drug**

We finalized with pharmacy protocol for storage and dispensing of study drug/placebo and randomization.
On 01/31/2018 Dr. Eric Hollander (AECOM/MMC) and Dr. Vera Nezgovorova (AECOM/MMC) met with Manager of Investigational Pharmacy at AECOM/MMC Dr. Clemencia Solorzano and Dr. Mark Sinett, Director of Clinical Services at AECOM/MMC to review dispensing of study drug/placebo strategy and confirmed storage space in GW designated safe, which is currently BNE and DEA approved.
As we were moving forward with BNE inspection, we were advised that an independent safe designated only for Dr. Hollander study would be required as a condition for BNE approval. Reconditioned Amsec Plate Steel Safe Model 2230 (right swing) UL-TL-30 1 Group 1R radiological lock: SG560 UL group 1 lock, SGD550 dial w/ 10" spindle; SGR167 ring, SC, SPKL was successfully ordered and installed on 04/16/18. We completed randomization protocol preparation on 08/01/2018.
On 09/27/2018, 10/19/18, 12/7/18, 1/9/19 we conducted a series of call between Dr. Clemencia Solorzano, Manager of Investigational Pharmacy at AECOM/MMC, Dr. Freda Afrifa (Pharmacist at AECOM/MMC) and GW Pharma team involved in drug shipment and operations (Hetal Patel, PharmD and Jan Joscak, PharmD). Randomization table was finalized. We prepared end-use letter for drug shipment. Due to unforeseen issues with drug labeling occurred from the GW side drug shipment was delayed, and was shipped from UK to the US depot on 02/05/2019. Study drug was received at the US depot on 02/15/2019, and was received at AECOM/MMC pharmacy on 03/20/19. On 03/25/2019 AECOM/MMC site staff members completed training on pharmacy operating procedures required for successful execution of this study protocol. On 09/27/2019 NYU site staff members completed training on pharmacy operating procedures required for successful execution of this study protocol. NYU site was activated as of 10/23/2019 following regulatory clearance by GW pharmaceuticals to initiate drug shipment. NYU site received drug on site on 11/19/2019.

**Subtask 6: Data Management Preparation**

Follow-up communication, which included calls and emails in regards to budget justification were conducted bi-weekly during October 2018 between AECOM/MMC team and GW Pharma team. GW agreed to provide funding support for the creation of a study-specific EDC (electronic data capture solution) using the Bioforum data masters. On 11/16/18 GW Pharma finalized approval of the additional funding support, and the CTA contract between AECOM/MMC and GW Pharma was signed by GW Pharma. AECOM/MMC signed a contract with Bioforum Data Masters on 01/30/2019. We finalized

eCRFs development and completed UAT (user acceptance testing) phase. Electronic data capture system went live on 12/11/2019 for data entry and data management. Data entry at both sites is ongoing. EDC system was adjusted for a protocol change due to COVID-19 Pandemic.

**Major Task: Participant Recruitment and Enrollment.**

**Subtask 1: Begin Subject recruitment.**

Currently, patients have been contacted in site databases, and 150 patients were identified. First patient was screened on 04/12/2019 and randomized on 04/26/2019 at AECOM MMC site. First patient was screened on 01/14/2020 and is waiting to be randomized after the COVID-19 pandemic situation subsides at NYU site.

**Subtask 2: Conduct study.**

First patient was screened on 04/12/2019 and randomized on 04/26/2019 at Montefiore Medical Center site. At the NYU site, the first patient was screened on 01/14/2020 and is waiting to be randomized after the COVID-19 pandemic situation subsides.

Study is ongoing. Prior to COVID-19 pandemic onset, we have projected a total of 100 patients enrolled by end of Q4 year 5, at the two sites, including AECOM/MMC and NYU (consisting of 16 subjects to be enrolled at year 2, i.e. 8 subjects at each site; 34 subjects to be enrolled at year 3, i.e. 17 subjects at each site; 34 subjects to be enrolled at year 4, i.e. 17 subjects at each site; 8 subjects to enrolled at quarter 1 of year 5, i.e. 4 each site and 8 subjects to be enrolled at quarter 2 of year 5, i.e. 4 subjects at each site ). Total number of subjects screened at AECOM/MMC site is 45 to date. Therefore 45 subjects were screened, 23 subjects have completed the study, 6 are active, 10 are screen failures, 5 have dropped out from the study and 1 is waiting to be randomized. Total number of subjects enrolled at NYU site is 9 (out of 50 projected for NYU site). Therefore 9 subjects were enrolled, 0 subjects are currently active, and 3 subjects completed the study. NYU site has been activated as of 10/23/2019. **On 04/13/2022 Dr. Hollander confirmed to the DOD GOR, Dr. Tschiffely that NYU is no longer enrolling subjects under the DOD award.**

Detailed information on enrollment for both sites, subject characteristics and listings of AEs is summarized in the tables 1a, 1b, 2a, 2b, 3a and 3b below.

**Table 1a): Screening and Enrollment Data for AECOM/MMC site**

| Total Screened | Total Waiting to Randomize | Total Randomized | Currently Active | Total Completed | Total Screen Failures | Total Dropped Out |
|---|---|---|---|---|---|---|
| 45 | 1 | 34 | 6 | 23 | 10 | 5 |

**Table 1b): Screening and Enrollment Data for NYU site**

| Total Screened | Total Waiting to Randomize | Total Randomized | Currently Active | Total Completed | Total Screen Failures | Total Dropped Out |
|---|---|---|---|---|---|---|
| 9 | 0 | 3 | 0 | 3 | 5 | 0 |

No study results have been obtained thus far. No serious adverse events have occurred.
Below is a demographic table for the randomized subjects:

**Table 2a. Subject Characteristics Randomized at AECOM/MMC**

| Category | Statistic | Total (n=34) | | |
|---|---|---|---|---|
| | | Male | Female | Total |
| **Gender** | n (%) | 30 (88%) | 4 (12%) | 34 (100%) |
| **Age (yrs)** | N<br>mean (std)<br>Median | 30<br>9.5 (3.2)<br>10 | 4<br>13 (2.4)<br>13 | 34<br>9.9 (3.3)<br>10 |

| | | | | |
|---|---|---|---|---|
| | min : max | 5 : 17 | 10 : 16 | 5 : 17 |
| **Age (yrs)** | | | | |
| Category 1: 5-6 | n (%) | 7 (21%) | 0 (0%) | 7 (21%) |
| Category 2: 7-12 | n (%) | 18 (53%) | 1 (3%) | 19 (56%) |
| Category 3: 13-17 | n (%) | 5 (15%) | 3 (9%) | 8 (24%) |
| **Race** | | | | |
| American Indian/Alaskan Native | n (%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Asian | n (%) | 1 (3%) | 0 (0%) | 1 (3%) |
| Black / African American | n (%) | 9 (26%) | 1 (3%) | 10 (29%) |
| Native Hawaiian / Pacific Islander | n (%) | 0 (0%) | 0 (0%) | 0 (0%) |
| White | n (%) | 14 (41%) | 3 (9%) | 17 (50%) |
| Mixed Race | n (%) | 6 (18%) | 0 (0%) | 6 (18%) |
| Unknown/Not reported | n (%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Ethnicity** | | | | |
| Hispanic | n (%) | 12 (35%) | 0 (0%) | 12 (35%) |
| Not Hispanic | n (%) | 18 (53%) | 4 (12%) | 22 (65%) |
| **Starting Height (cm)** | N<br>mean (std)<br>Median<br>min : max | 30<br>137.8 (20.2)<br>135<br>110 : 180.5 | 4<br>146.1 (17)<br>143.8<br>128 : 169 | 34<br>138.8 (19.8)<br>135.5<br>110:180.5 |
| **Starting Weight (kg)** | N<br>mean (std)<br>Median<br>min : max | 30<br>39 (22.7)<br>29.6<br>19.8 : 112.1 | 4<br>47.8 (12.5)<br>52.2<br>29.7 : 57.2 | 34<br>40 (21.8)<br>30.2<br>19.8 : 112.1 |
| **Starting BMI** | N<br>mean (std)<br>Median<br>min : max | 30<br>19.3 (5.4)<br>17.1<br>15.1 : 37.9 | 4<br>22.4 (5.4)<br>22.3<br>17.4 : 27.8 | 34<br>19.7 (3.9)<br>17.4<br>15.1 : 37.9 |
| **Starting BMI percentile** | N<br>mean (std)<br>Median<br>min : max | 30<br>64.5 (28.8)<br>70<br>3 : 99 | 4<br>68.8 (41.2)<br>84.5<br>9 : 97 | 34<br>65 (29.7)<br>72<br>3 : 99 |

**Table 2b. Subject Characteristics Randomized at NYU**

| **Category** | **Statistic** | **Total (n=9)** | | |
|---|---|---|---|---|
| | | Male | Female | Total |
| **Gender** | n (%) | 8 (88.9%) | 1 (11.1%) | 9 (100%) |
| **Age (yrs)** | N<br>mean (std)<br>median<br>min : max | 8<br>10.5 (3.3)<br>10.5<br>5 : 14 | 1<br>17<br>17<br>17 : 17 | 9<br>11.2 (3.7)<br>11<br>5 : 17 |
| **Age (yrs)** | | | | |
| Category 1: 5-6 | n (%) | 1 (11.1%) | 0 (0%) | 1 (11.1%) |
| Category 2: 7-12 | n (%) | 4 (44.4%) | 0 (0%) | 4 (44.4%) |
| Category 3: 13-18 | n (%) | 3 (33.3%) | 1 (11.1%) | 4 (44.4%) |
| **Race** | | | | |
| American Indian/Alaskan Native | n (%) | 0 | 0 | 0 |
| Asian | n (%) | 1 (11.1%) | 0 | 1 (11.1%) |
| Black / African American | n (%) | 1 (11.1%) | 0 | 1 (11.1%) |
| Native Hawaiian / Pacific Islander | n (%) | 0 | 0 | 0 |
| White | n (%) | 6 (66.67%) | 1 (11.1%) | 7 (77.78%) |
| Mixed Race | n (%) | 0 | 0 | 0 |
| Unknown/Not reported | n (%) | 0 | 0 | 0 |
| **Ethnicity** | | | | |

| | | | | |
|---|---|---|---|---|
| Hispanic | n (%) | 3 (33.3%) | 0 (0%) | 3 (33.3%) |
| Not Hispanic | n (%) | 5 (55.56%) | 1 (11.1%) | 6 (66.67%) |

No serious adverse events have occurred. No IND safety reports have been submitted thus far. No subjects have died or dropped out of the study due to adverse events, and no additional information has been learned about the drugs actions. Mild adverse events reported in Table 3 below will be submitted to Einstein IRB with annual continuing review per existing SOPs in place.

**Table 3a: Listing of Adverse Events at AECOM/MMC**

| System Organ Class | Adverse Event | Severity | Serious |
|---|---|---|---|
| **General disorders and Administration site conditions** | Fatigue (1) | Mild | No |
| | Fever (1) | Mild | No |
| | Poor Appetite (1) | Mild | No |
| | Sleep Disturbance (1) | Mild | No |
| | Sore Throat (1) | Mild | No |
| | Rhinorrhea (1) | Mild | No |
| | Hyperactivity (2) | Mild | No |
| | Left groin pain (1) | Mild | No |
| | Irritability (1) | Mild | No |
| **Infection and Infestations** | | | |
| | Upper Respiratory Infection (2) | Mild | No |
| | COVID-19 (3) | Mild | No |
| | Cough and runny nose (1) | Mild | No |
| | Urinary Incontinence (1) | Mild | No |
| **Ear and Labyrinth Disorders** | Otitis Media – L (2) | Mild | No |
| | Otitis Media – R (1) | Mild | No |
| **Skin and Subcutaneous Tissue Disorders** | Perioral Rash (1) | Mild | No |
| | Irritation Dermatitis-Facial (1) | Mild | No |
| | Superficial skin infection (facial) (1) | Mild | No |
| **Gastrointestinal Disorders** | Vomiting (2) | Mild | No |
| | Constipation (1) | Mild | No |
| | GI Upset (1) | Mild | No |
| | Diarrhea (1) | Mild | No |
| | Gastritis (1) | Mild | No |
| | GERD (1) | Mild | No |
| | Small intestinal bacterial overgrowth (1) | Moderate | No |
| **Nervous System Disorders** | n/a | | |

**Table 3b: Listing of Adverse Events at NYU**

| System Organ Class | Adverse Event | Severity | Serious |
|---|---|---|---|
| **General disorders and Administration site conditions** | Fever (1) | Mild | No |
| | Epistaxis (1) | Mild | No |
| **Infection and Infestations** | Strep throat (1) | Mild | No |
| **Ear and Labyrinth Disorders** | Ear infection (1) | Mild | No |
| | | Mild | No |
| **Skin and Subcutaneous Tissue Disorders** | Ecchymosis (1) | Mild | No |
| **Gastrointestinal Disorders** | Loose stool (2) | Mild | No |
| **Nervous System Disorders** | n/a | | |

**Listing of Severe Adverse events:** None reported to date at AECOM/MMC or NYU sites.

**Human Use Regulatory Protocols**

**TOTAL PROTOCOLS:** One human subject research protocol will be required to complete the Statement of Work.

**PROTOCOL (1 of 1 total):**

HRPO Log Number A-20351.a and b

Title: Cannabidivarin (CBDV) vs. Placebo in Children with Autism Spectrum Disorder (ASD)

Target required for clinical significance: TBD

Target approved for clinical significance: TBD

**SUBMITTED TO AND APPROVED BY:**

ORP HRPO, initial submission 10/31/17, documents submitted by Dr. Margaret Frederick (HRPO) to the Approval Authority by COB for pre-review on 02/08/2018. Comments received on 02/13/18, addressed and approved by HRPO and Einstein IRB (03/28/18). NYU IRB approval submitted to ORP HRPO on 05/02/2018. Einstein IRB#1 Approval letter #035849 submitted to ORP HRPO on 05/16/2018.

ORP HRPO approval for AECOM/MMC site HRPO Log Number A-20351.a granted on 05/25/2018. ORP HRPO approval for NYU site HRPO Log Number A-20351.b was granted on 02/05/2019.

On 12/19/2018 Albert Einstein College of Medicine Continuing Review report (Log Number A-20351.a) was submitted to ORP HRPO. On 01/14/2019 ORP HRPO accepted Albert Einstein College of Medicine Continuing Review report (Log Number A-20351.a) and supporting documents.

NYU site Continuing Review report (Log Number A-20351.b) was received by ORP HRPO on 04/01/2019 and accepted by ORP HRPO on 05/28/2019.

On 11/13/2019 Albert Einstein College of Medicine Continuing Review report (Log Number A-20351.a) was submitted to ORP HRPO. On 01/27/2020 ORP HRPO accepted Albert Einstein College of Medicine Continuing Review report (Log Number A-20351.a) and supporting documents.

NYU site Continuing Review report (Log Number A-20351.b) was submitted to ORP HRPO on 04/09/2020 and accepted by ORP HRPO on 04/16/2020.

On 10/29/2020 AECOM/MMC site submitted Continuing Review Report (Log Number A-20351.a) to ORP HRPO.

On 11/4/2020 ORP HRPO accepted Albert Einstein College of Medicine Continuing Review report and supporting documents.

NYU site Continuing Review report (Log Number A-20351.b) was submitted to ORP HRPO on 03/04/2021 and was accepted on 03/24/2021.

Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) received initial study application submission on 11/6/17.

On 01/08/2018 AECOM/MMC site received conditional IRB approval pending IND approval from the FDA, DEA license for schedule I substance, approval from Bureau of Narcotics, DEA approval to Pharmacy for additional storage space.

On 04/03/2018 AECOM/MMC site received conditional IRB approval pending approval from Bureau of Narcotics, DEA license for schedule I substance, DEA approval to Pharmacy for additional storage space.

On 05/11/2018 AECOM/MMC site received conditional IRB approval pending DEA license for schedule I substance and DEA approval to Pharmacy for additional storage space.

On 05/15/2018 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) Approval letter #035849. Progress report was submitted to Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) on 11/2/2018. It was reapproved on 11/12/2018 with reference # 046713

On 12/13/2018 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval #047991 for the protocol amendment. Non-substantial changes were made as outlined above on pp.10.

On 03/27/2019 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval #051123 for the protocol amendment. Non-substantial changes were made as outlined on pp.11.

On 04/16/2019 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval #051762 for the protocol amendment. Non-substantial changes were made as outlined on pp.11.

On 10/04/2019 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval # 056458 for the protocol amendment. Non-substantial changes were made as outlined on pp.11.

On 10/17/2019 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval #057064 for the protocol amendment. Non-substantial changes were made as outlined on pp.11.

Progress report was submitted to Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) on 10/11/2019. Study protocol was reapproved on 10/28/2019 with reference # 057029.

On 11/13/2019 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval #057577 for the protocol amendment. Non-substantial changes were made as outlined on pp.11.

On 01/29/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval #060025 for the protocol amendment. Non-substantial changes were made as outlined on pp.12.

On 03/14/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval #060950 combined with #059792.Non-substantial changes were made as outlined on pp. 12.

On 03/18/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval #062721. Non-substantial changes were made as outlined on pp.12.

On 04/11/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #063312 and subsequent clarification # 063901 was approved on 05/04/2020. Non-substantial changes were made as outlined on pp.12.

On 06/11/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board acknowledgement with reference #065366. Non-substantial changes were made as outlined on pp.12

On 07/06/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #066128. Non-substantial changes were made as outlined on pp.13.

On 08/10/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #067116 and formatting change was approved with reference #067785 on 08/17/2020. Non-substantial changes were made as outlined on pp. 13.

Progress report was submitted to Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) on 09/16/2020 with reference # 068608. Study protocol was reapproved on 10/08/2020 with reference # 068608.

On 09/18/20 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference # 068273. Non-substantial changes were made as outlined on pp.13.

On 10/30/20 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #070030. Non-substantial changes were made as outlined on pp.13.

On 12/07/2020 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference # 070974. Non-substantial changes were made as outlined on pp.14.

On 02/04/2021 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #073117. Non-substantial changes were made as outlined on pp. 14.

On 07/19/2021 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #078073. Non-substantial changes were made as outlined on pp. 14.

On 10/28/2021 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #081568. Non-substantial changes were made as outlined on pp.14.

On 01/24/2022 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board approval with reference #083623. Non-substantial changes were made as outlined on pp.14.

New York University Langone Medical Center IRB #6, initially submitted 02/16/18 and amended after HRPO and IND non-hold comments. Approval letter received on 05/02/2018. NYU site submitted Continuing review to their IRB on 03/15/2019 and received protocol reapproval on 03/20/2019. NYU site submitted protocol amendments (same as Einstein site, outlined on p.7) on 04/19/19 and received approval on 05/14/2019. They subsequently submitted protocol amendments (same as Einstein site, outlined on p.7) and received approvals on 1/7/2020, 1/15/2020 and 2/4/2020.
NYU site Continuing Review #2 was submitted on 3/5/2020 to the Office of Science and Research IRB, NYU Langone Health and the protocol was reapproved on 3/17/2020.
Modification #12 for NYU site was on submitted 3/13/2020, and approved on 3/17/2020 (removal of personnel Kimberly Menzer, NP). Modification #13 for NYU site was submitted on 3/19/2020 and approved 3/27/2020 (addition of personnel Dana Price, MD).
On 8/24/2020 NYU site submitted COVID-19 related amendment to their IRB, which was approved on 09/30/2020.
New York State Department of Health, Bureau of Narcotic Enforcement (BNE), initial submission received 11/7/17. BNE inspection (including safe and site inspection) completed on 04/18/18 by Inspector Johnson. Class 7 Individual Researcher and Class 9 Importer licenses approvals received on 05/11/2018. Renewal of BNE Class 7 license application to engage in a controlled substance activity was submitted by Dr. Hollander on 02/03/2020 and was approved on 03/13/2020. BNE Class 7 license is effective from April 25 2020 to April 25 2022.
Drug Enforcement Administration (DEA), Drug and Chemical Evaluation Section, initial submission for Schedule I license received on 02/13/18. DEA inspection completed on 04/11/2018 by Inspector Rivera. Additional inspection for the new safe is scheduled for 05/18/2018 with Inspector Rivera. DEA schedule I license was granted on June 26 2018.
Upon DEA annual renewal requirements, it was renewed 09/05/2018 and 09/18/2019 and was valid through 10/31/2020. As of March 20, 2020, DEA formally notified GW/Greenwich Biosciences Inc. that they considered GW's products, including CBDV and GWP42006 to be non-controlled substances. Recently, DEA also published this information in the Federal Register. We also received a memo from GW/Greenwich Biosciences Inc. on June 8 2020, which was acknowledged by Einstein IRB, #1 East on 06/11/2020 with reference #065366. Since the CBDV used in the study is no longer a controlled substance, there is no further need for Dr. Hollander to have the DEA Schedule I Researcher registration i.e. to extend his registration.
NYU site Continuing Review #3 was submitted on 2/19/2021 to the Office of Science and Research IRB, NYU Langone Health and the protocol was reapproved on 3/09/2021.

**AECOM/MMC site Progress report was submitted to Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) on 09/15/2021 with reference # 080502. Study protocol was reapproved on 10/06/2021 with reference # 080502.**

**AECOM/MMC site submitted Continuing Review Report to ORP HRPO (Log Number A-20351.a) on 10/14/2021.**
**ORP HRPO accepted Albert Einstein College of Medicine Continuing Review report and supporting documents on 10/26/2021.**

**NYU site submitted protocol amendments to their IRB on 11/5/2021 (same as Einstein site, outlined on p.10 with reference # 081568), and received approval on 12/2/2021.**

**NYU site Continuing Review #4 was submitted the Office of Science and Research IRB, NYU Langone Health on 01/19/2022 and received reapproval on 03/01/2022.**

**NYU site submitted Continuing Review Report to ORP HRPO (Log Number A-20351.b) on 05/11/2022.**

**STATUS:**
Study is ongoing. Prior to COVID-19 pandemic onset, we have projected a total of 100 patients enrolled by end of Q4 year 5, at the two sites, including AECOM/MMC and NYU (consisting of 16 subjects to be enrolled at year 2, i.e. 8 subjects at each site; 34 subjects to be enrolled at year 3, i.e. 17 subjects at each site; 34 subjects to be enrolled at year 4, i.e. 17 subjects at each site; 8 subjects to enrolled at quarter 1 of year 5, i.e. 4 each site and 8 subjects to be enrolled at quarter 2 of year 5, i.e. 4 subjects at each site ). Total number of subjects screened at AECOM/MMC site is 45 to date. Therefore 45 subjects were screened, 23 subjects have completed the study, 6 are active, 10 are screen failures, 5 have dropped out from the study and 1 is waiting to be randomized. Total number of subjects enrolled at NYU site is 9 (out of 50 projected for NYU site). Therefore 9 subjects were enrolled, 0 subjects are currently active, and 3 subjects completed the study. NYU site has been activated as of 10/23/2019. **On 04/13/2022 Dr. Hollander confirmed to the DOD GOR, Dr. Tschiffely that NYU is no longer enrolling subjects under the DOD award.**

**What opportunities for training and professional development has the project provided?**
Nothing to report

**How were the results disseminated to communities of interest?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

| Nothing to report |
|---|

**What do you plan to do during the next reporting period to accomplish the goals?**
*If this is the final report, state "Nothing to Report."*

*Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.*

| We will continue to screen and enroll subjects at AECOM/MMC site COVID-19 pandemic allowing. |
|---|

**4. IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practiceor behavior that has come about as a result of the project relative to:*

**What was the impact on the development of the principal discipline(s) of the project?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of*

*the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).*

| Nothing to report |
|---|

**What was the impact on other disciplines?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe how the findings, results, or techniques that were developed or improved, or other products from the project madean impact or are likely to make an impact on other disciplines.*

| Nothing to report |
|---|

**What was the impact on technology transfer?**

| Nothing to report |
|---|

**What was the impact on society beyond science and technology?**

| Nothing to report |
|---|

**5. CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*
*If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

| Nothing to report |
|---|

**Changes in approach and reasons for change.**
**Actual or anticipated problems or delays and actions or plans to resolve them.**
**Describe problems or delays encountered during the reporting period and actions or plans to resolve them.**

COVID-19 Pandemic situation has affected our enrollment at Montefiore and NYU sites. In 2020 during year 3 of the study, we have prepared and submittedto the IRBs and ORP HRPO an amendment of the study protocol adjusting our study to the COVID-19 Pandemic situationwhich included reducing in person visits of study subjects from 9 to 4, i.e. making 5 study visits remote. We are currently seeing patients in person at AECOM/MMC site.
We will continue to enroll patients to the study at Montefiore site. Research subaward agreement with NYU site was terminated on 03/09/2022 by AECOM/MMC and NYU officials. On 04/13/2022 Dr. Hollander confirmed to the DOD GOR, Dr. Tschiffely that NYU is no longer enrolling subjects under the DOD award and submitted a request to GOR to rebudget funds from NYU to AECOM/MMC site.
We will be submitting a new CDMRP DOD grant proposal on 08/18/2022 (LOI invited to full application on 06/21/2022) to complete an additional 50 subjects in the same protocol with addition of immune, metabolomics and endocannabinoid measures to better understand the mechanism of action of CBDV in childhood ASD.

**Changes that had a significant impact on expenditures.**
*Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delaysin hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.*

Nothing to report

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents.**

**Significant changes in use or care of human subjects.**

Nothing to report

**Significant changes in use or care of vertebrate animals**

Nothing to report

**Significant changes in use of biohazards and/or select agents**

Nothing to report

**6. PRODUCTS:** *List any products resulting from the project during the reporting period.If there is nothing to report under a particular item, state "Nothing to Report."*

**Publications, conference papers, and presentations**
*Report only the major publication(s) resulting from the work under this award.*

**Journal publications.**

Nezgovorova V., Ferretti C.J., Taylor B.P., Shanahan E.,Uzunova G., Hong K., Devinsky O., Hollander E. Potential of cannabinoids as treatments for autism spectrum disorders. J Psychiatr Res. 2021 May;137:194-201.

**Books or other non-periodical, one-time publications.**

Nezgovorova V., Ferretti C., Taylor B., Hollander E. Cannabinoids in Autism Spectrum Disorders. Chapter in Textbook of Autism Spectrum Disorders, 2nd Edition. Edited by Hollander E., Hagerman R.J., Ferretti C.J. Washington, DC American Psychiatric Association Publishing, 2022, pp 529-540.

**Other publications, conference papers and presentations.**

- In previous reporting period study outline was presented at Department of Psychiatry Grand Rounds on 11/15/2018 at AECOM/MMC; on 11/30/2018 at Annual Isabelle Rapin Conference on Communication Disorders at Rose F. Kennedy

Intellectual and Developmental Disabilities Research Center (IDDRC) at AECOM/MMC; in November 2018 at the Autism Speaks conference in New York; in December 2018 at American College of Neuropsychopharmacology conference panel entitled “No Longer Tarred With the Same Brush? Evidence for the Therapeutic Potential of Cannabidiol: Implications for Regulatory Policy”. Interview with Dr. Hollander about the study outline was aired on NPR on 12/4/2018.

- Study outline was presented by Dr. Eric Hollander on April 25 2019 at the Department of Psychiatry and Behavioral Sciences Grand Rounds at Stanford University.
- Study outline was presented by Dr. Eric Hollander on May 18 at American Psychiatric Association meeting in San-Francisco at the “Essentials of cutting-edge evidence based treatments for Autism Spectrum Disorders” symposia, chaired by Dr. Eric Hollander (PI).
- As we enrolled first patient in the study, publication about the study appeared at Einstein magazine (http://magazine.einstein.yu.edu/summer-fall-2019/search-for-autism-therapies). Following CNN article about the study (https://fox6now.com/2019/09/29/new-study-aims-to-find-out-if-marijuana-help-treat-autism-symptoms),165 local television reports were generated and reached nearly 2 million people in various markets across the country.
- Examples include:

  https://app.criticalmention.com/app/#/clip/public/ed76b72c-1692-4dff-b054-c1f7f290f028;
  https://app.criticalmention.com/app/#/clip/public/759e937a-ab09-4768-b42f-bc3b2d3861e7?show_sentiment=false
- CNN has followed two patients through the DOD CBDV ASD study for WEED documentary of Dr. Gupta. CNN interviewed Dr. Hollander on August 2 2021. Updated documentary was broadcasted on CNN on December 19 2021.

**Website(s) or other Internet site(s)**

- https://www.autismeye.com/us-army-cannabis/ Autism Eye publication
  https://www.childrenshospitals.org/newsroom/childrens-hospitals- today/articles/2018/03/military-funds-research-of-cannabis-based-autism-treatment-for-kids Children’s Hospital association newsroom
  http://www.montefiore.org/body.cfm?id=1738&action=detail&ref=1375
- Montefiore news release
- https://www.newsweek.com/2018/02/23/really-good-weed-why-cannabis-may-be-worlds-most- effective-remedy-core-806758.html
- Newsweek magazine publication
- https://nypost.com/2018/05/02/clinical-trials-will-test-if-cannabis-compound-can-treat-autism/ NY post publication
- Montefiore news release https://www.newsweek.com/2018/02/23/really-good-weed-why-cannabis-may-be-worlds-most- effective-remedy-core-806758.html
- Newsweek magazine publication https://nypost.com/2018/05/02/clinical-trials-will-test-if-cannabis-compound-can-treat-autism/ NY post publication
- https://app.frame.io/presentations/0363400c-4954-419f-904b-49af9ae38c80 Dr. Sanjay Gupta documentary (this link containing video of the broadcast of the Weed 6 documentary was shared with the DOD GOR, Dr. Tschiffely, for dissemination)
- https://cnnpressroom.blogs.cnn.com/2021/12/02/cnn-special-report-weed-6-cannabis-and-autism/

**Other Products**
**Technologies or techniques**

| |
|---|
| Nothing to report |

**Inventions, patent applications, and/or licenses**

| |
|---|
| Not applicable at this point |

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

**What individuals have worked on the project?**
**Funding support:**

**Name: Eric Hollander**
Project Role: Principal Investigator (AECOM/MMC Site):
Nearest Person Month Worked: 1.8 months, 15%

Contribution to Project: Dr. Hollander has performed work in monitoring study progress and development, protocol finalization. He oversaw regulatory documents submissions and assured that award reporting requirements are met.
Funding support: no change

**Name: Bonnie Taylor, PhD**
Project Role: Study Psychologist/Rater:
Nearest Person Month Worked: 1.8 months, 15%
Contribution to Project: Dr. Taylor has performed work in the areas of regulatory and source documents preparation and protocol development.
Funding support: no change

**Name: Casara Ferretti**
Project Role: Study Coordinator/Rater:
Nearest Person Month Worked: 0.6 months, 5%
Contribution to Project: Ms. Ferretti has performed work in the areas of grant writing, protocol drafting, and advertising materials preparation
Funding support: no change

**Name: Alyssa Josselsohn**
Project Role: Study Coordinator/Rater:
Nearest Person Month Worked: 6 months, 50%
Contribution to Project: Ms. Josselsohn has performed work in the areas of subjects recruitment and enrollment.
Funding support: no change

**Name: Vera Nezgovorova, MD**
Project Role: Study/Regulatory Coordinator:
Nearest Person Month Worked: 3 months, 25%
Contribution to Project: Dr. Nezgovorova has performed work in the areas of regulatory documents preparation, protocol development, NYS BNE/DEA licensure, inter-sites communication and report writing.
Funding support: AECOM/MMC

**Name: Yin Zhao, MD**
Project Role: Co-Investigator:
Nearest Person Month Worked: 0.6 months, 5%
Contribution to Project: Dr. Zhao has performed work in the areas of regulatory documents preparation and protocol development.
Funding support: AECOM/MMC

**Name: Orrin Devinsky**
Project Role: Principal Investigator (NYU Site):
Nearest Person Month Worked: 1.2 months, 10%
Contribution to Project: Dr. Devinsky has performed work in monitoring study progress and development, protocol finalization. He oversaw regulatory documents submissions and assured that award reporting requirements are met.
Funding support: NYU

**Name: Latoya King**
Project Role: Study Coordinator (NYU Site):
Nearest Person Month Worked: 3 months, 25%
Contribution to Project: Ms. King has performed work in the areas of regulatory documents preparation and submission.
Funding support: NYU

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

| |
|---|
| Nothing to report |

**What other organizations were involved as partners?**

NYU Langone Comprehensive Epilepsy Center Collaboration **(co-PI Dr. Orrin Devinsky).**
Jazz Pharmaceuticals (previously called GW Pharmaceuticals)

**8. SPECIAL REPORTING REQUIREMENTS**

Not applicable

**9. APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.