Parental Informed Consent for the Participation of a Minor in a Clinical Trial

Your child is invited to participate in a clinical trial. A clinical trial is an innovative process that is not yet established, accepted, or approved as routine treatment in Israel, and therefore there is uncertainty regarding its safety or efficacy. This form explains the trial your child has been invited to join. We ask that you read the information carefully and discuss it with anyone you wish: friends, relatives, physicians, or health professionals not directly involved in the trial. Additional information and answers to questions can be obtained from the trial physician or their representatives.

Before deciding whether to join the trial, it is very important to understand the risks and potential benefits in order to make an informed decision. This process is called "Informed Consent." As parents, you are responsible for providing consent on behalf of your child.

Participation in the trial is voluntary. You have the right not to enroll your child and not to sign the consent form. You may withdraw from the trial at any time without giving a reason. Refusal or withdrawal will not negatively affect your child's medical care now or in the future, and you will be informed of the treatment options available.

If you wish to enroll your child, you will be asked to sign this form. You will receive a signed copy to keep, and the original will be stored in the medical institution.

Your child will also receive an explanation about the study from the trial physician or their representatives, in your presence.

Child's Details

First name: _____ Last name: _____ID number: _____

Address: _____ Date of birth: _____

1) Trial Information [0336-24-SZMC]

Study Title: The effect of CBD- and terpene-enriched cannabis oil on behavioral problems and communication deficits in children with autism – a controlled trial.

1.1) Principal Investigator: Prof. Adi Aran. Approval has been granted by the Institutional Helsinki Committee and the Director of Shaare Zedek Medical Center, in accordance with the Public Health Regulations (Clinical Trials in Humans), 1980.

Objective: To examine whether cannabis enriched with cannabidiol (CBD) and terpenes can improve behavioral problems and communication deficits in children with autism compared to placebo.

1.2) **Treatment**:
Children with autism have core deficits in communication, restricted/repetitive behaviors, and often severe behavioral difficulties. Currently, no approved pharmacological treatments exist for the core symptoms, and behavioral treatments are often insufficient or associated with adverse effects.
This study will test a cannabis oil commonly given in Israel to children with autism. The investigational oil contains 28 times more CBD than THC (C28/T1) and is enriched with terpenes. A similar oil (CBD:THC ratio 20:1) was previously tested in a large randomized controlled trial at Shaare Zedek.
Treatment will be given in addition to ongoing behavioral, pharmacological, or nutritional therapies.
CBD (cannabidiol) is a non-psychoactive component of cannabis. An FDA-approved CBD drug (Epidiolex, Jazz Pharmaceuticals) is indicated for treatment-resistant epilepsy.
In this study, dosing is 7.2 mg CBD/kg/day in two divided doses.

Study Design:
Duration: 4 months.
First 8 weeks: randomized to investigational product vs. placebo.
Double-blind: neither investigators nor participants will know allocation.
Oil will be given sublingually via dropper; dose titrated over 8 days to target levels.
After 8 weeks: placebo group crosses over to CBD+terpenes, while the treatment group continues the same oil for another 8 weeks.

1.3) **Participants**: 78 children, ages 4–12, diagnosed with autism and moderate-to-severe behavioral problems.
In the first stage, participants will undergo an evaluation to determine their eligibility for the study.
Only those who meet all of the following criteria may participate:
a. Age 4–12 years.
b. Diagnosis of autism spectrum disorder according to DSM-5 and confirmed by CARS observation.
c. Presence of behavioral problems (based on the ABC-I questionnaire).

d. Overall symptom severity rated as moderate or greater, as assessed by the principal investigator.
e. Weight between 12.5 kg and 57.49 kg.

All participants will receive one of the following treatments for 8 weeks:
a. CBD-rich cannabis oil; 3.6 mg CBD/kg twice daily.
b. Placebo – an inactive oil identical in appearance to the investigational product in arm (a).
Treatment allocation will be determined by randomization. Neither the investigators nor the participants will know whether the treatment is active or placebo until the end of the study.
Participants who complete the first 8-week period and all required assessments (at baseline and at the end of the first period) will be eligible to join an extension study in which all participants will receive active treatment (either the same investigational oil or pure CBD without THC or terpenes) for an additional 2 months. Assessments will be repeated at the end of this period.

Over the entire study period (a total of 17 weeks), participants will attend five evaluation visits:

1. Screening visit to assess eligibility – approximately 2 to 3 hours.
2. Baseline visit (start of the randomized controlled study) – 2 to 3 hours.
3. One month after study initiation – a 30-minute visit at Shaare Zedek or via Zoom.
4. Two months after study initiation (end of the first treatment period) – 2 hours.
5. Four months after study initiation (end of the second period) – 2 hours.

In addition, parents (and sometimes the treating staff) will be asked to complete several questionnaires during and between visits. The same parent must complete all questionnaires throughout the study.

At the second and fourth visits (baseline and after 2 months, i.e., the end of the first period), a blood sample (15 mL ≈ 3 teaspoons) will be collected to test:

- Liver enzymes and complete blood count (to assess treatment safety).
- Main CBD metabolites (DTC, 7-COOH-CBD) to assess bioavailability.
- Biomarkers of treatment response: blood endocannabinoid levels, transcriptome, and proteome.

At the second and fourth visits (baseline and after 2 months), a stool sample will be collected for microbiome analysis (intestinal bacterial profile).

Completion of questionnaires and study assessments is for research purposes only and is not part of routine clinical follow-up.

Data & Samples:
All data coded and stored securely.
Samples stored coded in dedicated freezer.
Data confidentiality protected; identifying key kept in a safe.

1.4) **Parent Responsibilities**:
No participation in other investigational drug studies during the trial.
Consult the PI before giving any new medical, alternative, or nutritional treatment.
For cannabis licensing during the trial, parents must sign a confidentiality waiver form and agree to license conditions (no cannabis use in public or near minors, report loss or theft).

Father's signature: _____ ; Mother's signature: _____

1.5) **Risks**:
CBD-rich oils studied in children with autism and epilepsy. Common side effects: sleepiness, decreased appetite, fatigue, diarrhea (expected in <10%).
The investigational oil contains mostly CBD with very low THC, thus no intoxication and low psychiatric risk.
Long-term side effects beyond 10 years are unknown.
High-THC cannabis risks (e.g., psychosis, dependence) are not relevant here due to low THC content.

1.6) **Potential Benefits**:
May improve behavioral and core autism symptoms, but benefit is not guaranteed.

1.7) **Alternatives**:
Current treatment for severe behavioral problems includes behavioral therapy and medications (antipsychotics, antiepileptics). No approved pharmacological treatment exists for core autism symptoms.

1.8) **Stopping Participation**:
May be terminated due to safety concerns (elevated liver enzymes, severe side effects, misuse, regulatory decision).

1.9) Participation is free of charge.

2) **Samples**:

Use of the samples will be for the purposes of this study only.

The samples collected during the trial will include:

- Liver enzymes and complete blood count (to assess treatment safety).
- Main CBD metabolites (DTC, 7-COOH-CBD) to assess bioavailability, i.e., the efficiency of drug absorption into the blood.
- Biomarkers of treatment response: blood endocannabinoid levels, transcriptome, and proteome. These analyses may help identify the pathways mediating treatment response.

The samples will be stored in coded form (with numbers on the vials) in the principal investigator's freezer. Samples will be kept for 15 years after the end of the study. Samples may be sent coded to research laboratories in Israel and/or abroad.

Use of the data or samples collected during the study for any purpose not described in the current study plan will require additional consent from participants. Consent or refusal for such additional use will not affect participation in this study.

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3. General Information

For any problem related to the clinical trial, you may contact the investigator at any time, 24 hours a day, at the following phone number: [050-8685034]. In the event of any medical problem, injury, or other health event during the study, you must report immediately so that your child can receive appropriate medical care and so that you may be informed about your rights in this context.

If side effects occur due to the treatment, the participant will receive the best possible medical care for the problem, according to the participant's preferences and within Israel. The principal investigator is responsible for coordinating this medical care.

The investigator will notify your child's community physician of his/her participation in the trial, for awareness and medical follow-up. If clinically significant medical findings are identified during the trial that were not known beforehand, this information will also be conveyed to the community physician.

Any new information that could affect your decision to participate or continue in the trial will be communicated to you as soon as possible.

As part of the study, you may be asked to complete a questionnaire. You may choose not to answer all or part of the questions.

The investigational product will be provided free of charge for the entire trial duration. The sponsor and the medical institution have arranged insurance coverage in the event of harm resulting from the trial.

~~There is a possibility that your child may continue to receive the investigational product free of charge after the end of the trial for up to three years. This option (within a follow-up protocol) is subject to several conditions and is at the discretion of the investigator and the institution:~~

The trial results may be valuable and could serve as part of a patent or for the development of drugs, medical products, etc. Participants in the trial will have no rights regarding patents, drugs, or products developed as a result of their participation.

A description of this clinical trial appears on the Ministry of Health's clinical trials website (MyTrials). The site will not contain information that could identify your child. You may search this site at any time.

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4. Privacy and Confidentiality

4.1) In the trial you are asked to enroll your child in, medical and personal information will be collected. This information will be stored in the medical record, and the treating team is responsible for maintaining confidentiality. You are entitled to access the medical record according to the Patients' Rights Law. If you know the information is incorrect or incomplete, you must notify the treating team.

4.2) The medical record will include information such as medical test results, administration of investigational products, use of devices or implants, performance of treatments, or experimental procedures.

4.3) Your consent to enroll your child also constitutes consent for medical and personal data collected during the study to be transferred to an external party for data processing. This information will only be transferred in coded form. It will not include: name, surname, ID number, home address, or any other state-issued identifier.

As a rule, coded data are considered identifiable. The link between the code and your child's identifying details will be securely stored by the principal investigator in Israel. In certain cases, the code may be opened by the investigator.

4.4) These coded data will be stored by the sponsor for the legally required period (at least 15 years after the end of the study).

You will receive results of tests with clear clinical significance: liver enzymes and blood counts (to assess treatment safety).

You will not receive results of the following tests (which currently have no clear clinical significance):

- Main CBD metabolite (DTC, 7-COOH-CBD) to assess bioavailability.
- Blood endocannabinoid levels, transcriptome, and proteome.

4.5) Access for verification of trial methods and data will be granted only to authorized parties (e.g., sponsor representatives, the institutional Helsinki committee, the institutional auditor, and Ministry of Health inspectors). Such access will be coordinated through the investigator and carried out in accordance with confidentiality laws and regulations.

4.6) Your child's identifying details will not appear in any scientific or other publication.

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5. Withdrawal From the Trial

At any stage of the trial, you have the right to withdraw by notifying the principal investigator or their representative. You do not need to provide a reason. The investigator may only use coded samples and/or data collected up to the time of withdrawal.

From the moment you withdraw, no additional data will be collected about your child. However, if medically significant information about your child or family members emerges, you will be contacted. You have the right to refuse this information.

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6. Documentation of Consent

Both parents of the minor are responsible for giving consent on his/her behalf, in accordance with the Legal Capacity and Guardianship Law, 1962.

Parents of the participant: By signing, I declare that I have read this document, the study was explained to me, and I agree that my child will participate.

Parent name: _____ Signature: _____ Date: _____

Parent name: _____ Signature: _____ Date: _____

Explaining Investigator: By signing, I declare that I explained the study orally to the parents in accordance with this form. I believe the parents understood, had sufficient time to read the form, and gave their consent to enroll their child. In addition, I declare that I explained the study to the minor participant in the presence of the parents, and the child expressed willingness to participate.

Name: _____ Signature: _____ Date: _____
(including stamp and license number)

Independent Witness*: I, the undersigned, was present during the explanation of the study, confirm that the content of this document was delivered orally in my presence to the parents and their child, that they appeared to understand, and I heard them give verbal consent to enroll their child.

Name: _____ Signature: _____ Date: _____

* For use only when the parents cannot read the consent form (visually impaired or illiterate) or in urgent medical situations (as defined by law). The independent witness must be present throughout the explanation of the clinical trial.

Additional Consent (Optional)

The sponsor requests permission to use data and/or samples collected in this study for additional research. This additional use is not part of the current study plan.

Refusal will not prevent participation in this study.

8. Samples – Future Use Not Part of This Study

8.1) As part of this study, blood and stool samples are collected as explained in Section 2.
8.2) Samples will be stored coded in a locked freezer for 15 years and then destroyed.
8.3) We ask your permission to use leftover samples after the end of this study for future autism research, subject to approval by an ethics committee.

9. Use of Data for Future Research

9.1) As part of this study, data are collected from assessments and questionnaires as described in Section 1.3.

9.2) Data will be stored coded, without identifiers, for 15 years after study completion, then destroyed.

9.3) We ask your permission to use these data after the end of this study for future autism research, subject to approval by an ethics committee.

By signing, you agree that these data and/or samples may be used for future legally approved autism studies. You may withdraw this consent at any time by notifying the principal investigator or their representative, without providing a reason.

Parents of the participant: By signing, I declare that I have read the contents of Sections 8 and 9, their meaning was explained to me, and I agree to the additional use of samples and data in future legally approved autism research.

Parent name: _____ Signature: _____ Date: _____

Parent name: _____ Signature: _____ Date: _____

Explaining Investigator: By signing, I declare that I explained orally to the parents the content and meaning of Sections 8 and 9. I believe the parents understood, had sufficient time to read, and gave their consent for additional use of samples.

Name: _____ Signature: _____ Date: _____
(including stamp and license number)

Independent Witness*: I, the undersigned, was present during the explanation of the study, confirm that the content of this document was delivered orally in my presence to the parents and their child, that they appeared to understand, and I heard them give verbal consent to enroll their child.

Name: _____ Signature: _____ Date: _____

* For use only when the parents cannot read the consent form (visually impaired or illiterate) or in urgent medical situations (as defined by law). The independent witness must be present throughout the explanation of the clinical trial.