

# RSO

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May 2025

## 1 Introduction

Clinical Trial Protocol Outline:

A Multi-Phase Study of High-THC Full-Spectrum Cannabis Extract (Investigational Product X) in Advanced Cancer May 12, 2025

## 2 Introduction and Background

### 2.1 Cancer Burden and Unmet Need

Advanced solid tumors are associated with significant morbidity and mortality. Despite advances in standard treatments (chemotherapy, targeted therapy, immunotherapy), many patients experience disease progression and debilitating symptoms, highlighting the need for novel adjunctive therapies.

### 2.2 The Endocannabinoid System and Cancer

The endocannabinoid system (ECS), comprising endogenous ligands, receptors (CB1, CB2, etc.), and metabolic enzymes, plays a role in various physiological processes, including cell growth, survival, and immune function. Preclinical studies in cell lines and animal models suggest that cannabinoids, including  $\Delta^9$ -tetrahydrocannabinol (THC), may have anti-proliferative, pro-apoptotic, anti-angiogenic, and anti-metastatic effects, although findings are mixed and context-dependent. The exact mechanisms by which full-spectrum extracts like RSO might influence tumor biology are complex and may involve synergistic effects of multiple cannabinoids and terpenes (entourage effect), which are not yet fully understood.

### 2.3 Clinical Evidence Review

- **Symptom Management:** Clinical trials and reviews indicate that cannabis-based products, including those containing THC, can be effective in managing cancer-related symptoms such as chemotherapy-induced nausea and vomiting, chronic pain, and appetite loss in some patients. [15, 21, 24]

However, response is variable, and optimal dosing and ratios of cannabinoids are still being investigated. [23, 24]

- **Anti-Cancer Efficacy:** Despite preclinical promise, clinical evidence demonstrating that cannabinoids, including high-THC extracts like RSO, can cure cancer or significantly improve overall survival or progression-free survival as a primary anti-cancer treatment is currently lacking. [7, 20, 25] Most human studies to date have been small or observational, often using cannabis products not manufactured under pharmaceutical standards. [20, 25] ASCO guidelines recommend against using cannabis/cannabinoids as cancer-directed treatment outside of clinical trials. [1, 25] Some concerns exist regarding potential interactions with standard anti-cancer therapies, including immunotherapy. [25]
- **Rick Simpson Oil (RSO):** RSO is a term for high-THC cannabis oil, often associated with anecdotal claims of curing cancer. [20, 25] It is typically a full-spectrum extract with high THC concentration ( $\sim 90\%$ ) and low CBD ( $<1\%$ ). [20, 25] A major challenge with RSO is the lack of standardization and quality control in products not manufactured under strict pharmaceutical regulations, potentially containing residual solvents or contaminants. [25]

## 2.4 Rationale for this Study

Given the preclinical rationale, anecdotal reports associated with RSO, and patient interest, a rigorous, controlled clinical trial is warranted to evaluate the potential role of a standardized, high-THC full-spectrum cannabis extract as an *adjunctive* therapy in advanced cancer. This trial aims to investigate if IP-X, *in addition to standard supportive care*, can improve survival outcomes (as a potential direct or indirect anti-cancer effect or through improved symptom management allowing patients to tolerate treatment better) and symptom burden in a controlled setting. This seamless Phase Ib/II/III design allows for initial safety and dose-finding (Phase Ib), assessment of preliminary efficacy signals and expanded safety (Phase II), and if successful, confirmation of efficacy and safety in a larger population (Phase III).

## 3 Objectives

### 3.1 Primary Objective

- To assess the effect of IP-X versus placebo, when added to standard supportive care, on Overall Survival (OS) in patients with advanced solid tumors.
- To assess the effect of IP-X versus placebo on Progression-Free Survival (PFS) per RECIST v1.1. (Primary endpoint for Phase II).

## 3.2 Secondary Objectives

- To evaluate the safety and tolerability of IP-X.
- To assess the effect of IP-X on health-related Quality of Life (QoL) using the EORTC QLQ-C30 questionnaire.
- To evaluate the effect of IP-X on pain severity using a validated pain scale (e.g., VAS or NRS).
- To assess the effect of IP-X on sleep quality, appetite, and anxiety using validated instruments.
- To measure changes in selected immune and inflammatory biomarkers (e.g., IL-6, TNF- $\alpha$ ) and correlate them with clinical outcomes.
- To assess objective tumor response rate (ORR) and disease control rate (DCR) per RECIST v1.1.
- To characterize the pharmacokinetic profile of key cannabinoids (THC, CBD, and major metabolites) in plasma/serum and correlate levels with dose, efficacy, and safety outcomes.
- To assess blinding integrity among participants and investigators. [11, 17, 28]

## 4 Study Design

### 4.1 Overall Design

This is a multi-phase (Ib/II/III), multicenter, randomized, double-blind, placebo-controlled study comparing IP-X plus standard supportive care to placebo plus standard supportive care in patients with advanced solid tumors. [11, 17, 28]

### 4.2 Trial Schema/Phases

- **Phase Ib:** Open-label or partially-blinded dose escalation phase (anticipated N=30). The primary objective is to determine the Maximum Tolerated Dose (MTD) and/or Recommended Phase II Dose (RP2D) of IP-X in this population based on safety and tolerability. A standard 3+3 dose escalation design or an adaptive design will be used, starting at a very low dose of THC (significantly lower than 30 mg/day) and escalating in cohorts based on dose-limiting toxicities (DLTs). Preliminary pharmacokinetic data will be collected. [8, 13, 27]
- **Phase II:** Double-blind, placebo-controlled phase (anticipated N=100-150) using the RP2D determined in Phase Ib. The primary objective is to evaluate the preliminary efficacy of IP-X on PFS and further assess safety

and tolerability. [8, 13, 27] Secondary objectives include evaluating symptom control, QoL, and exploring biomarkers. A pre-defined efficacy signal based on Phase II results (e.g., a minimum improvement in median PFS or response rate in the IP-X arm compared to placebo) will be required to proceed to Phase III.

- **Phase III:** Double-blind, placebo-controlled phase (anticipated N=500+) using the RP2D. [8, 13, 27] Patients will be randomized to receive either IP-X or placebo. The primary objective is to confirm the effect of IP-X on OS and PFS. Secondary objectives include confirming effects on symptom control, QoL, and further characterizing the safety profile in a larger population.

### 4.3 Randomization and Blinding

- Patients will be randomized (e.g., 1:1 ratio in Phase II/III) to receive either IP-X or placebo. Randomization will be stratified by relevant prognostic factors (e.g., tumor type, performance status).
- The study will be double-blind. IP-X and placebo will be formulated to be identical in appearance, taste, and smell as much as possible to maintain blinding. [11, 17, 28] This may require adding terpenes or other excipients to the placebo.
- Blinding integrity will be assessed periodically throughout the trial by asking participants and study personnel to guess the treatment assignment. [11, 17, 28]

### 4.4 Study Duration

The total study duration is anticipated to be approximately 36 months for enrollment and primary analysis, with a follow-up period for OS extending beyond this. Individual patient participation will involve a treatment period (up to 90 days as per original framework, but potentially longer depending on Phase Ib findings and tolerance) followed by a survival follow-up period (minimum 90 days, but ongoing for OS).

### 4.5 Study Sites

The study will be conducted at multiple international cancer research centers (minimum 5-10 sites recommended for adequate recruitment in Phase II/III). [6, 29]

## 5 Study Population

### 5.1 Inclusion Criteria

- Adults aged 18-75 years.
- Histologically or cytologically confirmed advanced solid tumor that is refractory to or relapsed after standard therapy, or for which no standard curative therapy exists. (Specify eligible tumor types or require central review). [26]
- Measurable disease according to RECIST v1.1 (for efficacy phases).
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2.
- Life expectancy  $\geq 3$  months.
- Adequate organ function (specific laboratory parameter limits for hematologic, hepatic, renal, and cardiac function).
- Negative urine drug screen for illicit cannabis use at screening (to ensure baseline is free of external cannabis use).
- No use of any cannabis-containing products (medicinal or recreational) within 30 days prior to randomization.
- Ability to swallow oral medication.
- Provide written informed consent.

### 5.2 Exclusion Criteria

- Active brain metastases or leptomeningeal disease requiring acute treatment.
- Active psychosis or major psychiatric disorder (e.g., schizophrenia, bipolar disorder) as assessed by clinical evaluation or history, or significant risk of suicidal ideation. (Requires clear definition and assessment). [22]
- Severe organ dysfunction (define specific criteria for hepatic, renal, cardiac, pulmonary, etc.).
- History of severe adverse reaction to cannabis or cannabinoids. [22]
- Significant cardiovascular disease (e.g., unstable angina, recent MI, uncontrolled arrhythmias, severe heart failure) due to potential cardiac effects of high THC. [22]
- Pregnancy or breastfeeding. Women of childbearing potential and men must agree to use effective contraception.

- Known hypersensitivity to any component of the IP-X or placebo.
- Concurrent use of disallowed medications (e.g., other investigational agents, specific enzyme inhibitors/inducers that could interact with cannabinoids - list specific examples).
- Unstable opioid use or active substance use disorder (except cannabis use prior to the 30-day washout).

### 5.3 Enrollment Targets

- Phase Ib: Approximately 30 participants (for dose escalation/MTD).
- Phase II: Approximately 100-150 participants.
- Phase III: Approximately 500+ participants.

## 6 Interventions

### 6.1 Investigational Product (IP-X)

- Source and Manufacturing: IP-X will be a pharmaceutical-grade, high-THC full-spectrum cannabis extract manufactured under Good Manufacturing Practice (GMP) standards.
- Composition: Standardized to contain approximately 90% THC and <1% CBD. The concentration of other key cannabinoids (e.g., CBG, CBN, THCA, CBDA) and major terpenes will be analyzed and reported for each batch to ensure consistency.
- Formulation: Oral oil solution.
- Quality Control: Each batch will be tested for potency (cannabinoid profile), homogeneity, microbial contamination, heavy metals, and residual solvents according to strict specifications. [25]

### 6.2 Placebo

- Composition: An oil-based formulation matching IP-X in appearance, taste, smell, and viscosity. It will contain no cannabinoids but may include terpenes present in IP-X to aid blinding.
- Manufacturing: Manufactured under GMP standards.

### 6.3 Administration Method

Both IP-X and placebo will be administered orally, typically divided into 2 or 3 doses per day, as determined during Phase Ib.

## 6.4 Dosing Protocol

- **Phase Ib (Dose Escalation):** Dosing will start at a very low level (e.g., 5-10 mg THC equivalent per day) in the first cohort. Doses will be escalated in subsequent cohorts based on the observed safety and tolerability profile using a predefined dose escalation scheme (e.g., 3+3 design). [10, 13] The RP2D for Phase II/III will be determined based on safety, tolerability, and potentially preliminary PK data.
- **Phase II/III:** Participants will receive the RP2D of IP-X or placebo, administered orally daily.
- **Titration:** A brief initial titration phase may be incorporated at the start of treatment in Phase II/III to improve tolerability, based on findings from Phase Ib. [24]
- **Dose Modification:** Criteria for dose reduction or temporary interruption based on observed toxicities will be clearly defined.
- **Duration of Treatment:** Participants will continue treatment until disease progression, unacceptable toxicity, withdrawal of consent, or death.

## 6.5 Concurrent Treatments

- Standard supportive care (e.g., pain management, antiemetics, nutritional support) is permitted but should be optimized and stable before randomization. [24]
- Specific anti-cancer therapies (chemotherapy, radiation, surgery, immunotherapy, targeted agents) are generally **not** permitted concurrently with IP-X/placebo unless the trial is specifically designed as an *add-on* to a defined standard treatment regimen (which would require adjusting inclusion/exclusion criteria and endpoints). Assuming this is *adjunctive to supportive care* in treatment-resistant patients, concurrent anti-cancer therapy would be excluded.
- Use of other cannabis-containing products is prohibited during the study.
- Specific medications known to interact significantly with cannabinoids should be avoided or used with caution and appropriate monitoring.

# 7 Outcome Measures

## 7.1 Primary Endpoints

- Overall Survival (OS): Time from randomization to death from any cause.
- Progression-Free Survival (PFS): Time from randomization to the first documented date of objective tumor progression per RECIST v1.1 or death from any cause, whichever occurs first.

## 7.2 Secondary Endpoints

- Safety and Tolerability: Incidence, nature, and severity of Adverse Events (AEs) graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
- Quality of Life (QoL): Change from baseline in EORTC QLQ-C30 scores at specified time points.
- Pain: Change from baseline in pain scores (VAS/NRS) at specified time points.
- Other Symptoms: Change from baseline in scores for sleep quality, appetite, and anxiety at specified time points.
- Objective Response Rate (ORR): Proportion of patients with a confirmed Complete Response (CR) or Partial Response (PR) per RECIST v1.1.
- Disease Control Rate (DCR): Proportion of patients with a confirmed CR, PR, or Stable Disease (SD) per RECIST v1.1.
- Pharmacokinetic Profile: Plasma/serum concentrations of THC, CBD, 11-OH-THC, THC-COOH, and potentially other key cannabinoids/terpenes at specified time points.
- Biomarkers: Changes in serum/plasma levels of IL-6, TNF- $\alpha$ , and other exploratory immune/inflammatory markers.
- Blinding Integrity: Proportion of participants and investigators correctly guessing treatment assignment. [11, 17, 28]

## 7.3 Assessments Schedule

Tumor assessments (e.g., CT or MRI scans) will be performed at baseline and specific intervals (e.g., every 8-12 weeks) according to RECIST v1.1 criteria. QoL, symptom scores, safety assessments (AEs, labs, vital signs, physical exam), and PK sampling will be performed at baseline, during treatment visits (e.g., weekly during titration/Phase Ib, then every 2-4 weeks), at the end of treatment, and during the follow-up period.

## 8 Safety Assessments

### 8.1 Adverse Event Reporting

AEs will be systematically collected, documented, and graded according to CTCAE v5.0 from the time of consent until a specified period after the last dose.

### 8.2 Serious Adverse Events (SAEs)

SAEs must be reported immediately according to regulatory requirements.

### 8.3 Laboratory Assessments

Hematology, serum chemistry (including liver and renal function tests), and urinalysis will be performed at baseline and regular intervals during treatment. Liver enzymes (AST/ALT) are particularly important to monitor given potential cannabinoid effects and interactions.

### 8.4 Vital Signs and Physical Exams

Blood pressure, heart rate, respiratory rate, temperature, and a focused physical exam (including neurological and psychiatric assessment) will be performed at baseline and study visits.

### 8.5 Electrocardiograms (ECGs)

ECGs should be performed at baseline and during treatment, especially in Phase Ib and early Phase II, to monitor for potential cardiac effects of high-dose THC. [22]

### 8.6 Psychiatric and Neurological Assessments

Specific validated scales may be used to assess for changes in mood, anxiety, paranoia, cognition, and other psychoactive effects, particularly in Phase Ib/II. [22]

### 8.7 Dose Modification/Discontinuation

Clear guidelines will define criteria for dose reduction, temporary hold, or permanent discontinuation of IP-X/placebo based on the severity of AEs, changes in laboratory values, or other safety concerns.

### 8.8 Data Safety Monitoring Board (DSMB)

An independent DSMB will be established to review safety data at regular intervals, especially during the dose escalation (Phase Ib) and at planned interim analyses for efficacy and safety in Phases II and III. They will have the authority to recommend protocol modifications, stopping enrollment, or terminating the study based on safety or futility data.

## 9 Statistical Considerations

### 9.1 Sample Size Determination

- Phase Ib: Sample size driven by the dose escalation design (e.g., 3+3). [10, 13]

- Phase II: Sample size based on detecting a statistically significant signal of efficacy (e.g., improvement in PFS) with a specified power (e.g., 80%) and alpha level (e.g., 0.10 or 0.20 for a signal-finding phase).
- Phase III: Sample size calculated to detect a clinically meaningful improvement in OS (e.g., 20% hazard ratio reduction as per original framework, but requiring strong justification/prior data) with high power (e.g., 80-90%) and a two-sided alpha of 0.05. The assumption for the effect size on OS needs to be realistic given the adjunctive nature and lack of prior data.

## 9.2 Statistical Methods

- Primary efficacy endpoints (OS, PFS) will be analyzed using Kaplan-Meier methods and compared between groups using the log-rank test. Hazard ratios and confidence intervals will be estimated using a Cox proportional hazards model, potentially adjusted for stratification factors.
- Binary endpoints (ORR, DCR) will be compared using Fisher’s exact test or Chi-squared test.
- Continuous endpoints (QoL scores, symptom scores, biomarkers) will be analyzed using appropriate methods such as ANCOVA or mixed models for repeated measures, comparing change from baseline between groups.
- Safety data (AE rates) will be summarized descriptively by treatment group.
- Pharmacokinetic parameters will be calculated using non-compartmental analysis. Correlation with efficacy and safety will be explored using regression models.
- Blinding integrity will be assessed by comparing the proportion of correct guesses to 50% using a Chi-squared test. [11, 17, 28]
- Appropriate statistical software will be used.

## 9.3 Interim Analyses

Planned interim analyses are essential for this multi-phase design.

- An analysis after Phase Ib will determine the RP2D.
- An interim analysis after Phase II will assess the preliminary efficacy signal (PFS) and safety to determine if the study proceeds to Phase III. Stopping rules for futility may be included.
- One or more interim analyses may be planned during Phase III to monitor for overwhelming efficacy or safety concerns, with clear stopping guidelines linked to the DSMB review.

## **10 Data Management**

Data will be collected using electronic Case Report Forms (eCRFs). Data validation procedures will be implemented to ensure data accuracy and completeness. A secure database will be maintained.

## **11 Ethical Considerations**

### **11.1 Ethics Committee/IRB Approval**

The protocol, informed consent form, and all patient-facing materials will be reviewed and approved by the Institutional Review Boards or Ethics Committees at each participating site.

### **11.2 Informed Consent**

A comprehensive informed consent process will be conducted. Patients will be fully informed about the nature of the study, the investigational product (including its high THC content and potential psychoactive effects), known risks and potential unknown risks, lack of proven anti-cancer efficacy of cannabis products, potential drug interactions, alternative treatment options, confidentiality, and their right to withdraw at any time. [22, 30, 31]

### **11.3 Good Clinical Practice (GCP) and Declaration of Helsinki**

The study will be conducted in accordance with the principles of GCP and the Declaration of Helsinki.

### **11.4 Patient Confidentiality**

Patient anonymity and confidentiality will be maintained in all study data and reports.

### **11.5 Optional Crossover**

The optional crossover for the placebo group upon progression needs careful ethical and statistical justification. If implemented, it should be handled as a separate treatment phase with its own consent and clear plan for data collection and analysis, acknowledging the potential confounding effect on OS analysis in the main trial.

## **12 Regulatory Considerations**

The study will adhere to all applicable national and international regulatory requirements for clinical trials, including submission of an Investigational New

Drug (IND) application (if in the US) or equivalent regulatory submissions in other countries. Reporting of SAEs will comply with regulatory guidelines.

## 13 Challenges and Mitigation Strategies

- **Recruitment and Retention:** Patients with advanced cancer are a vulnerable population. High potential for side effects from high-dose THC may impact recruitment and retention. [22, 30, 31] Mitigation: Careful patient selection based on robust eligibility criteria, thorough informed consent emphasizing realistic expectations and potential side effects, dedicated study staff for patient support, and a well-managed dose escalation/modification plan.
- **Safety and Tolerability:** The high THC dose is a major concern. [22] Mitigation: Start with a very low dose in Phase Ib, use a conservative dose escalation scheme, implement frequent and comprehensive safety monitoring (including specific neurological/psychiatric and cardiac assessments), utilize a DSMB, and have clear dose modification/discontinuation rules.
- **Blinding:** Psychoactive effects may lead to unblinding. [11, 17, 28] Mitigation: Formulate a convincing placebo, assess blinding integrity, and plan statistical analyses that can explore the potential impact of perceived treatment assignment on outcomes.
- **Drug Interactions:** Potential for interaction with concurrent medications. Mitigation: Carefully review concomitant medications at screening and throughout the study, establish clear lists of prohibited medications, and monitor for signs of altered drug levels or increased toxicity.
- **Regulatory/Legal Status of Cannabis:** Navigating the varied and evolving legal status of cannabis internationally can be challenging. [29, 30] Mitigation: Ensure full compliance with all local and national regulations regarding cannabis research, product handling, and dispensing at each study site.
- **Product Consistency:** Ensuring batch-to-batch consistency of a "full-spectrum" extract is critical. [25] Mitigation: Implement rigorous analytical testing and quality control procedures for every batch of IP-X and placebo used in the trial.

## 14 Conclusion

This refined clinical trial framework provides a more robust and detailed approach to evaluating the safety and potential efficacy of a high-THC full-spectrum cannabis extract as adjunctive therapy in advanced cancer patients. While significant challenges exist, particularly regarding the high proposed dose and the limited clinical evidence for direct anti-cancer effects, a rigorously designed and

carefully monitored study is necessary to provide evidence-based answers regarding the role of such products in cancer care. The results of this trial, if successfully completed, could inform future clinical practice, regulatory decisions, and further research into the therapeutic potential of cannabinoids in oncology.

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