CLINICAL STUDY PROTOCOL

A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study of RAD011 (Cannabidiol Oral Solution) for the Treatment of Patients with Prader-Willi Syndrome

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements

Protocol Number:	Protocol SCOUT-015
Version Number:	5.0
IND Number:	136,374
Study Sponsor:	Radius Pharmaceuticals, Inc. (Radius) 22 Boston Wharf Rd 7th Floor Boston, MA 02210 Tel: [redacted]; Fax: [redacted]
Contract Research Organization	CTI Clinical Trial & Consulting 100 E. RiverCenter Blvd. Covington, KY 41011
Key Sponsor Contact	[redacted]
Medical Monitor	[redacted] CTI Clinical Trial & Consulting Phone: [redacted] Fax: [redacted] Email: [redacted]

Version number	Version date
5.0	10 March 2022

1. RADIUS SIGNATURE PAGE

Title	A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study of RAD011 (Cannabidiol Oral Solution) for the Treatment of Patients with Prader-Willi Syndrome
Protocol Number	SCOUT-015
Version Number	5.0
Version Date	10 March 2022
Amendment	4

The design of this study as outlined by this protocol has been reviewed and approved by:

[redacted]

11-Mar-2022 | 11:12:50 AM EST

[redacted]

Date

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I hereby acknowledge that I have received and read the Investigator's Brochure, read the protocol, appendices, and accessory materials related to Study SCOUT-015, Version 5.0 dated 10 March 2022, and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the patients under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products provided by the Sponsor and maintain records of the disposition of those products

To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by ICH E6(R2).

- To obtain approval for the protocol and all written materials provided to patients prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all patients enrolled at my study site prior to initiating any study specific procedures or administering investigational products to those patients
- To maintain records of each patient's participation and all data required by the protocol
- To ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Radius.

Principal Investigator

<table>
<tr><td rowspan="2">Printed Name:</td><td>Title:</td><td rowspan="2">Institution Address:</td></tr>
<tr><td>Phone:</td></tr>
<tr><td colspan="2">Signature:</td><td>Date (DD Month YYYY):</td></tr>
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Acronym	Definition
µM	micromolar
5-HT1A	5-hydroxytryptamine
ABC	Aberrant Behavior Checklist
ABC-I	Aberrant Behavior Checklist – Irritability subscale
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}inf}$	area under the curve from time 0 to infinity
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CaGI-C	Caregiver Global Impression of Change
CaGI-S	Caregiver Global Impression of Severity
C-SSRS	Columbia-Suicide Severity Rating Scale
CBC	complete blood count
CBD	cannabidiol
CB-1	endocannabinoid receptor
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximal concentration
CLB	clobazam
COS	cannabidiol oral solution
CRO	contract research organization
CYP	cytochrome P450
D	day

Acronym	Definition
DEXA	dual-energy X-ray absorptiometry
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
ESS-CHAD	Epworth Sleepiness Scale for Children and Adolescents
EU	European Union
F	female
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practices
GGT	gamma-glutamyl transferase
GH	growth hormone
GMP	Good Manufacturing Practices
HbA1c	glycosylated hemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HQ-CT	Hyperphagia Questionnaire for Clinical Trials
HR	heart rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
INR	international normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	intent-to-treat

Acronym	Definition
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LTE	long-term extension
M	male
MCT	medium chain triglycerides
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
nCLB	norclobazam
NOAEL	no-observed-adverse-effect-level
OTcF	QT interval corrected with Fridericia's Formula
PCP	phencyclidine
PK	pharmacokinetic
PP	per protocol
PPARγ	peroxisome proliferator-activated receptor γ
PT	prothrombin time
PWS	Prader-Willi Syndrome
RAND	randomization
RBC	red blood cells
RDW	red cell distribution width
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	System Organ Class
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	half-life
T_{max}	time to maximal concentration
TBD	to be determined

Acronym	Definition
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
TMF	Trial Master File
UGT	5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
W	week
WBC	white blood cells
WOCBP	women of childbearing potential

2. SYNOPSIS

Name of Sponsor/Company: Radius Pharmaceuticals, Inc. (Radius)

Name of Finished Drug: RAD011 (Cannabidiol Oral Solution) 100 mg/mL

Name of Active Ingredient: Cannabidiol (CBD)

Title of Study: A Phase 2/3, Randomized, Double-Blind, Placebo Controlled Study of RAD011 (Cannabidiol Oral Solution) for the Treatment of Patients with Prader-Willi Syndrome

Phase of Development: Phase 2/3

Study Center(s): Approximately 38 sites (20 NA, 18 non-NA)

Number of Patients Randomized (Planned): Ages 12 to 65 years (Phases 2 and 3): ~191 patients
Ages 8 to <12 years (Phase 3): ~30 patients

Objective: The primary objective of the Phase 2 part of this study is to assess the safety and tolerability of multiple doses levels of RAD011 in order to select 1 or 2 dose level(s) to further evaluate in the Phase 3 part of the study. The primary objective of the Phase 3 part of this study is to assess the effect of RAD011 on hyperphagia-related behavior in patients with Prader-Willi Syndrome (PWS).

Design and Methodology:

This is a seamless Phase 2/3, double-blind, randomized, placebo-controlled clinical study in patients diagnosed with PWS. Following consent (or legal guardian consent and patient assent as appropriate), patients will be screened for eligibility to participate in this study.

The study will consist of six similar periods for the Phase 2 and Phase 3 parts of the study:

1. Screening Period (3 weeks)
    a. Review of eligibility prior to proceeding to the Tolerability Period
2. Tolerability Period (6 weeks)
    a. Determination of randomization eligibility †
3. Dose Escalation Period (3 weeks)
4. Maintenance Period (24 weeks) ‡
5. Taper Period (2 weeks)‡
6. Follow-Up Period (2 weeks)‡.

†Patients who do not meet criteria for randomization eligibility will not be randomized to study SCOUT-015.

‡All patients participating in the Maintenance Period may be offered participation in the long-term extension study (SCOUT-016). Patients who do not enroll in the SCOUT-016 study will have their investigational product (RAD011 or placebo [IP]) tapered off over 2 weeks (14 days), followed by a 2-week (14-day) safety follow-up.

After approximately 45 patients complete 4 weeks of the Maintenance Period of the Phase 2 part of the study, the Data Monitoring Committee (DMC) will meet to review safety and tolerability data and to recommend 1 or 2 RAD011 dose level(s) for evaluation in the Phase 3 part of the study.

Screening Period (3 weeks, Visit 1 [Weeks -3 to 0]):

Phase 2 and Phase 3 Parts of the study

All patients with a signed informed consent/assent will undergo Screening assessments. Screening assessments will include a full medical history and physical exam, a review of documentation of PWS

diagnosis, an electrocardiogram (ECG), laboratory and questionnaire assessments (including the HQ-CT). To be eligible for the Tolerability Period, patients must meet the following criterion:

- Mean HQ-CT score ≥13

Patients not meeting Inclusion/Exclusion criteria for entry in the study will not be eligible for the study and may not be screened again. Caregivers will be required to either assist the patient or complete the questionnaires on behalf of the patient. The same caregiver should be available throughout the study to help in completing the questionnaires for purposes of consistency.

Tolerability Period (6 weeks, Visits 2 to 5 [Weeks 1 to 7])

Phase 2 and Phase 3 of the study

Patients who meet the eligibility criteria will undergo a 6-week Tolerability Period. During this Period, all patients will receive placebo at a dose of 0.1 mL/kg/day to assess tolerability of the formulation without active CBD and give patients time to adjust to study procedures and future IP administration. Patients unable to tolerate the 0.1 mL/kg/day dose level will be withdrawn from the study.

Patients/caregivers will also complete serial HQ-CT questionnaires at 2-week intervals. At the end of the 6-week Tolerability Period and prior to randomization, patient randomization eligibility based on tolerability and HQ-CT scores will be evaluated. To be eligible for randomization, patients must meet both of the following criteria:

- Mean HQ-CT score ≥13 obtained from prior HQ-CT scores
- Decrease from the Tolerability Period to the Screening Period in HQ-CT score ≤7 points

Patients who do not meet criteria for randomization eligibility will not be randomized to study SCOUT-015.

Randomization (Visit 5 [Week 7])

Phase 2 of the study

Following the Tolerability Period, patients meeting randomization eligibility criteria will be randomized to 1 of 6 groups (3 active and 3 placebo with the ratio of 2:2:2:1:1:1): low dose (10 mg/kg/day [0.1 mL/kg/day]) RAD011, mid dose (20 mg/kg/day [0.2 mL/kg/day]) RAD011, high dose (40 mg/kg/day [0.4 mL/kg/day]) RAD011, low volume (0.1 mL/kg/day) placebo, mid volume (0.2 mL/kg/day) placebo, or high volume (0.4 mL/kg/day) placebo divided twice daily.

Phase 3 of the study

Following review of the Phase 2 safety and tolerability data by the DMC, 1 or 2 dose level(s) will be recommended for further development and assessment in the Phase 3 part of the study.

Dose Escalation Period (3 weeks, Visits 5 to 7 [Weeks 7 to 9])

Phase 2 of the study

After completing the Screening and Tolerability Periods, all randomized patients will be initiated on the IP 10 mg/kg/day (0.1 mL/kg/day) for a period of 1 week at Visit 5 (Week 7). Patients randomized to low dose or low volume IP (10 mg/kg/day) will continue at a dose of 10 mg/kg/day (0.1 mL/kg/day) until the end of Visit 7 (Week 9). Patients randomized to mid dose or mid volume IP (20 mg/kg/day) will have their dose increased to 20 mg/kg/day (0.2 mL/kg/day) at Visit 6 (Week 8) and will continue at that dose until the end of Visit 7 (Week 9). Patients randomized to high dose or high volume IP (40 mg/kg/day) will have their dose increased to 20 mg/kg/day (0.2 mL/kg/day) at Visit 6 (Week 8) and to 40 mg/kg/day (0.4 mL/kg/day) at Visit 7 (Week 9).

The Investigator, or designee, will contact patients/caregivers by phone call, video call, email, or other remote means of communication at Visits 6 (Week 8) and 7 (Week 9) to determine if the patient's dose may be escalated to the next dose level. Dose reductions will not be allowed during the Dose Escalation Period. Patients unable to tolerate their assigned dose level(s) during the Dose Escalation Period will be withdrawn from the study.

Phase 3 of the study

After completing the Screening and Tolerability Periods, all patients will be initiated on 10 mg/kg/day IP (0.1 mL/kg/day) for a period of 1 week at Visit 5 (Week 7). Dose escalation will occur as in the Phase 2 of the study, according to the DMC-recommended Phase 3 dose level(s).

The Investigator, or designee, will contact patients/caregivers by phone call, video call, email, or other remote means of communication at Visits 6 (Week 8) and 7 (Week 9) to determine if the patient's dose may be escalated to the next dose level. Dose reductions will not be allowed during the Dose Escalation Period. If a patient cannot be escalated to the next dose level, the patient will be discontinued from the study.

Maintenance Period (24 weeks, Visits 8 to 14 [Weeks 10 to 34])

Phase 2 and Phase 3 of the study

After completing the 3-week Dose Escalation Period, patients will enter the 24-week Maintenance Period.

Some patients may have their dose adjusted based on tolerability during the Maintenance Period.

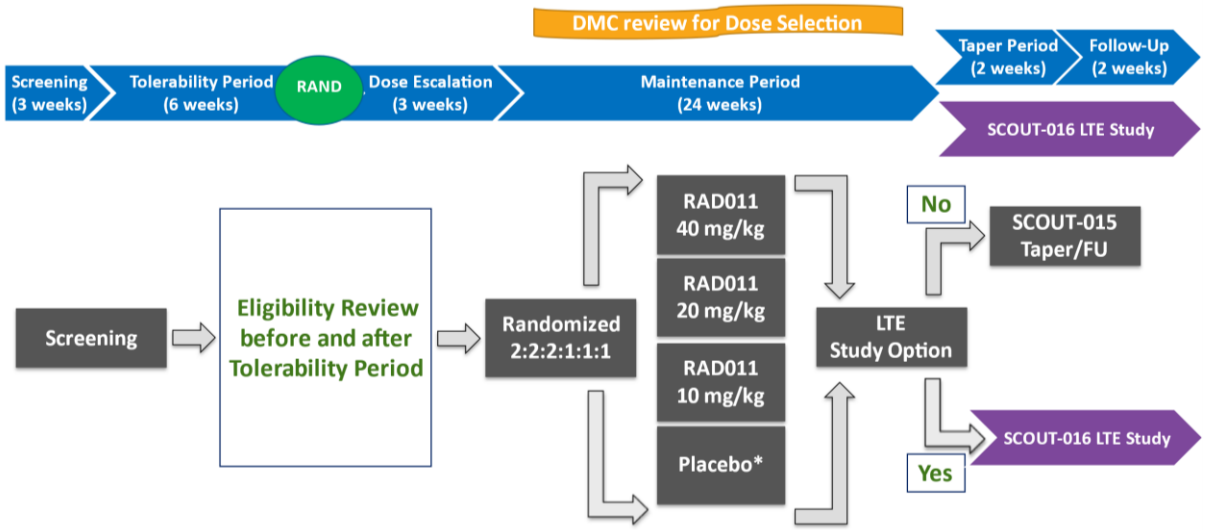
After completion of the Maintenance Period, patients may be offered the opportunity to enroll in the long-term extension study (SCOUT-016). Patients who do not elect to enroll will be tapered off the IP.

Taper Period (14 days, Visit 14 [Week 34]) and Follow-up Period (14 days, Visits 15 and 16 [Weeks 36 and 38])

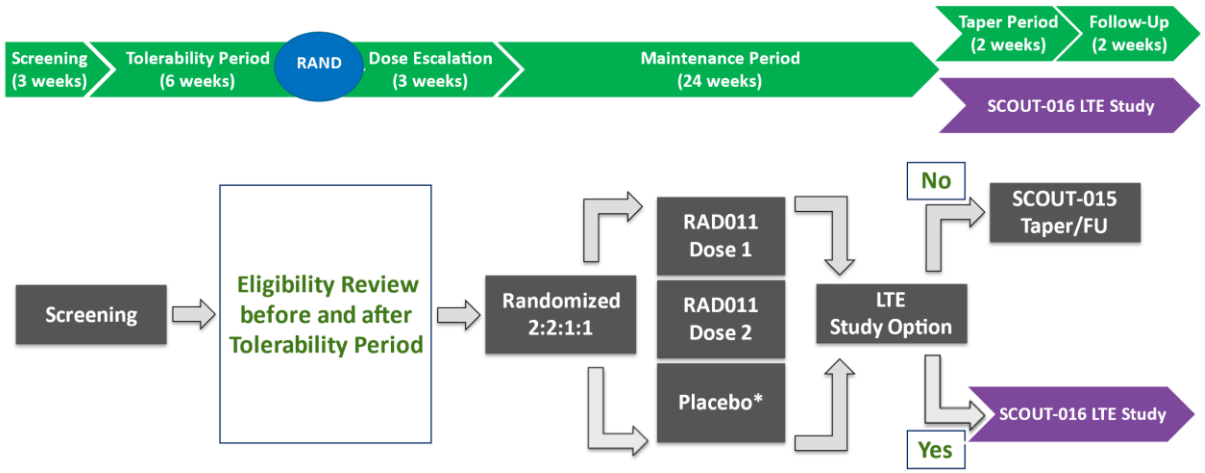
Patients who do not enroll in the long-term extension study (SCOUT-016) will have their IP tapered off over 14 days according to the following schedule: the IP should be decreased by 50% during the first 7 days, followed by an additional 50% during the following 7 days, and then discontinued. The taper schedule may be modified at the discretion of the Investigator but cannot be extended to a total period lasting more than 14 days. A final follow up will be conducted 2 weeks after the last dose of IP for patients who are tapered off.

A schematic representation of the Phase 2 and Phase 3 of the study is provided in the figures below:

Study Design Schematic – Phase 2 of the Study



* Patients assigned to placebo will include low, mid, and high volume placebo to match active drug and will be combined for statistical analysis.



Study Design Schematic – Phase 3 of the Study

*Patients assigned to placebo will be further broken down to achieve balanced exposure between placebo and RAD011 patients. The number of doses to be studied will be determined by the DMC's safety review.

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria:

To be eligible for this study, patients must meet all of the following inclusion criteria:

1. Presence of a parent/legal guardian that is able to consent for their participation. Parent/caregiver/legal guardian can complete the required assessments throughout the study. Patient Consent/Assent will be obtained if the patient is 8 years of age or older and has the mental capacity to understand and sign a written consent/assent form and/or give verbal assent
2. Males and females between:
    a. Phase 2: 12 and 65 years of age (inclusive) at time of consent/assent
    b. Phase 3: 8 and 65 years of age (inclusive) at time of consent/assent
3. Documentation of genetically confirmed PWS diagnosis

4. If a caregiver helps in completing the HQ-CT or other questionnaires, the same caregiver is available to complete the questionnaire throughout the duration of the study
5. If female, is either not of childbearing potential (defined as premenarchal or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or practicing one of the following medically acceptable methods of birth control up to 4 weeks after the last dose of RAD011 or placebo:
    a. Double barrier method (i.e., condom plus occlusive cap (diaphragm or cervical/vault caps), condom or occlusive cap plus spermicide)
    b. Hormonal methods such as oral, implantable, injectable, vaginal ring, or transdermal contraceptives at a stable dose for a minimum of 1 full cycle (based on the patient's usual menstrual cycle period) before IP administration
    c. Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
    d. If not using hormonal contraceptives or IUD or IUS, then all male partners throughout the study must have been vasectomized and have received medical assessment of the surgical success
6. If male, is vasectomized and has received medical assessment of the surgical success or agrees to use an approved method of contraception (double barrier method as described in Inclusion Criterion 5, female partner's use of an IUD or IUS [in place at least 12 weeks prior to dosing], oral contraceptives or female partner who is surgically sterile or 2 years postmenopausal) and agrees to use this method for 4 weeks after last administration of RAD011 or placebo
7. If receiving growth hormone (GH), psychotropic therapy, metabolic treatments that could affect appetite (including metformin), and other treatment including thyroid hormone, must be on the same medication and stable dose for at least 90 days prior to consent/assent
8. Any non-medical interventions (eg, counseling, behavior modification) should be stable for at least 90 days prior to consent/assent
9. HQ-CT eligibility automatically calculated in the electronic data capture (EDC) system:
    a. Visit 2
        i. Patients with a mean HQ-CT score ≥13 (from Visit 1 and Visit 2) will be eligible to continue in the Tolerability Period
    b. Visit 5
        i. Patients with a mean HQ-CT score ≥13 (from Visit 3, Visit 4 and Visit 5) will be eligible for randomization, and
        ii. Patients with a decrease in HQ-CT score (from Tolerability Period to the Screening Period) ≤7 will be eligible for randomization

Exclusion criteria:

Patients meeting any of the following criteria will be excluded from the study:

1. Hypersensitivity or intolerance to CBD, or any other excipients used in the RAD011 preparation
2. Known use of cannabis or cannabinoid containing products (including topical products) within 90 days prior to consent/assent
3. History of chronic liver disease, such as cirrhosis or chronic hepatitis due to any cause
4. Positive urine test for drugs of abuse, including tetrahydrocannabinol (THC), or known history of drug, alcohol, or substance abuse

5. Use of prescription or over-the-counter weight loss agents within 90 days prior to consent/assent
6. Implementation of new food restrictions or environmental restrictions within 90 days of consent/assent
7. Any significant comorbid condition or disease:
    a. Respiratory disease, heart disease, or psychiatric disorder which in the opinion of the Investigator would preclude the patient from participating or
    b. Uncontrolled type 1 or type 2 diabetes as determined by the Investigator or
    c. Clinically significant ECG abnormalities or other evidence of clinically significant heart disease as determined by the Investigator or
    d. Uncontrolled sleep apnea as determined by the Investigator or
    e. Neutropenia with neutrophil counts <1,000 /microL (grade 3 or grade 4 neutropenia as defined by CTCAE v5.0) or
    f. History or presence of gastrointestinal disorders or any other condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs taken orally as determined by the Investigator
8. QT interval corrected for heart rate (HR) according to Fridericia's formula (QTcF) meeting the following criteria:
    a. For males and females aged 8 to <20 years: QTcF >439 msec
    b. For males aged 20 to 65 years: QTcF >450 msec
    c. For females aged 20 to 65 years; QTcF >470 msec
9. At consent/assent, patients with age-matched hypertensive levels of systolic and/or diastolic blood pressure may be excluded at the Investigator's discretion if deemed to be in the best interest of the patient.
10. Pregnant (determined by a positive serum pregnancy test) or lactating female
11. Unwillingness or inability to follow the procedures outlined in the protocol
12. Estimated glomerular filtration rate <30 mL/min/1.73m^2 or protein/creatinine ratio ≥0.4
13. Bilirubin >1.5 × upper limit of normal (ULN), or aspartate aminotransferase (AST), alanine aminotransferase (ALT) >3 × ULN, or international normalized ratio (INR) >1.5 × ULN
14. Patient judged by the Investigator or Sponsor (or designee) as unable to comply with the treatment protocol, including appropriate supportive care, follow up, and research tests
15. Other genetic, hormonal, chromosomal, cognitive, or behavioral impairment
16. If living in a group home, patient spends less than 25 waking hours with their caregiver per week.
17. Significant risk of committing suicide based on history, routine psychiatric examination, or based on the Investigator's judgment
18. Participation in any other study involving an investigational product or device within 4 weeks or 5 half-lives (whichever is longer) of consent/assent or longer as required by local regulations

Investigational Product, Dosage, and Mode of Administration:

RAD011 (Cannabidiol Oral Solution) 100 mg/mL, 10 mg/kg/day to 40 mg/kg/day, administered orally in two divided doses

Duration of Study Participation:

37 to 40 weeks

Reference Therapy, Dosage, and Mode of Administration:

Placebo (medium-chain triglyceride vehicle used in RAD011 formulation)

Criteria for Evaluation:

Primary objective

The primary objective of the Phase 2 of this study is to assess the safety and tolerability of multiple doses levels of RAD011 in order to select 1 or 2 dose level(s) to further evaluate in the Phase 3 of the study.

The primary objective of the Phase 3 of this study is to assess the effect of RAD011 on hyperphagia-related behavior in patients with PWS.

Secondary objectives

The secondary objectives are to assess the following:

- Effect of RAD011 on irritability
- Effect of RAD011 on Clinician Global Impression of Change (CGI-C) in Hyperphagia
- Effect of RAD011 on Clinician Global Impression of Severity (CGI-S) of Hyperphagia
- Safety and tolerability of RAD011

Other objectives

The other objectives of this study are to assess the:

- Effect of RAD011 on Caregiver Global Impression of Change (CaGI-C) in Hyperphagia
- Effect of RAD011 on Caregiver Global Impression of Severity (CaGI-S) of Hyperphagia
- Effect of RAD011 on Caregiver Global Impression of Change (CaGI-C) in Irritability
- Effect of RAD011 on overall behavior
- Effect of RAD011 on sleep
- Effect of RAD011 on body mass index (BMI) and weight
- Effect of RAD011 on skin-picking behavior
- Effect of RAD011 on total muscle/fat composition (performed at selected United States [US] sites)

Endpoints:

Primary efficacy endpoint:

- Change in HQ-CT scores from Baseline through End of Study/Week 34 Visit for RAD011 compared to placebo

Secondary efficacy endpoints:

- Change in PWS-associated Irritability from Baseline through End of Study/Week 34 Visit using the Aberrant Behavior Checklist (ABC) questionnaire – Irritability subscale (ABC-I) for RAD011 compared to placebo
- Change in hyperphagia as defined by the Clinician Global Impression of Change (CGI-C) in Hyperphagia through End of Study/Week 34 Visit
- Change in Clinician Global Impression of Severity (CGI-S) of Hyperphagia from Baseline through End of Study/Week 34 Visit

Other endpoints:

- Change in hyperphagia as defined by the Caregiver Global Impression of Change (CaGI-C) in Hyperphagia response through End of Study/Week 34 Visit for RAD011 compared to placebo

- Change in Caregiver Global Impression of Severity (CaGI-S) of Hyperphagia from Baseline through End of Study/Week 34 Visit
- Change in irritability as defined by the Caregiver Global Impression of Change (CaGI-C) in Irritability through End of Study/Week 34 Visit
- Change in overall behavior from Baseline through End of Study/Week 34 Visit using the ABC questionnaire subscales for RAD011 compared to placebo
- Change in sleep from Baseline through End of Study/Week 34 Visit using the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) for RAD011 compared to placebo
- Change in weight and BMI from Baseline through End of Study/Week 34 for RAD011 compared to placebo
- Change in skin picking behavior using the Skin Picking Questionnaire from Baseline through End of Study/Week 34 for RAD011 compared to placebo
- Change in muscle/fat composition using a dual-energy X-ray absorptiometry (DEXA) scan from Randomization through End of Study/Week 34 for RAD011 compared to placebo

Pharmacokinetic endpoints

Throughout the study, plasma samples will be collected to establish the PK profile of CBD and 2 metabolites, 7-OH-CBD and 7-COOH-CBD in patients with PWS. Furthermore, an exposure response analysis using CBD and 7-OH-CBD concentrations as well as a population PK model will be derived from the data.

Safety and Tolerability Endpoints:

Treatment-emergent adverse events, vital signs (blood pressure, HR, body temperature, respiratory rate, oxygen saturation), ECGs, and laboratory tests (chemistry, hematology, coagulation, and urinalysis)

Sample Size and Power Calculation:

DMC Recommendation of Two RAD011 Doses

For the primary efficacy analysis, a total of 150 patients (50 patients per treatment group) aged 12 to 65 years will provide 90% power to compare each dose group vs. placebo with a two-sided alpha of 0.025. The study is powered to detect a difference in the HQ-CT from Baseline to Week 34 of 5 points with a standard deviation of 7 points. The 0.05 Type 1 error is split equally between groups (low dose and high dose). The low- and high-volume placebo groups will be combined for all comparisons to placebo. Assuming a 15% post-randomization dropout rate, approximately 176 patients (~59 patients per treatment group) will be evaluated for the primary efficacy analysis.

Thus, if the DMC recommends two RAD011 doses for Phase 3 of the study, approximately a total of 191 patients (target approximately 200 patients) aged 12 to 65 years will be randomized in this study. The 191 reflects 176 patients required for primary efficacy analysis plus 15 patients randomized in the Phase 2 part of the study to the dose not selected for the Phase 3 part of the study.

Assuming a 20% pre-randomization eligibility failure rate (including HQ-CT eligibility criteria), approximately 240 patients will be enrolled in the Screening Period. An additional 10 patients per treatment group aged 8 to <12 years may be allowed to participate in the Phase 3 part of the study and will be randomized in a way to obtain a balanced number of patients on RAD011 (at dose levels recommended by the DMC) and placebo. Patients aged 8 to <12 will not be included in the primary efficacy analysis.

DMC Recommendation of One RAD011 Dose

For the primary efficacy analysis, a total of 100 patients (50 patients per treatment group) aged 12 to 65 years will provide 94% power to compare active vs. placebo with a two-sided alpha of 0.05. The study is powered to detect a difference in the HQ-CT from Baseline to Week 34 of 5 points with a standard deviation of 7 points. Assuming a 15% post-randomization dropout rate, approximately 118 patients (~59 patients per treatment group) will be evaluated for the primary efficacy analysis.

Thus, if the DMC recommends one RAD011 dose for the Phase 3 part of the study, approximately 148 patients (target approximately 150 patients) aged 12 to 65 years will be randomized in this study. The 148 reflects 118 patients required for primary efficacy analysis plus 30 patients randomized in the Phase 2 part of the study to the two doses not selected for the Phase 3 part of the study.

Assuming a 20% pre-randomization eligibility failure rate (including HQ-CT eligibility criteria), approximately 185 patients will be enrolled into the Screening Period. An additional 10 patients per treatment group aged 8 to <12 years may be allowed to participate in the Phase 3 part of the study and will be randomized in a way to obtain a balanced number of patients on RAD011 (at dose level recommended by the DMC) and placebo. Patients aged 8 to <12 will not be included in the primary efficacy analysis.

Statistical Methods:

Analysis Populations:

The following patient populations will be defined for analysis:

- Safety Population: the Safety Population will include all randomized patients who were treated with at least one dose of IP
- Intent-to-Treat (ITT) Population: the ITT Population will include all randomized patients
- Modified ITT (mITT) Population: the mITT Population will include all patients aged ≥12 years who were randomized, received at least 1 dose of IP, had at least 1 post-randomization HQ-CT questionnaire completed, and were randomized to receive the dose level(s) recommended for development in the Phase 3 part of the study, including patients in the Phase 2 part of the study who received the chosen dose level(s)
- Per Protocol (PP) Population: the PP Population will include all patients aged ≥12 years who were randomized, received at least 1 dose of IP, completed Week 34 without significant protocol deviations that were prospectively defined to impact efficacy (see SAP) and received the dose level(s) recommended for development in the Phase 3 part of the study, including patients in Phase 2 of the study who received the chosen dose level(s)
- Pharmacokinetic (PK) Evaluable Population: the PK Evaluable Population will include all patients who received at least 1 dose of IP and underwent at least 1 PK sample collection.

Efficacy Analyses:

The primary endpoint, change in HQ-CT score from Baseline to End of Study (Week 34), will be analyzed for the mITT population based on the treatment policy estimand using a mixed model for repeated measures (MMRM) with change in HQ-CT score as the response variable and randomization assignment, Baseline HQ-CT score and stratification variables (age [≥16 or <16 years] at randomization and GH treatment at randomization [yes/no]) and time × treatment interaction as fixed effects. Patient will be included as a random effect with an unstructured covariance matrix. A multiple imputation will be used for missing data. Baseline will be defined as the mean HQ-CT score (Visit 1, Visit 2).

DMC Recommendation of two RAD011 Doses

The primary comparison will be mean change in HQ-CT as calculated via least square means comparing RAD011 low dose vs. placebo and RAD011 high dose vs. placebo at Week 34. Low dose and high dose groups will be compared to placebo at the two-sided 0.025 level so overall Type 1 error is maintained at two-sided 0.05 level.

DMC Recommendation of one RAD011 Dose

The primary comparison will be mean change in HQ-CT as calculated via least square means comparing RAD011 vs. placebo at Week 34. RAD011 will be compared to placebo at the two-sided 0.05 level.

Pharmacokinetic Analyses:

All PK analyses will be described in the pharmacokinetic analysis plan prior to performing statistical analyses. A pharmacodynamic analysis may be completed to evaluate exposure with efficacy and safety.

Safety Analyses:

The Safety Population will be used for all safety assessments. Safety assessments will be based on adverse events (AEs), Columbia-Suicide Severity Rating Scale (C-SSRS), vital signs, ECGs, and laboratory assessments. All analyses of safety will be described in the Statistical Analysis Plan (SAP).

All safety assessments will be descriptive, and no inferential statistics will be performed. All data listings will be provided for protocol specified safety data. The Medical Dictionary for Regulatory Activities will be used to classify all AEs with respect to System Organ Class (SOC) and preferred term. Adverse event summaries will include only treatment-emergent adverse events (TEAEs) by treatment group. Assessment of severity and relationship will also be presented. Adverse events leading to study discontinuation will also be summarized by SOC, Preferred Term, severity, and relationship.

The C-SSRS will be used to evaluate suicidal ideation and intensity of ideation. Ideation and intensity will be grouped by categories, with separate groupings for the Baseline/Screening and the "Since Last Visit" questionnaires.

Clinical laboratory and vital signs will be summarized for the Safety Population for observed values and change from Baseline. Shifts from Baseline according to normal range criteria will also be presented for all patients in the Safety Population.

3. INTRODUCTION

3.1. Background

3.1.1. Overview of Prader-Willi Syndrome

Prader-Willi Syndrome (PWS), first described in 1956, is a multifaceted developmental disorder and the most common genetic syndrome associated with obesity (Gunay-Aygun, 1997; McAllister, 2011). It is caused by the absent expression of paternally inherited genes in the PWS region on chromosome 15q11-q13 (Ledbetter, 1981). While it presents with generalized hypotonia and developmental delay in infancy, PWS then manifests with uncontrollable appetite, hyperphagia, and excessive weight gain leading to severe obesity (Elena, 2012). Obesity is the major cause of death in adults with PWS (Laurance, 1981).

Clinically, PWS patients suffer a complex pattern of physical, behavioral, endocrine, and intellectual deficiencies. Endocrine abnormalities lead to hypogonadism and short stature. In particular, growth hormone (GH) deficiency is reported to occur in 40% to 100% of the population with PWS (Griggs, 2015) and is commonly treated with GH (Angulo, 2015). Behavioral disorders include obsessive compulsive behaviors such as skin picking, hoarding, redoing, and repetitive speech (Griggs, 2015).

However, it is the appetite behavior classified as hyperphagia in PWS that is the most life threatening (Dykens, 2007; Griggs, 2015). Until recently, no patient survived over the age of 50 due to morbid obesity and its related complications (Aycan, 2014). The mortality rate in patients with PWS is 6 times higher than patients with other intellectual disabilities (Einfeld, 2006) and mortality in patients not treated with GH was estimated to be 3% per year between the ages of 6 and 56 compared to the general population yearly mortality of 0.13% below 55 years.

Hyperphagic behaviors can also be dangerous in persons who are relatively slim, with increased risks of death due to choking while sneaking food, and gastric perforations after consuming more food than usual (Dykens, 2007). Approximately 8% of deaths in individuals with PWS was reported due to choking (Stevenson, 2007). PWS patients are also known to eat discarded (contaminated) food and items that are not intended for human consumption such as pet food, or non-food items, such as paint or paper (Griggs, 2015).

The treatment of PWS is currently based on treating the symptoms of the disorder as they arise.

Growth hormone deficiency is present in almost all children and many adults with PWS. In multiple studies, GH has been found to be beneficial for those with PWS (Passone, 2020). In June of 2000, GH was approved by Food and Drug Administration (FDA) in the United States (US) for use in patients with PWS. Growth hormone is effective in increasing height, decreasing body fat, increasing muscle mass, improving weight distribution, increasing stamina, and increasing bone mineral density (Goldstone, 2008; McCandless, 2011).

Despite GH treatment, many challenging symptoms associated with PWS remain difficult to treat. The inability to control food intake is often the biggest obstacle keeping those with PWS from living independently. Although the hyperphagia has been well identified and there exists a well-validated hyperphagia questionnaire (Hyperphagia Questionnaire for Clinical Trials [HQ-CT]), there is no current therapeutic that effectively controls hyperphagia (Dykens, 2007). Therefore, strict environmental control and constant supervision are the only means to prevent

life-threatening overeating and extreme obesity at present. A well-balanced diet, along with careful control of the environment to minimize uncontrolled access to food is the main recommendation provided by the Foundation for PWS Research (https://www.fpwr.org/prader-willi-syndrome-diagnosis-treatments).

The greatest unmet medical need in PWS is to address hyperphagia, low energy expenditure, and the progression to obesity, morbid obesity, diabetes and their resulting cardiovascular complications. Prader-Willi Syndrome-related anxiety, irritability and other behavioral issues are also among the unmet needs of individuals with PWS. Safe and efficacious therapies are needed to address hyperphagia and other prominent symptoms in patients with PWS.

3.1.2. The Endocannabinoid System and Appetite Regulation

The endocannabinoid system appears to be critically involved in the regulation of appetite, body weight, metabolism, hypothalamic-pituitary-adrenal axis, and reward brain circuitry in both animals and humans (Edwards, 2016; Parsons, 2015). The endocannabinoid receptor, CB1, is widely expressed in the central nervous system, autonomic gastric vagus nerve endings of the peripheral nervous system, and other key cells involved in body energy metabolism, including adipocytes, hepatocytes, and myocytes (Bensaid, 2003; Liu, 2005; Osei-Hyiaman, 2008). Several nonclinical studies have suggested an effect of cannabidiol (CBD) on appetite, such as a decrease in food intake without a decrease in water intake (Farrimond, 2012; Silveira Filho, 1981). In addition, CBD has been shown to block the hyperphagia associated with CB1 and 5-hydroxytryptamine (5-HT1A) agonists (Scopinho, 2011) and cause weight loss via its activity on peripheral CB2 receptors (Ignatowska-Jankowska, 2011). Furthermore, CBD may reduce the resultant hyperphagia associated with sweet food (Silveira Filho, 1981).

Cannabidiol is a low-affinity antagonist of CB1, and may also modulate CB1 receptor signaling through its inhibition of the metabolism of the endogenous cannabinoid, anandamide (Ibeas Bih, 2015; Laprairie, 2015). As for appetite, CBD has been shown to decrease food intake in rats under stressful conditions and reduce ad lib intake of high-sugar feed when compared to vehicle-treated controls (Silveira Filho, 1981). In addition, CBD has been shown to diminish daily food consumption without affecting daily water intake (Wierucka-Rybak, 2014) as well as inhibited hyperphagia induced by CB1 receptor or 5-HT1A serotonin receptor agonists, suggesting a role for CBD as a regulator of food intake.

In vitro studies with CBD and some other cannabinoids used in high concentrations have also been shown to activate peroxisome proliferator-activated receptor γ (PPARγ), possibly through direct binding. Peroxisome proliferator-activated receptor γ involvement may contribute to the weight control mechanism of CBD (Booz, 2011).

Clinically, while no studies have investigated the effect of CBD in patients with PWS, a multi-center clinical study of plant-derived CBD in pediatric epilepsy reported appetite suppression in 19% of patients (Devinsky, 2016). Because of the well-characterized orexigenic activity of tetrahydrocannabinol (THC, a strong CB1 agonist), the CB1 antagonist, rimonabant, was studied and found to be effective in treating obesity in adults without PWS (Pi-Sunyer, 2006). Rimonabant demonstrated suppression of appetite (Seely, 2012) and was subsequently approved in the European Union (EU) for the treatment of obesity; however, psychiatric side effects led to the drugs withdrawal from the market. The demonstrated effect of the cannabinoid

system in appetite control supports the development of CBD for the treatment of hyperphagia in patients with PWS.

Based on experience of the effect of modifying the endocannabinoid system via the CB1 receptor in animals (Riedel, 2009) and in obese humans (rimonabant) (Pi-Sunyer, 2006), the significant decrease in risk of obesity in chronic cannabis users despite the known effect of THC to stimulate the appetite (Le Strat, 2011; Penner, 2013), the significant reported adverse events (AE) of weight loss and appetite suppression in epilepsy patients treated with a plant-derived CBD (EPIDIOLEX®) (Devinsky, 2016), and the dose-dependent effect on weight seen in the long-term safety study INS011-14-030 (Section 3.1.5), Radius is studying RAD011 in patients with PWS for the treatment of hyperphagia.

3.1.3. Overview of RAD011

Cannabidiol is a non-psychoactive physiologically relevant phytocannabinoid isomer of THC. RAD011 is a synthetic CBD formulated as a 100 mg/mL oral solution with medium chain triglycerides (MCT) that overcomes the need for ethanol to solubilize CBD in an oral solution presentation.

3.1.4. Summary of Nonclinical Experience

Nonclinical information is available from RAD011 studies, and the label of the FDA approved botanical extract CBD product, EPIDIOLEX.

The completed RAD011 toxicology studies include chronic toxicology studies, 6-month rat and 9-month monkey with 28-day recovery phases, juvenile rat toxicology studies, dose range-finding and 6-week with 5-month recovery, and a full battery of genotoxicity studies (Ames Test, in vitro micronucleus and in vivo micronucleus assays). The genotoxicity studies were negative and the chronic and juvenile toxicology studies demonstrated that RAD011 was well-tolerated with sufficient safety margins over the anticipated clinical exposures (Table 1).

In summary, the RAD011 nonclinical program supports chronic dosing in PWS patients at doses of 20 mg/kg/day and 40 mg/kg/day.

The EPIDIOLEX US Package summarizes the nonclinical findings on in vitro metabolism, reproductive, developmental, fertility, and abuse-related toxicology studies.

Cannabidiol is metabolized in the liver and the gut (primarily in the liver) by cytochrome P450 (CYP) 2C19 and CYP3A4 enzymes, and uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A7, UGT1A9, and UGT2B7 isoforms. Cannabidiol has the potential for inactivation of CYP450 isozymes and therefore has the potential to induce drug- drug interactions.

Oral administration of CBD to pregnant rats throughout the period of organogenesis resulted in embryofetal mortality at the highest dose (250 mg/kg/day) tested. There were no other drug-related maternal or developmental effects. Oral administration of CBD (125 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in decreased fetal body weights and increased fetal structural variations at the highest dose (125 mg/kg/day) tested, which was also associated with maternal toxicity.

Table 1: Pivotal Toxicology Studies and Safety Margins Over Clinical Exposures at 10, 20 and 40 mg/kg Twice Daily

Nonclinical experience								
Study	**Study Number**	**Species/ Strain**	**NOAEL (mg/kg/day)**	**C_{max} (ng/mL)**	**AUC (hr*ng/mL)**	**Safety Margin: C_{max} (fold)**	**Safety Margin: AUC (fold)**	**Route of Administration**
6-month rat	2508-001-003	Rat/Sprague Dawley	70	2683M 8403F	32492M 77407F	13-46	20-95	Gavage
9-month monkey	2508-001-001	Monkey/ Cynomolgus	100	374M 140F	6093M 1723F	0.6-2	1.4-7	Gavage
6-week juvenile rat	20096193	Rat	140	2610M 3640F	34300M 50500F	6-30	13-87	Gavage
Clinical Study Experience								
Study Number		**Population**	**Total Daily Dose[a] (mg/kg/day)**	**C_{max} (ng/mL)**	**AUC (hr*ng/mL)**			**Route of Administration**
INS011-14-029		Pediatric patients with treatment-resistant seizures	10	119.6	581.6	--	--	Oral solution
			20	220.0	1098	--	--	
			40	426.8	2708	--	--	

Abbreviations: AUC = area under the curve; C_{max} = maximal concentration; F = female; M = male; NOAEL = no-observed-adverse-effect-level.

[a] Total daily doses were divided in approximately 2 equal doses administered twice daily.

When CBD was orally administered to rats throughout pregnancy and lactation, decreased growth, delayed sexual maturation, neurobehavioral changes (decreased activity), and adverse effects on male reproductive organ development (small testes in adult offspring) and fertility were observed in the offspring at the mid (150 mg/kg/day) and high (250 mg/kg/day) dose. These effects occurred in the absence of maternal toxicity.

Oral administration of CBD (evaluated in doses up to 250 mg/kg/day) to male and female rats, prior to and throughout mating and continuing in females during early gestation, produced no adverse effects on fertility.

Animal abuse-related studies show that CBD does not produce cannabinoid-like behavioral responses, including generalization to THC in a drug discrimination study; and animal self-administration studies, which suggests that it does not produce rewarding effects.

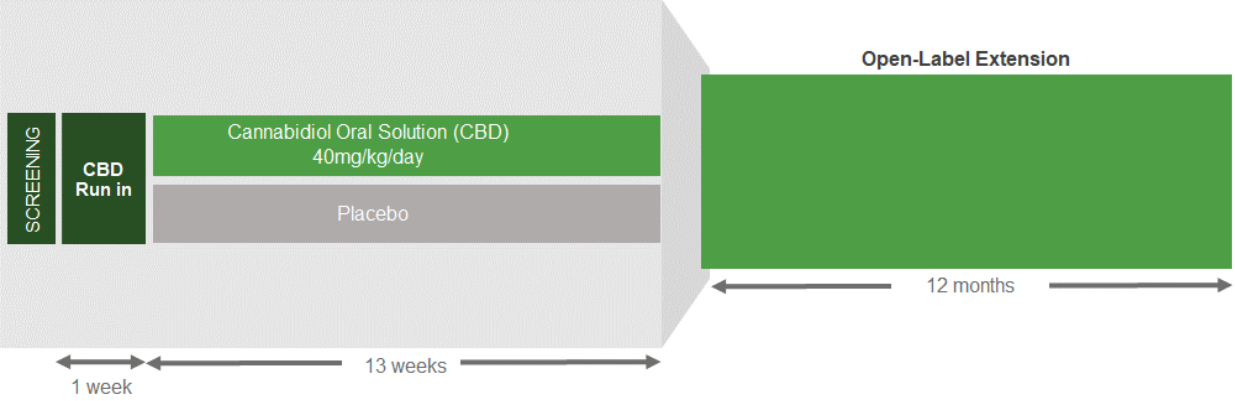
3.1.5. Summary of Clinical Experience

Two clinical studies have been initiated with RAD011 in patients with PWS. Both were terminated early due to reasons other than safety.

3.1.5.1 Phase 2 Study (INS011-16-085)

A Phase 2 study of the compound entitled, "A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Efficacy, Safety, and Tolerability of Cannabidiol Oral Solution for the Treatment of Patients with Prader-Willi Syndrome" was initiated by a previous Sponsor (Insys Therapeutics) with the study design provided in Figure 1.

Figure 1: Study Design of Phase 2 Study of RAD011 in Prader-Willi Syndrome



Abbreviation: CBD = cannabidiol.

The study planned to enroll 66 patients but was terminated prematurely due to the closure of Insys Therapeutics, under circumstances unrelated to the study with 7 patients enrolled. Of these 7 patients, 4 patients received RAD011 and 3 received placebo. The baseline demographics of the population are described in Table 2.

Table 2: Demographic Data from Phase 2 Study of RAD011 in Prader-Willi Syndrome

	Cannabidiol N=4	**Placebo N=3**
Median age (years) (range)	14.5 (11.0 to 16.0)	12 (8.0 to 15.5)
Male:Female	2:2	2:1
Baseline Weight (kg) Median (range)	88.4 (47.9 to 112.4)	56.7 (45.5 to 109.7)
Growth Hormone Use	2 (50%)	2 (67%)

The primary endpoint of this Phase 2 study was to assess the efficacy of Cannabidiol Oral Solution (COS) on hyperphagia related behavior in patients with PWS as measured by the change in HQ-CT scale. A secondary endpoint assessed the effect of COS on weight in patients with PWS.

Despite the abbreviated nature of the Phase 2 study, mean duration of exposure was 9-weeks, the data are directionally supportive of reducing hyperphagia with an approximate 6.5-point reduction in the HQ-CT scale. Treatment with RAD011 was also well tolerated with the most frequent AEs of diarrhea, rash, and abdominal cramping.

3.1.5.2 Phase 2 Study Open-Label Extension (INS011-17-115)

A Phase 2 study entitled, "A Multicenter, Open Label Study to Assess the Long Term Safety of Pharmaceutical Grade Synthetic Cannabidiol Oral Solution in Patients with Prader-Willi Syndrome" was initiated by a previous Sponsor (Insys Therapeutics). Patients had to have completed INS011-16-085 to be eligible. Approximately 66 male and female patients aged 8 to 17 years, inclusive, with a genetically confirmed diagnosis of PWS were planned to be enrolled in the study. All patients were to receive COS at 40 mg/kg/day, divided into two daily doses with standard meals, for up to 48 weeks.

This study was terminated prematurely due to the closure of Insys Therapeutics, under circumstances unrelated to the study, with 2 patients enrolled. Each patient experienced at least one AE. Both patients experienced diarrhea and one patient experienced a seizure (also occurred on placebo in study INS011-16-085).

No deaths, serious adverse events (SAE), or discontinuations were reported during the study. No clinically meaningful changes in laboratory, vital sign, or electrocardiogram (ECG) parameters were observed during the study.

3.1.6. Pharmacokinetic Experience

Three studies have characterized the pharmacokinetics (PK) and additional details on the PK studies can be found in the Investigator's Brochure. Overall conclusions from the PK studies include:

- Cannabidiol Oral Solution, 100 mg/mL is a suitable formulation for use in clinical investigations of CBD, ensuring better, faster, and less variable systemic exposure with food. Exposure is expected to be dose proportional- under the fed state (enabling comparison between two formulations). Administration of cannabidiol under fed conditions may be optimal to achieve consistent exposure in patients. A PK study was completed in healthy volunteers in a fed state with the 100 mg/mL formulation. Parameters for time to maximal concentration (T_{max}), C_{max}, AUC, and half-life ($T_{1/2}$) are provided in Table 3.
- Steady state- levels of CBD appeared to be attained with approximately 2 to 6 days of repeated dosing, with median CBD time to C_{max} of 2 to 3 hours for pediatric patients. Repeated twice daily administrations of COS resulted in highly variable systemic exposures of CBD with some accumulation (approximately 3- to 4-fold). There were no clear trends for age related differences in CBD peak exposures; however, exposures in infants tended to be lower than older age groups.

Table 3: Pharmacokinetic Parameters of RAD011 (Medium Chain Triglyceride Formulation) Administered to Healthy Subjects in a Fed State

Parameter	Cannabidiol 100 mg/kg MCT in Fed State			
	N	Mean	SD	CV%
T_{max} (h)[a]	8	6.00 (2.5,12.0)		
C_{max} (ng/mL)	8	878	322	36.7
$AUC_{0\text{-}inf}$ (h*ng/mL)[b]	5	4360	933	21.4
$T_{1/2}$ (h)[b]	5	14.0	1.30	9.3

Abbreviations: $AUC_{0\text{-}inf}$ = area under the curve from time 0 to infinity; C_{max} = maximal concentration; MCT = medium chain triglycerides; $T_{1/2}$ = half-life; T_{max} = time to maximal concentration.

[a] Tmax presented as median (min, max).

[b] λ_2 acceptance criteria was not met for some subjects.

3.1.7. Potential for Pharmacokinetic Drug-Drug Interactions

In vitro studies using human liver microsomes or recombinant CYP enzymes have shown CBD to be a potent mechanism-based inhibitor of human CYP1A1 and can inhibit to a lesser extent (by >15-fold) CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 independent of metabolism (Yamaori, 2014). The half maximal inhibitory concentration values for CBD using recombinant human CYP1A1 was 0.671 µM without pre-incubation and 0.0678 µM with a 20-minute pre-incubation. It was proposed that the methyl resorcinol structure in CBD may be required for CYP1A1 inactivation.

Clinically, CBD (600 mg/day PO; i.e. 10 mg/kg/day) given for 5 to 12 days yielded a 36% decrease in the clearance and a 35% decrease in the volume of distribution of hexobarbital in normal patients (Benowitz, 1980). Cannabidiol inhibited barbiturate metabolism to an extent

substantially greater than that observed for Δ9-THC. In another clinical study, oral dosing with CBD (1500 mg or 25 mg/kg) to patients did not significantly affect the total clearance, volume of distribution, or terminal elimination half-lives of Δ9-THC metabolites (Hunt, 1981).

In a clinical report of 13 patients with refractory epilepsy receiving co-administration of clobazam (CLB) and EPIDIOLEX, the mean (± standard deviation [SD]) increase in CLB levels was 60 ± 80% (95% confidence interval (CI) [-2-91%]) at 4 weeks, the mean increase in norclobazam (nCLB), the major metabolite, was 500 ± 300% (95% CI [+90-610%]) at 4 weeks (Geffrey, 2015). Since CLB is metabolized by CYP3A4 to nCLB which is then metabolized by CYP2C19, this confirms the in vitro studies.

After analysis of the PK data from INS011-14-029, approximately 50% of the patients enrolled were also receiving CLB. In these patients, co-administration of CBD and CLB resulted in increased levels of CBD (by approximately 2.5-fold), as well as increased levels of CLB and nCLB (by approximately 2.5-fold), compared with patients not taking CLB.

As expected, based on the findings above, because CBD is metabolized by CYP3A4 and CYP2C19, it may act as a competitive inhibitor and increase levels of other drugs also metabolized by these enzymes. Therefore, care should be taken when CBD is given in conjunction with other drugs metabolized by the CYP system.

3.2. Study Rationale

The rationale for development of RAD011 for the treatment of hyperphagia in patients with PWS is based on preliminary evidence from a prematurely terminated Phase 2 study as well as reports of appetite reduction and weight loss as an AE in epilepsy studies with RAD011 and other cannabidiol products.

In addition, in the open label study of EPIDIOLEX for the treatment of refractory seizures in patients aged between 1 and 30 years old (Devinsky, 2016), 19% of patients experienced AE of decreased appetite, second only to somnolence (25%).

3.2.1. Risk-Benefit of RAD011 in Patients with Prader-Willi Syndrome

3.2.2. Summary of Potential Risks

3.2.2.1 Potential for Testicular Toxicity

The effects of CBD and cannabinoids on male fertility are summarized in more detail in the Investigator's Brochure.

3.2.2.2 Expected Adverse Events

The most common AEs in study INS011-14-029 were somnolence and diarrhea. In 85% of the cases of somnolence observed, there was concomitant use of CLB, resulting in elevated levels. These events all resolved with reduction of dose of CLB and/or CBD. Thus, caution should be used in patients taking CLB.

One SAE occurred in Study INS011-14-029 of an infant developing a thrombosis associated with a peripherally inserted central catheter. The thrombosis resolved without incident with treatment. While this SAE was felt to be not related to cannabidiol, given the increased risk for

thrombosis in PWS patients, CBD should be used with caution in the presence of an indwelling catheter.

Review of the final safety data from the recently completed long-term safety study INS011-14-030 has not identified any safety signals not seen with INS011-14-029.

Two adult patients in Study INS011-15-043 developed self-limited, uncomplicated mild/moderate neutropenia that was possibly related to the use of cannabidiol. Caution should be taken in patients at risk for neutropenia from other causes, such as concomitant medications. No patient on the MCT-based formulation at 100 mg/mL reported an AE in the study INS016-093.

3.2.3. Summary of Potential Benefits

The appetite behavior classified as hyperphagia in PWS is the most life threatening (Dykens, 2007; Griggs, 2015) and until recently, no patient lived over the age of 50 due to morbid obesity and its related complications (Aycan, 2014). The mortality rate in patients with PWS is six times higher than patients with other intellectual disabilities (Einfeld, 2006) and mortality in patients not treated with GH was estimated to be 3% per year between the ages of 6 and 56 compared to the general population mortality of 0.13% below 55 years. The results from the abbreviated Phase 2 study in individuals with PWS, along with the clinical findings of a decrease in appetite and weight loss across other indications, and the nonclinical evidence, supports targeting the endocannabinoid system with cannabidiol to treat hyperphagia. Radius believes that this evidence along with the safety and tolerability of the synthetic COS, RAD011, further supports exploration of RAD011 in individuals with PWS to address hyperphagia and alter the subsequent morbid obesity and related complications.

4. STUDY OBJECTIVES

4.1. Objectives

4.1.1. Phase 2 Part

4.1.1.1 Primary Objective

The primary objective of the Phase 2 part of this study is to assess the safety and tolerability of multiple doses levels of RAD011 in order to select 1 or 2 dose level(s) to further evaluate in the Phase 3 part of the study.

4.1.2. Phase 3 Part

4.1.2.1 Primary Objective

The primary objective* of the Phase 3 part of this study is to assess the effect of RAD011 on hyperphagia-related behavior in patients with PWS.

*The Phase 3 part of the study will include all patients from the Phase 2 part of the study who were treated with dose level(s) selected for development in the Phase 3 part of the study.

4.1.2.2 Secondary Objectives

The secondary objectives* are to assess the following:

- Effect of RAD011 on irritability
- Effect of RAD011 on Clinician Global Impression of Change (CGI-C) in Hyperphagia
- Effect of RAD011 on Clinician Global Impression of Severity (CGI-S) of Hyperphagia
- Safety and tolerability of RAD011.

*The Phase 3 part of the study will include all patients from the Phase 2 part of the study who were treated with dose level(s) selected for development in the Phase 3 part of the study.

4.1.2.3 Other Objectives

The other objectives* of this study are to assess the:

- Effect of RAD011 on Caregiver Global Impression of Change (CaGI-C) in Hyperphagia
- Effect of RAD011 on Caregiver Global Impression of Severity (CaGI-S) of Hyperphagia
- Effect of RAD011 on Caregiver Global Impression of Change (CaGI-C) in Irritability
- Effect of RAD011 on overall behavior
- Effect of RAD011 on sleep
- Effect of RAD011 on body mass index (BMI) and weight
- Effect of RAD011 on skin-picking behavior
- Effect of RAD011 on total muscle/fat composition (performed at selected US sites).

*The Phase 3 part of the study will include all patients from the Phase 2 part of the study who were treated with dose level(s) selected for development in the Phase 3 part of the study.

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design

This is a seamless Phase 2/3, double-blind, randomized, placebo-controlled clinical study in patients diagnosed with PWS. Following consent (or legal guardian consent and patient assent as appropriate), patients will be screened for eligibility to participate in this study.

The Phase 2 portion of the study is to assess safety and tolerability. Dose safety and tolerability decisions will be made in Phase 2. All patients randomized to placebo and to the selected dose level(s) for Phase 3 evaluation will be included in the Phase 3 efficacy evaluation.

The study will consist of the following six similar periods for Phase 2 and Phase 3 of the study:

1. Screening Period (3 weeks)
    a. Review of eligibility prior to proceeding to the Tolerability Period
2. Tolerability Period (6 weeks)

a. Determination of randomization eligibility[†]

3. Dose Escalation Period (3 weeks)
4. Maintenance Period (24 weeks)[‡]
5. Taper Period (2 weeks)[‡]
6. Follow-Up Period (2 weeks)[‡].

[†]Patients who do not meet criteria for randomization eligibility will not be randomized to study SCOUT-015.

[‡]All patients participating in the Maintenance Period may be offered participation in the long-term extension study (SCOUT-016). Patients who do not enroll in the SCOUT-016 study will have their IP tapered over 2 weeks (14 days), followed by a 2-week (14-day) safety follow-up.

After approximately 45 patients complete 4 weeks of the Maintenance Period of the Phase 2 part of the study, the Data Monitoring Committee (DMC) will meet to review safety and tolerability data and to recommend 1 or 2 RAD011 dose level(s) for evaluation in the Phase 3 part of the study. Details regarding the dose selection for the Phase 3 part of the study will be described in the DMC charter.

A schematic overview of the study is presented in Figure 2 for the Phase 2 part, and in Figure 3 for the Phase 3 part.

Screening Period (3 weeks, Visit 1 [Weeks -3 to 0])

Phase 2 and Phase 3 of the study

All patients with a signed informed consent/assent will undergo Screening assessments. Screening assessments will include a full medical history and physical exam, a review of documentation of PWS diagnosis, an ECG, laboratory assessments, and questionnaires (including the HQ-CT) as described in Section 5.8.2. To be eligible for the Tolerability Period, patients must meet the following criterion:

- Mean HQ-CT score ≥13 obtained from HQ-CT scores as defined in Section 6.4.

Patients not meeting Inclusion/Exclusion criteria for entry in the study will not be eligible for the study and may not be screened again. Caregivers will be required either to assist the patient or complete the questionnaires on behalf of the patient. The same caregiver should be available throughout the study to help in completing the questionnaires for purposes of consistency.

Tolerability Period (6 weeks, Visits 2 to 5 [Weeks 1 to 7])

Phase 2 and Phase 3 of the study

Patients who meet the eligibility criteria will undergo a 6-week Tolerability Period. During this Period, all patients will receive placebo at a dose of 0.1 mL/kg/day to assess tolerability of the formulation without active CBD and give patients time to adjust to study procedures and future

IP administration. Patients unable to tolerate the 0.1 mL/kg/day dose level will be withdrawn from the study.

Patients/caregivers will also complete serial HQ-CT questionnaires at 2-week intervals. At the end of the 6-week Tolerability Period and prior to randomization, patient randomization eligibility based on tolerability and HQ-CT scores will be evaluated. To be eligible for randomization, patients must meet both of the following HQ-CT criteria:

- Mean HQ-CT score ≥13 obtained from HQ-CT scores as defined in Section 6.4
- Decrease from the Tolerability Period to the Screening Period in HQ-CT score ≤7 points as defined in Section 6.4.

Patients who do not meet criteria for randomization eligibility will not be randomized to study SCOUT-015.

Randomization (Visit 5 [Week 7])

Phase 2 of the study

Following the Tolerability Period, patients meeting randomization eligibility criteria will be randomized to 1 of 6 groups (3 active to 3 placebo with the ratio of 2:2:2:1:1:1): low dose (10 mg/kg/day [0.1 mL/kg/day]) RAD011, mid dose (20 mg/kg/day [0.2 mL/kg/day]) RAD011, high dose (40 mg/kg/day [0.4 mL/kg/day]) RAD011, low volume (0.1 mL/kg/day) placebo, mid volume (0.2 mL/kg/day) placebo, or high volume (0.4 mL/kg/day) placebo divided in two daily doses. Additional details are provided in Section 7.5.

Phase 3 of the study

Following review of Phase 2 safety and tolerability data by the DMC (Section 10.4), 1 or 2 dose level(s) will be recommended for further development and assessment in Phase 3 of the study. Therefore, following the Tolerability Period, patients meeting randomization eligibility criteria will be randomized in a way to obtain a balanced number of patients on RAD011 and placebo to receive double-blind treatment with Investigational Product (IP) at dose levels recommended by the DMC. Additional details are provided in Section 7.5.

Dose Escalation Period (3 weeks, Visits 5 to 7 [Weeks 7 to 9])

Phase 2 of the study

After completing the Screening and Tolerability Periods, all randomized patients will be initiated on IP (RAD011 or placebo) 10 mg/kg/day (0.1 mL/kg/day) for a period of 1 week at Visit 5 (Week 7). Patients randomized to low dose or low volume IP (10 mg/kg/day) will continue at a dose of 10 mg/kg/day (0.1 mL/kg/day) until the end of Visit 7 (Week 9). Patients randomized to mid dose or mid volume IP (20 mg/kg/day) will have their dose increased to 20 mg/kg/day (0.2 mL/kg/day) at Visit 6 (Week 8) and will continue at that dose until the end of Visit 7 (Week 9). Patients randomized to high dose or high volume IP (40 mg/kg/day) will have their dose increased to 20 mg/kg/day (0.2 mL/kg/day) at Visit 6 (Week 8) and to 40 mg/kg/day (0.4 mL/kg/day) at Visit 7 (Week 9).

Details of the dose escalation schema are provided in Table 4. Patients' weight at Visit 5 (Last Tolerability Period visit / first Dose Escalation Period visit) will be used to determine the

patient's actual doses (mL/day) to be administered from Visit 5 (Week 7) through completion of the maintenance phase Visit 14 (Week 34).

The Investigator, or designee, will contact patients/caregivers by phone call, video call, email, or other remote means of communication at Visits 6 (Week 8) and 7 (Week 9) to determine if the patient's dose may be escalated to the next dose level. Dose reductions will not be allowed during the Dose Escalation Period. If a patient cannot be escalated to the next dose level, the patient will be discontinued from the study.

Phase 3 of the study

After completing the Screening and Tolerability Periods, all patients will be initiated on 10 mg/kg/day IP (0.1 mL/kg/day) for a period of 1 week at Visit 5 (Week 7).

The dose escalation schema for the DMC-recommended Phase 3 dose level(s) will follow the same dose escalation schedule as in the Phase 2 part of the study. Details of the dose escalation schema are provided in Table 4. Patients' weight at Visit 5 (Last Tolerability Period visit / first Dose Escalation Period visit) will be used to determine the patient's actual doses (mL/day) to be administered from Visit 5 (Week 7) through Visit 14 (Week 34).

The Investigator, or designee, will contact patients/caregivers by phone call, video call, email, or other remote means of communication at Visits 6 (Week 8) and 7 (Week 9) to determine if the patient's dose may be escalated to the next dose level. Dose reductions will not be allowed during the Dose Escalation Period. If a patient cannot be escalated to the next dose level, the patient will be discontinued from the study.

Maintenance Period (24 weeks, Visits 8 to 14 [Weeks 10 to 34])

Phase 2 and Phase 3 of the study

After completing the 3-week Dose Escalation Period, patients will enter the 24-week Maintenance Period. Patients' weight at Visit 5 (last Tolerability Period visit / first Dose Escalation Period visit) will be used to determine the patient's actual doses (mL/day) to be administered between Visits 8 (Week 10) and 14 (Week 34).

Some patients may have their dose adjusted based on tolerability during the Maintenance Period as detailed in Section 5.7.2.

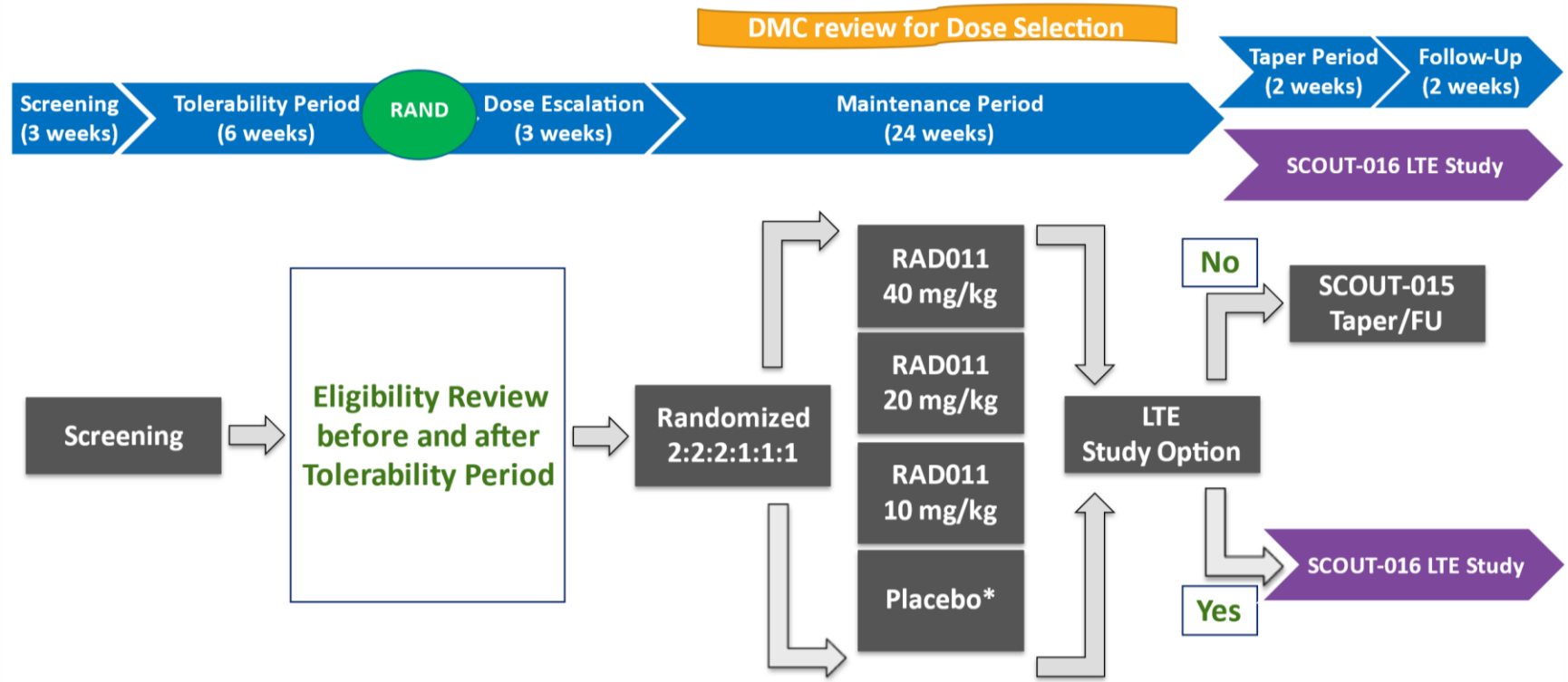
After completion of the Maintenance Period, patients may be offered the opportunity to enroll in the long-term extension study (SCOUT-016). Patients who do not elect to enroll will be tapered off the IP.

Taper Period (14 days, Visit 14 [Week 34]) and Follow-up Period (14 days, Visits 15 and 16 [Weeks 36 and 38])

Patients who do not enroll in the long-term extension study (SCOUT-016) will have their IP tapered off over 14 days according to the following schedule: the IP should be decreased by 50% during the first 7 days, followed by an additional 50% during the following 7 days and then discontinued. The taper schedule may be modified at the discretion of the Investigator but cannot

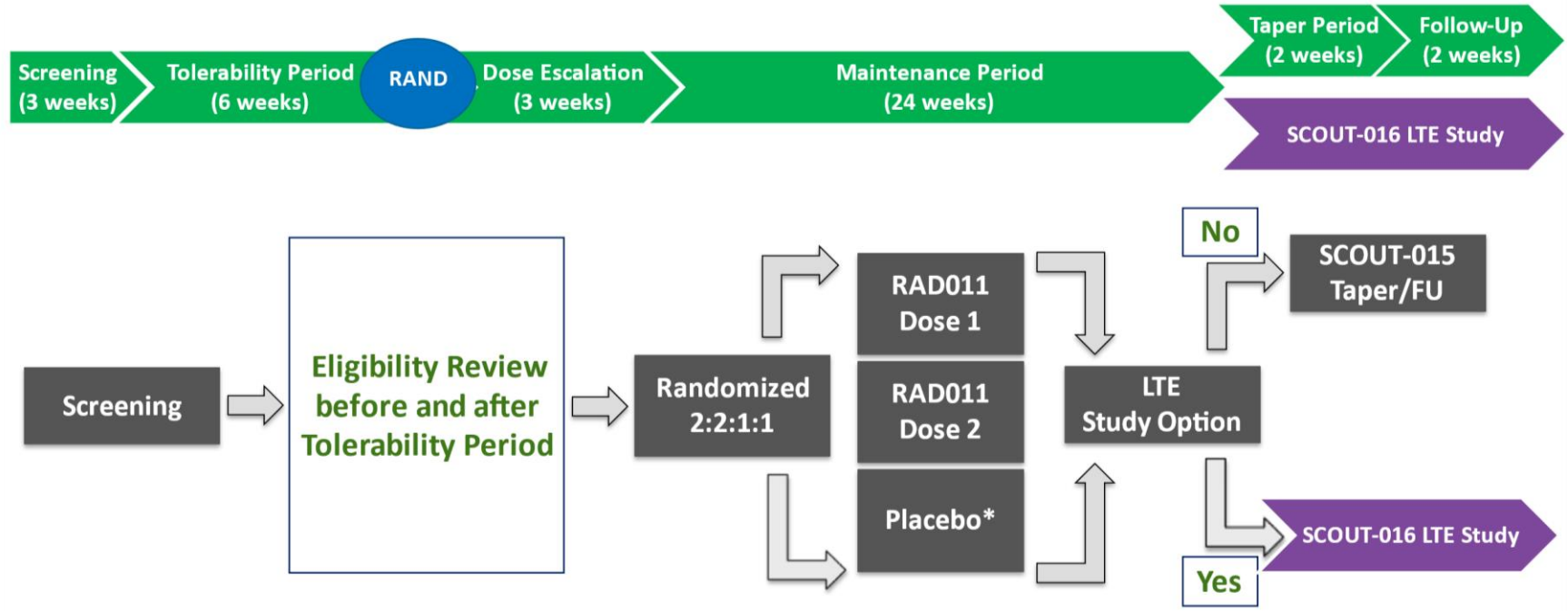
be extended to a total period lasting more than 14 days. A final follow-up will be conducted 2 weeks after the last dose of IP for patients who are tapered off as described in Section 5.8.6.

Figure 2: Study Design Schematic – Phase 2 of the Study



Abbreviations: DMC = Data Monitoring Committee; FU = follow-up; LTE = long-term extension; RAND = randomization.
*Patients assigned to placebo will include low, mid, and high volume placebo to match active drug and will be combined for statistical analysis.

Figure 3: Study Design Schematic – Phase 3 of the Study



Abbreviations: FU = follow-up; LTE = long-term extension; RAND = randomization; TBD = to be determined.
* Patients assigned to placebo will be further broken down to achieve balanced exposure between placebo and RAD011 patients. Patients in the placebo group (matching volume) will be combined for statistical analysis.

5.2. Scientific Rationale for Study Design

Despite a large safety database with a well-characterized safety profile and dose-response relationship of EPIDIOLEX in multiple indications, data on safety and efficacy of CBD remains limited in patients with PWS. However, as PWS is a rare disease with significant unmet needs, multiple large-scale studies would be impractical and may delay access to efficacious therapies.

Therefore, this study is designed as a seamless Phase 2/3 study to assess safety and tolerability of multiple candidate doses in Phase 2 of the study (10 to 40 mg/kg/day), followed by Phase 3 of the study. In Phase 3 of the study, 1 or 2 candidate dose level(s) will be recommended by the DMC for further development and assessment based on safety and tolerability data. This approach will allow a streamlined way to confirm the safety and tolerability profile of RAD011 in patients with PWS while limiting the number of patients exposed to lesser tolerated doses. In addition, data from patients who participated in Phase 2 of the study in the dose group(s) chosen for continued development and assessment in Phase 3 of the study will contribute to the overall intent-to-treat (ITT) population. This, in turn, allows for more efficient recruitment in this rare disease population.

The double-blind design will minimize patient and Investigator bias, whereas the placebo control will allow better delineation of efficacy and safety profiles of RAD011. The use of placebo groups in this study is acceptable as there are no FDA approved treatments for hyperphagia in patients with PWS. In addition, the IP will be administered in addition to standard of care therapy, which can include GH supplementation and any additional behavioral interventions that have been implemented and maintained stable throughout the study.

The 3-week Screening Period and the 6-week Tolerability Period will allow for the characterization of HQ-CT scores and help minimize potential bias in patient/caregiver completion of the HQ-CT questionnaire. These Periods will result in the exclusion of patients with too low mean scores or significant changes from Screening to the end of the Tolerability Period without any active treatment. The 6-week duration of the Tolerability Period will be sufficient to evaluate the HQ-CT scores and the tolerability of the MCT vehicle used in the RAD011 formulation. The use of inactive treatment periods in PWS studies is common as there is a recognized variability in hyperphagia behavior and HQ-CT response behaviors.

Once randomized, patients will enter the 3-week Dose Escalation Period followed by a 24-week Maintenance Period. This combined 26-week treatment period was designed to allow for potential placebo effect to wane and allow for the evaluation of separation of effects between placebo and RAD011 groups.

The target population for this study has also been carefully selected to include patients with moderate to severe hyperphagia (HQ-CT scores ≥13) (Fehnel, 2015). This is in line with baseline severity in other PWS development programs. In terms of age, the primary efficacy analysis will be based on the modified ITT (mITT) population (Section 11.4.1) which comprises patients aged 12 to 65 years. However, as the median age of transition into Phase 3 hyperphagia is 8 years (interquartile range of 5 to 13 years), patients aged 8 to <12 years may also benefit from efficacious hyperphagia management (Miller, 2011). However, since a significant proportion of patients below the age of 12 years may not have established hyperphagia because developmental milestones may significantly affect food-seeking behaviors and environmental interactions, and

because families are in the process of instating environmental controls, hyperphagia may not be well established or stable prior to 12 years of age. Inconsistent, less severe, or unestablished hyperphagia may therefore render efficacy assessment impossible. In addition, the population aged <12 years with severe hyperphagia remains limited, thereby enhancing the difficulty of recruiting such patients. For these reasons, and given the small sample size of Phase 2 of the study, patients aged 8 to <12 years of age will not be included in Phase 2 of the study, but will be allowed to randomize in Phase 3 of the study in order to obtain safety and preliminary efficacy data.

5.3. Number of Patients

The total number of patients for the study will depend on the number of doses recommended by the DMC.

If the DMC recommends two RAD011 doses for Phase 3 of the study, approximately a total of 191 male and female patients aged 12 to 65 years (approximate target of 200 patients) will be randomized in this study. Up to approximately 30 patients aged 8 to <12 years will be allowed to randomize in the Phase 3 part of the study in order to obtain safety and preliminary efficacy data.

If the DMC recommends one RAD011 dose for Phase 3 of the study, approximately a total of 148 male and female patients aged 12 to 65 years (approximate target of 150 patients) will be randomized in this study. An additional 20 patients aged 8 to <12 years will be allowed to randomize in Phase 3 of the study in order to obtain safety and preliminary efficacy data.

Additional information on sample size estimation is provided in Section 11.1.

5.4. Replacement of Patients

Patients who are randomized but do not receive a dose of assigned IP due to withdrawal of consent/assent or other reasons may be replaced. Any patients receiving at least 1 dose of IP will not be replaced and will be included in study analyses.

5.5. Investigational Products

Once randomized, patients will receive their assigned IP, defined as RAD011 or placebo, and enter a Dose Escalation Period as defined in Table 4. Additional information on IP and IP preparation are presented in Section 6.4 and in the Pharmacy Manual.

Table 4: Dose Escalation Regimen

Group for Analysis	**Dosing Group** Target dose	**Visit 5** Week 7	**Visit 6** Week 8	**Visit 7** Week 9
RAD011 low dose	RAD011 low dose (10 mg/kg/day = 0.1 mL/kg/day)	10 mg/kg/day 0.1 mL/kg/day	10 mg/kg/day 0.1 mL/kg/day	10 mg/kg/day 0.1 mL/kg/day
RAD011 mid dose	RAD011 mid dose (20 mg/kg/day = 0.2 mL/kg/day)	10 mg/kg/day 0.1 mL/kg/day	20 mg/kg/day 0.2 mL/kg/day	20 mg/kg/day 0.2 mL/kg/day
RAD011 high dose	RAD011 high dose (40 mg/kg/day = 0.4 mL/kg/day)	10 mg/kg/day 0.1 mL/kg/day	20 mg/kg/day 0.2 mL/kg/day	40 mg/kg/day 0.4 mL/kg/day
Placebo	Placebo low volume (0.1 mL/kg/day)	0.1 mL/kg/day	0.1 mL/kg/day	0.1 mL/kg/day
	Placebo mid volume (0.2 mL/kg/day)	0.1 mL/kg/day	0.2 mL/kg/day	0.2 mL/kg/day
	Placebo high volume (0.4 mL/kg/day)	0.1 mL/kg/day	0.2 mL/kg/day	0.4 mL/kg/day

5.6. RAD011 Dose Rationale

Clinical studies in various human populations indicate that CBD has a favorable side-effect profile. Doses as high as 1500 mg were well-tolerated (Zuardi, 1995). No significant reactions or SAEs have been reported across a wide range of dosages, nor have they been reported in acute or chronic settings. Bergamaschi and collaborators (Bergamaschi, 2011) recently reviewed the safety of CBD in humans examined in 221 patients across 21 studies.

Regarding doses of CBD that have been examined in other studies, daily doses of 200 to 300 mg CBD (or potentially more) are typical (Cunha, 1980; Gloss, 2014). Clinical evaluation and therapeutic ranges of CBD doses have been reported to be between 10 and 1500 mg/day, with the majority of reports evaluating doses in the 300 to 600 mg/day CBD range. Furthermore, between 300 and 1500 mg have been used in humans without toxicity or SAEs (Borgwardt, 2008; Consroe, 1991; Zuardi, 1993; Zuardi, 1995).

Doses up to 40 mg/kg/day were administered in the Phase 1/2 PK study (Protocol INS011-14-029) and the long-term safety study (Protocol INS011-14-030). The maximum dose given was 3200 mg/day in an adolescent. These doses were generally well tolerated even without dose escalation. Because PWS patients enrolled in this Phase 2/3 study may be obese and there may be concerns that distribution of RAD011 to fat would decrease the effective dose in these patients, the maximum tolerated dose identified in the previous PK and safety studies (40 mg/kg/day) will be given. To maximize tolerability, all patients will be initiated on 10 mg/kg/day (0.1 mL/kg/day) IP for a period of 1 week. Patients randomized to the low dose (10 mg/kg/day [0.1 mL/kg/day]) will continue at that dose for Weeks 8 and 9. Patients randomized to the mid dose groups will be escalated to 20 mg/kg/day (0.2 mL/kg/day) on Week 8 and remain at that dose through Week 9. Patients randomized to the high dose groups

(40 mg/kg/day [0.4 mL/kg/day]) will have their dose escalated to 20 mg/kg/day (0.2 mL/kg/day) on Week 8 and have a further dose escalation to 40 mg/kg/day (0.4 mL/kg/day) on Week 9.

5.7. Dose Reduction Criteria

All patients will receive a dose on a mg/kg/day basis, and dose reductions will be allowed per the criteria below.

5.7.1. Dose Level (mg/kg/day) Reduction for Tolerability During the Dose Escalation Period

Dose reductions for tolerability are not allowed during the Dose Escalation Period. Patients unable to tolerate their assigned dose level(s) during the Dose Escalation Period will be withdrawn from the study.

5.7.2. Dose Level (mg/kg/day) Reduction for Tolerability During the Maintenance Period (Weeks 10 to 34)

In the event that a patient does not tolerate their assigned dose level on a mg/kg/day basis during the Maintenance Period, the Investigator may decrease the patient's dose by 25% at any time during the Maintenance Period after consultation with the Sponsor as detailed in Table 5. Patients undergoing a dose reduction may not have their dose increased back to their originally assigned dose. If a second dose reduction is required for tolerability during the Maintenance Period, the patient should be discontinued from the study in consultation with the Sponsor.

Table 5: Dose Level (mg/kg/day) Reduction for Tolerability during the Maintenance Period

Dose Prior to Performing Dose Reduction	Dose Following Dose Reduction (25% Decrease)
10 mg/kg/day 0.1 mL/kg/day	7.5 mg/kg/day 0.075 mL/kg/day
20 mg/kg/day 0.2 mL/kg/day	15 mg/kg/day 0.15 mL/kg/day
40 mg/kg/day 0.4 mL/kg/day	30 mg/kg/day 0.3 mL/kg/day

Reasons for dose reduction due to tolerability may include, but are not limited to, diarrhea, somnolence, lethargy, hepatotoxicity, insomnia, psychomotor hyperactivity, aggression, anemia, and ataxia.

5.7.3. Total Daily Dose (mg/day) Adjustment for Weight Change During the Maintenance Period

All patients will be dosed using their actual body weight at Visit 5 (Week 7), and this dose will be maintained through the course of the study.

5.8. Study Visits and Procedures

A summary of the study assessments is described below. More information is provided in the Study Operations Manual.

5.8.1. Study Windows

All study visits will have a ± 3 day study window, except for Visit 1 (Screening) which must happen 3 weeks (21 days) prior to Visit 2.

5.8.2. Screening Period (3 weeks, Visit 1 [Weeks -3 to 0])

The Screening Period will occur 3 weeks (21 days) prior to initiation of the Tolerability Period. The Schedule of Assessments table for the Screening Period is presented in Table 6. Assessments may occur over multiple days, but the HQ-CT and Aberrant Behavior Checklist (ABC) questionnaires must be completed a minimum of 14 days prior to Visit 2.

5.8.2.1 Visit 1 (Weeks -3 to 0)

The following assessments must be performed in person during Visit 1:

- Informed consent by the patient, or informed consent by the parent and assent by the patient if aged <18 years prior to conducting any study procedures. The signed and dated consent form will be kept by the Principal Investigator and a signed and dated copy provided to the patient
- Review of Inclusion/Exclusion criteria
    - Patients must fulfill all Inclusion/Exclusion criteria to be eligible to continue in the Tolerability Period
- Collection of full medical/surgical history, seizure history, and confirmation of PWS genetic diagnosis including genetic subtypes
- Collection of demographics
- Review of prior/concomitant medications
- Start collection/recording of AEs
- Weight and height
- Vital signs, including, blood pressure (BP), heart rate (HR), temperature, respiratory rate (RR), and oxygen saturation
- Complete physical examination
- Completion of the HQ-CT, CaGI-S Hyperphagia, and ABC questionnaires
    - To complete the questionnaires, the same caregiver should be available throughout the study to complete the questionnaires with the patient
    - Must be completed a minimum of 14 days prior to Visit 2
- Resting 12-lead ECG in the supine position

- Collection of laboratory samples
    - Serum pregnancy test for females of childbearing potential only, to be performed centrally
    - Urine drug screen for drugs of abuse including THC
    - Urinalysis
    - Chemistry (renal and liver function panels),
    - Hematology
    - Glycosylated hemoglobin (HbA1c)
    - Prothrombin time (PT)/international normalized ratio (INR)
    - Serologies for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV)
    - Follicle stimulating hormone (FSH) for menopausal females only
    - Appetite hormones (including insulin, ghrelin, and leptin). Ghrelin samples will only be collected for Phase 3 patients at sites where proper collection is feasible.
    - Biomarker samples. Biomarker assessments will only be performed in patients enrolled in the Phase 3 part of the study and be optional. Biomarker assessments will not be conducted in the Phase 2 part of the study
- Review of eligibility
    - Review of eligibility at Visit 1 includes all inclusion and exclusion criteria with the exception of HQ-CT. Eligibility related to HQ-CT scores will be assessed at Visit 2 and Visit 5 (Section 6.4).

5.8.2.2 Documentation of Genetic Diagnosis of Prader-Willi Syndrome

The proof of prior genetic diagnosis of PWS should be provided as part of the source records and used to assess Inclusion/Exclusion criteria. Type(s) of test(s) used (such as deoxyribonucleic acid [DNA] methylation assays, in situ hybridization, etc.) as well as the identified variants (deletion, disomy, imprinting defect, etc.) should be documented, whenever available.

5.8.3. Tolerability Period (6 weeks, Visits 2 to 5 [Weeks 1 to 7])

The Schedule of Assessments table for the Tolerability Period is provided in Table 6. Prior to initiating dosing of patients at Visit 2 of the Tolerability Period, patients/caregivers must complete the HQ-CT questionnaire and have met the defined HQ-CT criteria (Section 6.4). Patients who do not meet criteria for randomization eligibility will not be randomized to study SCOUT-015.

5.8.3.1 Visits 2 to 4 (Weeks 1 to 6)

The following assessments must be performed in person during Visits 2 to 4 (Weeks 1 to 6):

- Review of concomitant medications

- Review of AEs
- Weight and height
- Vital signs, including, BP, HR, temperature, RR, and oxygen saturation
- Completion of the HQ-CT questionnaire
    - The same caregiver should be available throughout the study to complete the questionnaires with the patient
    - At Visit 2, HQ-CT must be completed pre-dose
- Review of HQ-CT questionnaire scores for eligibility (Visit 2 only)
    - The electronic data capture (EDC) system will automatically calculate mean HQ-CT score from Visit 1 and Visit 2. Patients with a mean HQ-CT score ≥13 will be eligible to continue in the Tolerability Period. Further details are described in Section 6.4
- Completion of the and Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD), CGI-S Hyperphagia, Skin Picking, and Columbia Suicide Severity Rating Scale (C-SSRS) questionnaires (predose-, only to be performed at Visit 2)
- Placebo dispensing (Visit 2 only)
- Placebo dosing (Visit 2 only)
- Drug accountability (only Visits 3 and 4)
- Food Diary Reminder and Food Diary Distribution (only Visit 4).

5.8.4. Dose Escalation Period (3 weeks, Visits 5 to 7 [Weeks 7 to 10])

The Schedule of Assessments table for the Dose Escalation Period is provided in Table 7.

5.8.4.1 Visit 5 (End of Screening, Beginning of Dose Escalation Period, Week 7)

The following assessments must be performed in person during Visit 5 (Week 7). All assessments must be performed prior to dosing on Visit 5, unless specified otherwise. Prior to assessing randomization eligibility, patients/caregivers must complete the HQ-CT.

- Review of concomitant medications
- Review of AEs
- Weight and height
- Vital signs, including BP, HR, temperature, RR, and oxygen saturation
- Complete physical examination
- Completion of the HQ-CT questionnaire (pre-dose)
    - The same caregiver should be available throughout the study to complete the questionnaires with the patient
    - HQ-CT must be completed prior to randomization

- Review of HQ-CT questionnaire scores and Inclusion/Exclusion criteria for eligibility
    - The EDC system will automatically calculate mean HQ-CT score from Visit 3, Visit 4 and Visit 5 inclusively. Patients with a mean HQ-CT score ≥13 will be eligible for randomization. Patients not eligible for randomization because of a HQ-CT score <13 will not have the opportunity to participate in the long-term extension study (SCOUT-016)
    - The EDC system will also automatically calculate the change in HQ-CT score from Visit 2 (beginning of the Tolerability Period) to Visit 5 (end of the Tolerability Period/Beginning of Dose Escalation Period) inclusively. Patients must have a decrease in HQ-CT score ≤7 to be eligible for randomization and able to proceed to the Dose Escalation Period. Further details are defined in Section 6.4
    - Laboratory values collected prior to visit 5 should be used to assess eligibility
    - Patients meeting all inclusion and exclusion criteria should proceed to randomization.
    - Completion of the C-SSRS questionnaire (predose)
- Randomization
- Completion of the ABC, ESS-CHAD, CGI-S Hyperphagia, CaGI-S Hyperphagia, and Skin Picking questionnaires
- Resting 12-lead ECG in the supine position
- Collection of laboratory samples (Section 10.1)
    - Urinalysis
    - Urine dipstick pregnancy test for females of childbearing potential only to be performed locally
    - Urine drug screen for drugs of abuse including THC
    - Chemistry panels (renal and liver function panels)
    - Hematology
    - Appetite hormones (including insulin, ghrelin, and leptin) Ghrelin samples will only be collected for Phase 3 patients at sites where proper collection is feasible.
- Pharmacokinetic sample (Section 10.1.13)
    - Blood draws for PK analyses of CBD, 7-OH-CBD, and 7-COOH-CBD will be drawn at the same time as the other laboratory samples. Time of sampling will be recorded
- Food diary collection
- Drug Accountability
- Investigational product (IP) dispensing

- Dosing of IP after randomization, to be completed in clinic
- Dual-energy X-ray absorptiometry (DEXA) scan
    - To be performed at certain US sites only
    - Can be performed before or after dosing of IP, within ± 7 days of Visit 5.

5.8.4.2 Visits 6 and 7 (Weeks 8 and 9)

The following assessments must be performed (remotely or in person) during Visits 6 and 7 (Weeks 8 and 9):

- Review of concomitant medications
- Review of AEs
- Food Diary Reminder and Food Diary Distribution (Visit 7 only): patients will be instructed to record the time of their evening and morning doses of study medication on the night prior to and the day of their next clinic visit with the type of meal administered.

5.8.5. Maintenance Period (24 Weeks, Visits 8 to 14 [Weeks 10 to 34])

The Schedule of Assessments table for the Maintenance Period is provided in Table 7.

5.8.5.1 Visits 8, 10, 12, and 14 (Weeks 10, 19, 27, and 34)

The following assessments must be performed in person during Visits 8, 10, 12, and 14 (Weeks 10, 19, 27, and 34):

- Review of concomitant medications
- Review of AEs
- Weight and height
- Vital signs, including BP, HR, temperature, RR, and oxygen saturation
- Abbreviated, symptom-directed physical examination
- Completion of the HQ-CT, C-SSRS, CGI-S Hyperphagia, CaGI-S Hyperphagia and ABC questionnaires
    - The same caregiver should be available throughout the study to complete the questionnaires with the patients
- Visits 10 and 14 only: completion of the ESS-CHAD and Skin Picking questionnaires
- Resting 12-lead ECG in the supine position (except Visit 12)
- Collection of laboratory samples (Section 10.1)
    - Urinalysis
    - Urine dipstick pregnancy test for females of childbearing potential only, to be performed locally
    - Chemistry panels (renal and liver function panels)

  - Hematology
  - Glycosylated hemoglobin at Visits 8, 12, and 14 only
  - Appetite hormones (including insulin, ghrelin, and leptin). Ghrelin samples will only be collected for Phase 3 patients at sites where proper collection is feasible. To be collected at Visits 8, 12, and 14 only
  - Pharmacokinetic sample at Visits 8, 12, and 14 only (Section 10.1.13)
    - Blood draws for PK analyses of CBD, 7-OH-CBD, and 7-COOH-CBD will be drawn at the same time as the other laboratory samples. The time of sampling will be recorded, with the exception of Visit 8 (Week 10). Pharmacokinetic sampling on Visit 8 should occur within 6 ± 2 hours of dose. The food diary completed prior to each Visit 8, 12, and 14 will be collected prior to the blood draw.

- Food diary collection (Visits 8, 12, and 14 only): patients will have been instructed to record the time of their evening and morning doses of study medication on the night prior to and the day of their Visits 8, 12, and 14, with the type of meal administered
- Drug accountability
- Dispensing of IP (at Visit 14, only dispense if the patient proceeds to the Taper Period)
- Visit 14 only: completion of the CGI-C Hyperphagia, CaGI-C Irritability, and CaGI-C questionnaires, and patient's impression of seizures
- Visit 14 only: Biomarker samples. Biomarker assessments will only be performed in patients enrolled in the Phase 3 part of the study and be optional. Biomarker assessments will not be conducted in the Phase 2 part of the study)
- Visit 14 only: Dual-energy X-ray absorptiometry (DEXA) scan
  - To be performed at certain US sites only
  - Can be performed before or after dosing of IP, within ± 7 days of Visit 14
- Patients may be offered enrollment in the long-term extension study (SCOUT-016) (Visit 14 only).

5.8.5.2 Visits 9, 11, and 13 (Weeks 15, 24, and 30)

The following assessments must be performed (remotely or in person) during Visits 9, 11, and 13 (Weeks 15, 24, and 30):

- Review of concomitant medications
- Review of AEs
- Food diary reminder and food diary distribution (Visits 11 and 13 only). Patients will be instructed to complete a food diary and record the time of their evening and morning doses of study medication on the night prior to and the day of their next clinic visit
- Dispensing of IP

5.8.6. Taper and Follow-Up Periods (4 Weeks, Visits 14 to 16 [Weeks 34 to 38])

Following completion of the Maintenance Period, patients may be offered enrollment in the long-term extension study (SCOUT-016). Patients who elect not to enroll in the long-term extension study will undergo a 2-week Taper Period (14 days) followed by a 2-week Follow-Up Period (14 days), as detailed in Table 7 and Section 7.1.1.long-term extension study SCOUT-016, the following assessments must be performed in person during Visit 15 (Week 36):

- Review of concomitant medications
- Review of AEs
- Abbreviated, symptom directed physical examination
- Drug Accountability.

The following assessments can be performed remotely during Visit 16 (Week 38):

- Review of concomitant medications
- Review of AEs.

5.9. Adjustments of Study Assessments for Visits Impacted by COVID-19

The COVID-19 pandemic continues to affect the conduct of clinical studies around the world. For this reason, patients and/or Investigators may be unable to perform planned in-person assessments. Radius' first priority is to protect the safety of study participants. Additional priorities include optimizing safety- and efficacy-related data acquisition and maintaining the integrity of the study. In accordance with FDA's Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency, Radius will provide guidance (e.g. out of window visits, remote assessments, etc.) on a case by case basis.

5.9.1. Schedule of Assessments for the Screening, Tolerability, Dose Escalation, Maintenance, Taper, and Follow-Up Periods

Table 6: Schedule of Assessments – Screening and Tolerability Periods

Period	Screening	Tolerability		
Visit Number	1	2	3	4
Study Time Point	D -21 to 0 (W -3 to 0)	D 1 (W 1)	D 15 (W 3)	D 29 (W 5)
Visit Window (Days)	0	±3	±3	±3
Informed consent/assent (if appropriate)	X			
Review of inclusion and exclusion criteria	X			
Medical/surgical history including PWS genetic diagnosis, seizure history	X			
Demographics	X			
Review of prior/concomitant medications	X	X	X	X
Start collection/recording of AEs	X			
Review of AEs		X	X	X
Weight and height[a]	X	X	X	X
Record vital signs[b]	X	X	X	X
Physical exam[c]	X			
HQ-CT Questionnaire[d]	X	X[pre-dose]	X	X
Review of HQ-CT scores for eligibility[e]		X		
ABC Questionnaire[d]	X			
ESS-CHAD Questionnaire[d]		X[pre-dose]		
CGI-S Hyperphagia Questionnaire[d]		X[pre-dose]		
CaGI-S Hyperphagia Questionnaire	X			
Skin Picking Questionnaire[d]		X[pre-dose]		
C-SSRS[d,f]		X[pre-dose]		
Resting 12-lead ECG	X			
Serum pregnancy test[g]	X			
Urine drug screen[h]	X			
Urinalysis	X			
Chemistry panels[i]	X			
Hematology[j]	X			
HbA1c	X			

Period	Screening	Tolerability		
Visit Number	1	2	3	4
Study Time Point	D -21 to 0 (W -3 to 0)	D 1 (W 1)	D 15 (W 3)	D 29 (W 5)
Visit Window (Days)	0	±3	±3	±3
PT-INR	X			
Serologies for HBV, HCV, and HIV	X			
FSH for menopausal women only[k]	X			
Appetite hormones[l]	X			
Biomarkers[m]	X			
Review of eligibility[n]	X			
Placebo dispensing		X		
Placebo dosing[o]		X		
Drug accountability			X	X
Food Diary Reminder[p]				X
Food Diary Distribution				X

Abbreviations: ABC = Aberrant Behavior Checklist questionnaire; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; BP = blood pressure; CBC = complete blood count; CGI-S = Clinical Global Impression of Change – Severity questionnaire; C-SSRS = Columbia-Suicide Severity Rating Scale; D = day; ECG = electrocardiogram; EDC = electronic data capture; ESS-CHAD = Epworth Daytime Sleepiness Scale; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HbA1c = glycosylated hemoglobin; HQ-CT = Hyperphagia Questionnaire for Clinical Trials; HR = heart rate; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume ; PT-INR = prothrombin time-international normalized ratio; PWS = Prader-Willi Syndrome; RBC = red blood cells; RDW = red cell distribution width; RR = respiratory rate; THC = tetrahydrocannabinol; WBC = white blood cells; W = week; WOCBP = women of childbearing potential.

[a] Weight and height must be documented at every in-person visit as the EDC system will automatically calculated BMI (or BMI z-score) using both variables (Section 10.1.3).

[b] Vital signs include BP, HR, RR, oxygen saturation, and temperature (Section 10.1.2).

[c] A full physical exam should be performed at Screening Visit 1 (Section 10.1.4). Other physical exams should be abbreviated, symptom -directed.

[d] If a caregiver is required to assist the patient in completing the questionnaire, the same caregiver should be available throughout the study.

[e] The EDC system will automatically calculate mean HQ-CT score from Visit 1 and Visit 2. Patients with a mean HQ-CT score ≥13 will be eligible to continue in the Tolerability Period. Further details are described in Section 6.4.

[,f] If the patient is the mental equivalent of 6 or younger then the children's version of the C-SSRS should be used.

[g] For WOCBP only.

[h] Drugs of abuse include THC. May be repeated at the Investigator's discretion.

[i] Chemistry panels include renal and liver function panels. Renal function panel includes sodium, potassium, chloride, calcium, bicarbonate, glucose, phosphorus, blood urea nitrogen, creatinine, and estimated glomerular filtration rate. Should be obtained after a 10-hour fast if possible. Liver function panel includes ALT, AST, albumin, alkaline phosphatase, direct bilirubin, total bilirubin, indirect bilirubin, and total protein (Table 9).

[j] Hematology panel includes hematocrit, hemoglobin, MCV, MCH, MHCH, RDW, RBC, WBC, platelets, and differential (Table 9).

[k] FSH levels must be ≥30 mIU/mL with absence of menstruation for ≥1 year to be considered menopausal status (Section 10.1.11).
[l] Includes insulin, ghrelin, and leptin (Table 9). Ghrelin samples will only be collected for Phase 3 patients at sites where proper collection is feasible.
[m] Will only be performed in patients enrolled in the Phase 3 part of the study and be optional. Biomarker assessments will not be conducted in the Phase 2 part of the study.
[n] Review of eligibility at Visit 1 includes all inclusion and exclusion criteria with the exception of HQ-CT. Eligibility related to HQ-CT scores will be assessed at Visit 2 and Visit 5 (Section 6.4).
[o] Dosing should be completed at the site when patients are present for a study visit during Visit 2 and Visit 5 (Section 7.1)
[p] Patients will be instructed to record the time of their evening and morning doses of study medication on the night prior to and the day of their next clinic visit with the type of meal administered. Patients should also be contacted approximately 1 week prior to their next visit to remind them to complete their food diary prior to their next visit (Section 10.1.14).

Table 7: Schedule of Assessments – Dose Escalation, Maintenance, Taper, and Follow-Up Periods

	DOUBLE-BLIND TREATMENT PHASE[a]										TAPER PERIOD[b] (2 weeks)	FOLLOW-UP PERIOD[b] (2 weeks)	
Period	DOSE ESCALATION PERIOD[a] (3 Weeks)			MAINTENANCE PERIOD (24 Weeks)									
Visit Number	5[c,d]	6[e]	7[e,f]	8[c]	9[e]	10[c]	11[e,f]	12[c]	13[e,f]	14[c,g,aa,bb]		15[c]	16[e]
Study Time Point	D 43 (W 7)	D 50 (W 8) (Remote)	D 57 (W 9) (Remote)	D 64 (W 10)	D 99 (W 15) (Remote)	D 127 (W 19)	D 155 (W 23) (Remote)	D 183 (W 27)	D 204 (W 30) (Remote)	D 232 / ET/EOS (W 34)	D 232 (W 34)	D 246[c] (W 36[c])	D 260[e]/ EOS[e] (W 38) (Remote)
Visit Window (D)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Review of concomitant medications	X	X	X	X	X	X	X	X	X	X		X	X
Review of AEs	X	X	X	X	X	X	X	X	X	X		X	X
Weight and height[h]	X			X		X		X		X			
Record vital signs[i]	X			X		X		X		X			
Physical exam[j]	X			X		X		X		X		X[k]	
HQ-CT Questionnaire[l,m]	X[pre-dose]			X		X		X		X			
Review of HQ-CT scores and I/E [n,o]	X												
C-SSRS[l,m,p]	X[pre-dose]			X		X		X		X			
Randomization[o]	X[q]												
ABC Questionnaire[l,m]	X			X		X		X		X			
ESS-CHAD Questionnaire[l,m]	X					X				X			
CGI-S Hyperphagia Questionnaire[l,m]	X			X		X		X		X			
CaGI-S Hyperphagia Questionnaire[l,m]	X			X		X		X		X			
CGI-C Hyperphagia Questionnaire[l,m]										X			
CaGI-C Irritability Questionnaire[l,m]										X			
CaGI-C Questionnaire[l,m]										X			

	DOUBLE-BLIND TREATMENT PHASE[a]										TAPER PERIOD[b] (2 weeks)	FOLLOW-UP PERIOD[b] (2 weeks)	
Period	DOSE ESCALATION PERIOD[a] (3 Weeks)			MAINTENANCE PERIOD (24 Weeks)									
Visit Number	5[c,d]	6[e]	7[e,f]	8[c]	9[e]	10[c]	11[e,f]	12[c]	13[e,f]	14[c,g,aa,bb]		15[c]	16[e]
Study Time Point	D 43 (W 7)	D 50 (W 8) (Remote)	D 57 (W 9) (Remote)	D 64 (W 10)	D 99 (W 15) (Remote)	D 127 (W 19)	D 155 (W 23) (Remote)	D 183 (W 27)	D 204 (W 30) (Remote)	D 232 / ET/EOS (W 34)	D 232 (W 34)	D 246[c] (W 36[c])	D 260[e]/ EOS[e] (W 38) (Remote)
Visit Window (D)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Skin Picking Questionnaire[l,m]	X					X				X			
Resting 12-lead ECG	X			X		X				X			
Urinalysis	X			X		X		X		X			
Urine dipstick pregnancy test[r]	X			X		X		X		X			
Urine drug screen[s]	X												
Chemistry panels[t]	X			X		X		X		X			
Hematology[u]	X			X		X		X		X			
HbA1c				X				X		X			
Appetite hormones[v]	X			X				X		X			
Biomarkers[w]										X			
Pharmacokinetic	X			X[x]				X		X			
Food Diary Collection	X			X				X		X			
Food Diary Reminder[f]			X				X		X				
Food Diary Distribution			X[cc]				X[cc]		X[cc]				
Drug accountability	X			X		X		X		X		X	
IP dispensing	X			X	X	X	X	X	X		X		
Dosing[y]	X												
Seizure Patient Impression										X			
DEXA scan[z]	X									X			
Tapering of IP over 14 days[b]											X[b,g]		

Abbreviations: ABC = Aberrant Behavior Checklist questionnaire; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; BP = blood pressure; CaGI-C = Caregiver Global Impression of Change; CBC = complete blood count; CGI-C= Clinical Global

Impression of Change; CGI-S= Clinical Global Impression of Change – Severity questionnaire; C-SSRS = Columbia-Suicide Severity Rating Scale; D = day; DEXA = dual-energy x-ray absorptiometry; DMC = Data Monitoring Committee; EDC = electronic data capture; ECG = electrocardiogram; ESS-CHAD = Epworth Daytime Sleepiness Scale; EOS = End of Study; HbA1c = glycosylated hemoglobin; HQ-CT = Hyperphagia Questionnaire for Clinical Trials; HR = heart rate; IP = investigational product (RAD011 or placebo); MCH = mean corpuscular hemoglobin; I/E = Inclusion/Exclusion Criteria; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PK= Pharmacokinetic; PWS = Prader-Willi Syndrome; RBC = red blood cells; RDW = red cell distribution width; RR = respiratory rate; THC = tetrahydrocannabinol; W = week; WBC = white blood cells.

[a] In the Phase 2 part of the study, all patients will be initiated on IP (RAD011 or placebo) 10 mg/kg/day (0.1 mL/kg/day) for a period of 1 week at Visit 5 (Week 7). Patients randomized to low dose or low volume IP (10 mg/kg/day) will continue at a dose of 10 mg/kg/day (0.1 mL/kg/day) until the end of Week 9. Patients randomized to mid dose or mid volume IP (20 mg/kg/day) will have their dose increased to 20 mg/kg/day (0.2 mL/kg/day) at Visit 6 (Week 8) and will continue at that dose until the end of Week 9. Patients randomized to high dose or high volume IP (40 mg/kg/day) will have their dose increased to 20 mg/kg/day (0.2 mL/kg/day) at Visit 6 (Week 8) and to 40 mg/kg/day at Visit 7 (Week 9). Details of the dose escalation schema are provided in Table 4.
In the Phase 3 part of the study, all patients will be initiated on IP (RAD011 or placebo) 10 mg/kg/day IP (0.1 mL/kg/day) for a period of 1 week at Visit 5 (Week 7). Dose escalation will occur similarly to the Phase 2 part of the study with the 1 or 2 doses recommended by the DMC following their review of safety and tolerability data from the Phase 2 part of the study. Details of the dose escalation schema are provided in Table 4.
No dose decreases will be allowed during the Dose Escalation Period (Section 5.7.1).

[b] The Taper and Follow Up Period visits (Visits 14 to 16) are only for patients who do not proceed to enroll in the active long-term extension study SCOUT-016 and who are tapering off the IP. Patients will return to the site for assessment of concomitant medications, AEs, and to return and reconcile IP on Visit 15. Visit 16 may be done remotely (Section 5.8.6).

[c] To be performed in person at the research site.

[d] All assessments must be performed prior to dosing, unless specified otherwise.

[e] Assessments may be conducted remotely via a phone call, video call, or other remote means of communication. Dispensing of IP may be done at the research site or remotely, using direct-to-patient shipping methods in accordance with all local laws and regulations. Sites may elect to conduct the entire visit in person.

[f] At Week 9 (Visit 7), Week 23 (Visit 11), and Week 30 (Visit 13), patients will be instructed to record the time of their evening and morning doses of study medication on the night prior to and the day of their next clinic visit with the type of meal administered. Patients should also be contacted approximately 1 week prior to their next visit to remind them to complete their food diary prior to their next visit (Section 10.1.14).

[g] At visit 14, patients may be offered participation in the long-term extension study SCOUT-016. Patients eligible and electing to participate in the long-term extension study SCOUT-016 should continue treatment with IP as per the SCOUT-016 protocol. Patients who are not eligible or decide not to participate in the long-term extension study SCOUT-016 should proceed to the Taper and Follow-Up Periods (footnote b, Section 5.8.5.1).

[h] Weight and height must be documented at every in-person visit (Section 10.1.3).

[i] Vital signs include BP, HR, RR, oxygen saturation, and temperature (Section 10.1.2).

[j] A full physical exam should be performed at Week 7 (Visit 5). Other physical exams should be abbreviated, symptom directed (Section 10.1.4).

[k] To be performed at Visit 15 (Week 36) only.

[l] If a caregiver is required to assist the patient in completing the questionnaire, the same caregiver should be available throughout the study.

[m] When possible, study questionnaires should be completed prior collection of ECG and blood samples.

[n] Patients meeting all inclusion and exclusion criteria should proceed to randomization.

[o] The EDC system will automatically calculate mean HQ-CT score from Visit 3, Visit 4 and Visit 5 inclusively. Patients with a mean HQ-CT score ≥13 will be eligible for randomization. In addition, the EDC system will also automatically calculate the change in HQ-CT score from the Tolerability Period to the Screening Period. Patients must have a decrease in HQ-CT score ≤7 to be eligible for randomization. Further details are defined in Section 6.4.

[p] If the patient is the mental equivalent of 6 or younger, then the children's version of the C-SSRS should be used.

[q] Randomization cannot be performed prior to evaluation and review of HQ-CT questionnaire scores for eligibility. Prior to assessing randomization eligibility, patients must complete the Visit 5 HQ-CT questionnaire (Section 6.4.2).
[r] For WOCBP only. If positive, a quantitative serum pregnancy test must be sent to the central laboratory for confirmation.
[s] Drugs of abuse include THC. May be repeated at the Investigator's discretion.
[t] Chemistry panels include renal and liver function panels. Renal function panel includes sodium, potassium, chloride, calcium, bicarbonate, glucose, phosphorus, blood urea nitrogen, creatinine, and glomerular filtration rate. Should be obtained after a 10-hour fast if possible. Liver function panel includes ALT, AST, albumin, alkaline phosphatase, direct bilirubin, total bilirubin, indirect bilirubin, and total protein (Table 9).
[u] Hematology panel includes hematocrit, hemoglobin, MCV, MCH, MHCH, RDW, RBC, WBC, platelets, and differential (Table 9).
[v] Includes insulin, ghrelin, and leptin (Table 9). Ghrelin samples will only be collected for Phase 3 patients at sites where proper collection is feasible.
[w] Will only be performed in patients enrolled in the Phase 3 part of the study and be optional. Biomarker assessments will not be conducted in the Phase 2 part of the study
[x] Must be drawn 6 ± 2 hours after the previous IP dose. Patients may take their IP dose at home prior to presenting to the site for their visit in order to comply with the PK timing requirements.
[y] Dosing should be completed at the site during Visit 2 and Visit 5. Dosing is not required to be done at the site when patients have remote or other visits (Section 7.1).
[z] Can be performed before or after dosing. The DEXA scan can be performed within ± 7 days of the visit time point (Section 9.3.6). The DEXA scan will be performed at a certain number of US sites only.
[aa] All assessments will be collected regardless of if the patient enters the taper period or completes the study and enter the long-term extension study.
[bb] The two-week taper period does not have any visits associated with it.
[cc] The food diary can be provided at the previous in-person visit.

5.10. Criteria for Study or Site Termination

Throughout the course of the study, new information may become available to the Sponsor, its designee, or regulatory authorities indicating that the study or a study site should be terminated. Such decisions will be made after consultation between the Sponsor or its designee and the Investigator. The Sponsor or its designee has the right to terminate the participation of an individual site or the entire study at any time, for any reason, which may include:

- The incidence or severity of AEs in this study or other studies indicate a potential safety hazard to patients
- Unsatisfactory patient enrollment
- Inadequate data recording
- Non-adherence to protocol or applicable regulatory guidelines in study conduct.

6. SELECTION AND WITHDRAWAL OF PATIENTS

Patients will be male and non-pregnant female volunteers between 12 and 65 years of age inclusive (Phase 2) and between 8 and 65 years of age (Phase 3) at Screening with a genetically confirmed diagnosis of PWS, able to understand and provide written consent or assent, and who meet all the inclusion and none of the exclusion criteria. Eligibility for this study will be confirmed during the Screening and Tolerability Periods.

6.1. Patient Inclusion Criteria

To be eligible for this study, patients must meet all of the following inclusion criteria:

1. Presence of a parent/legal guardian that is able to consent for their participation. Parent/caregiver/legal guardian can complete the required assessments throughout the study. Patient consent/assent will be obtained if the patient is 8 years of age or older and has the mental capacity to understand and sign a written consent/assent form and/or give verbal assent
2. Males and females between:
    a. Phase 2: 12 and 65 years of age (inclusive) at time of consent/assent
    b. Phase 3: 8 and 65 years of age (inclusive) at time of consent/assent
3. Documentation of genetically confirmed PWS diagnosis
4. If a caregiver helps in completing the HQ-CT or other questionnaires, the same caregiver is available to complete the questionnaire throughout the duration of the study
5. If female, is either not of childbearing potential (defined as premenarchal or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or practicing one of the following medically acceptable methods of birth control up to 4 weeks after the last dose of RAD011 or placebo:
    a. Double barrier method (i.e., condom plus occlusive cap (diaphragm or cervical/vault caps), condom or occlusive cap plus spermicide),

   b. Hormonal methods such as oral, implantable, injectable, vaginal ring, or transdermal contraceptives at a stable dose for a minimum of 1 full cycle (based on the patient's usual menstrual cycle period) before IP administration
   c. Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
   d. If not using hormonal contraceptives or IUD or IUS, then all male partners throughout the study must have been vasectomized and have received medical assessment of the surgical success
6. If male, is vasectomized and has received medical assessment of the surgical success or agrees to use an approved method of contraception (double barrier method as described in Inclusion Criterion 5, female partner's use of an IUD or IUS [in place at least 12 weeks prior to dosing], oral contraceptives or female partner who is surgically sterile or 2 years postmenopausal) and agrees to use this method for 4 weeks after last administration of RAD011 or placebo
7. If receiving growth hormone (GH), psychotropic therapy, metabolic treatments that could affect appetite (including metformin), and other treatment including thyroid hormone, must be on the same medication and stable dose for at least 90 days prior to consent/assent
8. Any non-medical interventions (e.g., counseling, behavior modification) should be stable for at least 90 days prior to consent/assent
9. HQ-CT eligibility automatically calculated in the electronic data capture (EDC) system:
   a. Visit 2
      i. Patients with a mean HQ-CT score ≥13 (from Visit 1 and Visit 2) will be eligible to continue in the Tolerability Period
   b. Visit 5
      i. Patients with a mean HQ-CT score ≥13 (from Visit 3, Visit 4 and Visit 5) will be eligible for randomization, and
      ii. Patients with a decrease in HQ-CT score (from Tolerability Period to the Screening Period) ≤7 will be eligible for randomization

6.2. Patient Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Hypersensitivity or intolerance to CBD, or any other excipients used in the RAD011 preparation
2. Known use of cannabis or cannabinoid containing products (including topical products) within 90 days prior to consent/assent
3. History of chronic liver disease, such as cirrhosis or chronic hepatitis due to any cause
4. Positive urine test for drugs of abuse, including tetrahydrocannabinol (THC), or known history of drug, alcohol, or substance abuse
5. Use of prescription or over-the-counter weight loss agents within 90 days prior to consent/assent
6. Implementation of new food restrictions or environmental restrictions within 90 days of consent/assent

7. Any significant comorbid condition or disease:
    a. Respiratory disease, heart disease, or psychiatric disorder which in the opinion of the Investigator would preclude the patient from participating or
    b. Uncontrolled type 1 or type 2 diabetes as determined by the Investigator or
    c. Clinically significant ECG abnormalities or other evidence of clinically significant heart disease as determined by the Investigator or
    d. Uncontrolled sleep apnea as determined by the Investigator or
    e. Neutropenia with neutrophil counts <1,000 /microL (grade 3 or grade 4 neutropenia as defined by CTCAE v5.0) or
    f. History or presence of gastrointestinal disorders or any other condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs taken orally as determined by the Investigator
8. QT interval corrected for heart rate (HR) according to Fridericia's formula (QTcF) meeting the following criteria:
    a. For males and females aged 8 to <20 years: QTcF >439 msec
    b. For males aged 20 to 65 years: QTcF >450 msec
    c. For females aged 20 to 65 years; QTcF >470 msec
9. At consent/assent, patients with age-matched hypertensive levels of systolic and/or diastolic blood pressure may be excluded at the Investigator's discretion if deemed to be in the best interest of the patient.
10. Pregnant (determined by a positive serum pregnancy test) or lactating female
11. Unwillingness or inability to follow the procedures outlined in the protocol
12. Estimated glomerular filtration rate <30 mL/min/1.73m^2 or protein/creatinine ratio ≥0.4
13. Bilirubin >1.5 × upper limit of normal (ULN), or aspartate aminotransferase (AST), alanine aminotransferase (ALT) >3 × ULN, or international normalized ratio (INR) >1.5 × ULN
14. Patient judged by the Investigator or Sponsor (or designee) as unable to comply with the treatment protocol, including appropriate supportive care, follow up, and research tests
15. Other genetic, hormonal, chromosomal, cognitive, or behavioral impairment
16. If living in a group home, patient spends less than 25 waking hours with their caregiver per week.
17. Significant risk of committing suicide based on history, routine psychiatric examination, or based on the Investigator's judgment
18. Participation in any other study involving an investigational product or device within 4 weeks or 5 half-lives (whichever is longer) of consent/assent or longer as required by local regulations

6.3. Patient Withdrawal Criteria

A patient is free to withdraw consent/assent and/or discontinue participation in the study at any time, for any reason, without prejudice to further treatment. A patient may also be withdrawn from the study at any time at the discretion of the Investigator.

6.3.1. Discontinuation of Investigational Product

The IP may be prematurely discontinued by the patient or the Investigator for reasons including, but not limited to:

- Patient's inability to comply with protocol requirements
- The IP is no longer in the patient's best interest, at the Investigator's discretion
- Patient's decision to discontinue the IP
- Discontinuation due to patient becoming pregnant
- An unexpected, related SAE, or a SUSAR
- Requirement for prohibited concomitant medication (Section 7.2).

Patients who discontinue IP but do not withdraw consent/assent will continue to be followed according to the planned Schedule of Assessments but will not undergo drug dispensing or drug accountability. Patients who are unwilling or unable to complete planned assessments should undergo the End of Study Visit Assessments (Visit 14, Week 34).

Patients who discontinue IP may have their IP tapered over up to 14 days, at the Investigator's discretion.

6.3.2. Drug-Induced Liver Injury

Increase of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or total bilirubin to >3 × ULN should be followed by repeat testing within 48 to 72 hours of awareness of the increase, of ALT, AST, ALP, and total bilirubin to confirm the abnormalities and to determine if they are increasing or decreasing. Repeat laboratory testing can be done locally and/or centrally depending on clinical availability and turnaround time for prompt evaluation. There also should be an inquiry made about the symptoms. Repeat laboratory testing should also be done centrally as soon as possible, if not already tested centrally within 48-72 hours of awareness of the increase.

It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible drug-induced liver injury, and not to wait until the next scheduled visit or monitoring interval. If additional testing, beyond that specified in the study protocol, is carried out, it is important that the patient's information be added to the case report forms and database.

Close observation includes:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the IP has been discontinued and the patient is asymptomatic;
- Obtaining a more detailed history of symptoms and prior or concurrent diseases;
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets;

- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease;
- Obtaining a history of exposure to environmental chemical agents;
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., international normalized ratio, direct bilirubin);
- Considering gastroenterology or hepatology consultations.

Discontinuation of IP should be considered if:

- ALT or AST >8 × ULN;
- ALT or AST >5 × ULN for more than 2 weeks;
- ALT or AST >3 × ULN **and** (total bilirubin >2 × ULN **or** international normalized ratio >1.5);
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

All study patients showing possible drug-induced liver injury should be followed until all abnormalities return to normal or to the baseline state. Drug-induced liver injury may develop or progress even after the causative drug has been stopped. Results should be recorded in the electronic case report form (eCRF) and in the database. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be drug-induced liver injury, indicating that liver injury was related to underlying liver disease.

All potential cases of drug-induced liver injury should be reviewed with the Medical Monitor. The IP should be discontinued at the Investigator's discretion and the Sponsor notified at the earliest convenience.

6.3.3. Patient Withdrawal

The Investigator should withdraw the patient from the study if they believe that participation is no longer in the patient's best interest, or in the event of study termination by the Sponsor. If the patient elects to withdraw from the study, reason(s) for withdrawal should be documented. The Investigator will discuss with the patient procedures for withdrawal and any additional care or treatment alternatives available at that time. In addition, patients unable to tolerate the 0.1 mL/kg/day dose level during the Tolerability Period or their assigned dose level(s) during the Dose Escalation Period will be withdrawn from the study.

If a patient withdraws consent/assent from the study, the patient should be encouraged to complete all End of Study Visit assessments (Visit 14, Week 34) completed as described in the Schedule of Assessments (Table 7). At time of withdrawal of consent/assent, the patient will be withdrawn from all additional study procedures and follow-up.

Data collected until patient withdrawal will be retained and included in the analysis of the study in accordance with local rules and regulations.

6.3.4. Lost to Follow-Up

A patient will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- Attempt to contact the patient and reschedule the missed visit(s) as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule
- Make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address) and document these efforts in the patient's medical record
- Ascertain if the patient wishes to and/or should continue in the study
- Consider the patient lost to follow-up once the aforementioned steps have been taken, contact with the patient has not been regained and document the reason for loss to follow-up if known.

6.4. Evaluation of Eligibility at the End of the Screening and Tolerability Periods

6.4.1. Screening Period

During the Screening Period, Investigators will have to review a patient's eligibility to proceed to the Tolerability Period. This will include review of inclusion/exclusion criteria, laboratory assessments, a review of PWS diagnosis, and ECG reading.

In addition, at the end of the Screening Period (Visit 2) and prior to initiating dosing of patients at Visit 2, patients/caregivers must first complete the HQ-CT.

The EDC system will automatically calculate a mean HQ-CT score from Visit 1 and Visit 2. Patients must have a mean HQ-CT score ≥13 to be eligible to continue in the Tolerability Period. Patients with a mean score <13 will not be eligible to continue in the Tolerability Period and will be discontinued from the study.

6.4.2. Tolerability Period

At the end of the Tolerability Period (Visit 5), Investigators will review a patient's eligibility to be randomized and proceed to the Dose Escalation Period.

Patients/caregivers must first complete the HQ-CT. The EDC system will automatically calculate a mean HQ-CT score from Visit 3, Visit 4 and Visit 5. Patients must have a mean HQ-CT score ≥13 to be eligible to be randomized and proceed to the Dose Escalation Period. Patients with a mean score <13 will not be eligible for randomization and will not have the opportunity to participate in the long-term extension study (SCOUT-016).

In addition, the EDC system will also automatically calculate the change in HQ-CT score from the Tolerability Period to the Screening Period. This change is calculated as:

Mean HQ-CT score (Visit 3, Visit 4, Visit 5) – Mean HQ-CT score (Visit 1, Visit 2)

Patients with a decrease HQ-CT score ≤7 will be eligible for randomization. Patients with a decrease in HQ-CT score >7 will not be eligible for randomization and unable to proceed to the Dose Escalation Period.

7. TREATMENT OF PATIENTS

7.1. Investigational Product Administration

The IP (RAD011 or placebo) will be administered orally twice daily with food, approximately 12 hours apart. Patients must take the IP with food throughout the study.

When patients are seen at the research site, dosing should be performed at the research site at the time points indicated in Table 7, during the Visit 2 and Visit 5 assessments. The dose prior to Visit 8 (Week 10) should be taken approximately 4 to 6 hours prior to the visit to allow for PK collection approximately 6 ± 2 hours after the dose (Section 10.1.14). When patients have a remote visit, dosing does not need to be performed at the research site.

7.1.1. Tapering of Investigational Product for Patients Entering the Taper and Follow-Up Periods

For patients not participating in the long-term extension study (SCOUT-016) and entering the Taper and Follow-Up Periods, the IP will be tapered over 14 days. Following completion of Visit 14 (End of Study/Week 34 Visit), the IP should be decreased by 50% during the first 7 days, followed by an additional 50% taper during the following 7 days and then discontinued. The taper schedule may be modified at the discretion of the Investigator but cannot occur over a longer time than 14 days. A final safety follow-up will be conducted 14 days after the IP is discontinued for patients who do not elect to continue into the long-term extension study.

7.2. Concomitant Medications

Growth hormone, psychotropic medications, and other therapies such as thyroid hormones (including homeopathic or naturally sourced thyroid supplements), started prior to enrollment and at stable doses for at least 90 days prior to enrollment are permitted in this study. Doses of psychotropic medications, thyroid hormones, and GH may be adjusted during the study if clinically required, at the discretion of the Investigator. However, change in such medications must be documented in the EDC.

7.2.1. RAD011 Drug-Drug Interactions Overview

The major biotransformation pathway for CBD is similar to that of other cannabinoids and is mediated by hydroxylation by CYP enzymes. Its interactions with human drug metabolizing enzymes (as a substrate, inhibitor, or inducer) were recently reviewed (Forster, 2021). Cannabidiol is metabolized primarily in the liver by CYP3A4 and to a lesser extent by CYP2C19. Specifically, CBD inhibits CYP3A4, CYP3A5, and CYP1A1 in vitro. It also appears to inhibit CYP2C9 and the transport protein P-glycoprotein. Thus, Cannabidiol may inhibit these two isozymes (CYP3A4 and CYP 2C19), as well as having small effects on CYP3A5, CYP2D6, CYP1A1, CYP1A2, and CYP2C9 (see Investigator's Brochure for more information).

Medications that are strong inhibitors/inducers/sensitive substrates with a narrow therapeutic index for those CYP enzymes, although not prohibited, may require that the patient is monitored with special care to identify any AEs arising due to the potential for altered drug metabolism. Thus, the Investigator and study center staff should monitor patients who are taking concomitant medications that are metabolized by CYP3A4/5, CYP2C19, CYP1A1/2, CYP2C8/9, CYP2D6, or by P-glycoprotein with special care.

Patients who experience adverse events due to significant drug/ drug interactions may have treatment discontinued while remaining on the study, at the Investigator's discretion.

7.3. RAD011 Precautions

The following precautions should be communicated to patients or observed during the course of the study:

- Somnolence and sedation: monitor for somnolence and sedation and advise patients not to drive or operate machinery until they have gained sufficient experience on RAD011. Concomitant use of RAD011 with other central nervous system depressants (including alcohol) may increase the risk of sedation and somnolence
- Hypersensitivity reactions: advise patients to seek immediate medical care. Discontinue and do not restart RAD011 if hypersensitivity occurs.
- Withdrawal of antiepileptic drugs: should be gradually withdrawn to minimize the risk of increased seizure frequency and status epilepticus.

7.4. Treatment Adherence

Importance of adherence to regimen will be reviewed with patients and study staff should ensure that patients remain compliant with the IP and study assessments. In addition, drug accountability will be completed at each study visit as detailed in the Pharmacy Manual.

7.5. Randomization and Blinding

Randomization will occur at Visit 5 (Week 7) after review of all eligibility criteria by the Investigator.

Both Investigators and patients will be blinded to the randomization assigned treatment. During the Tolerability Period, all patients will receive 0.1 mL/kg/day of placebo. To maintain the blind, multiple placebo groups were created to mimic the RAD011 groups: low volume (0.1 mL/kg/day), mid volume (0.2 mL/kg/day), and high volume (0.4 mL/kg/day). During the dose escalation period, the volume of blinded therapy for the mid volume and high volume placebo groups will increase in the same manner as the mid dose and high dose RAD001 groups, further ensuring blinding between RAD011 and placebo

The matching (appearance, smell and taste) placebo and RAD011 product will utilize the same MCT vehicle.

Phase 2 of the study

Patients who meet eligibility criteria will be randomized in a 2:2:2:1:1:1 manner to receive double-blind treatment with IP, defined as either low dose (10 mg/kg/day, [0.1 mL/kg/day])

RAD011, mid dose (20 mg/kg/day, [0.2 mL/kg/day]) RAD011, high dose (40 mg/kg/day [0.4 mL/kg/day]) RAD011, low volume (0.1 mL/kg/day) placebo, mid volume (0.2 mL/kg/day) placebo, or high volume (0.4 mL/kg/day) placebo using a centralized randomization system. Randomization will be stratified according to current use of GH treatment (yes/no) and age (≥16 or <16 years old).

Phase 3 of the study

Following review by the DMC (Section 10.4), 1 or 2 dose levels will be recommended for continued development and assessment in Phase 3 of the study. Therefore, following the Tolerability Period, patients meeting randomization eligibility criteria will be randomized using a centralized randomization system in a way to obtain a balanced number of patients on RAD011 and placebo to receive double-blind treatment with IP at dose levels recommended by the DMC.

If 1 dose is recommended for continued development and assessment in Phase 3 of the study, randomization will be 1:1 (RAD011: placebo).

If 2 doses are recommended for continued development and assessment in the Phase 3 part of the study, randomization will be 2:2:1:1 (RAD011 dose 1: RAD011 dose 2: placebo: placebo).

Patients aged 8 to <12 years may be allowed to participate in the Phase 3 part of the study and will be randomized in a way to obtain a balanced number of patients on RAD011 (at dose levels recommended by the DMC) and placebo.

7.5.1. Breaking the Blind

Breaking the treatment blind for a patient should be done only in the event of a medical emergency where the identity of the IP is necessary to appropriately treat the patient. The Investigator may unblind the treatment received by the patient through the interactive response technology (IRT). The IRT will automatically document and record any such unblinding and notify the Sponsor Medical Monitor of the unblinding event. If possible, the Sponsor and/or designee should be contacted prior to unblinding of the treatment. The study monitor will not be apprised of the actual treatment assignment.

7.6. Treatment After the End of the Study

All patients completing the End of Study Visit (Visit 14, Week 34) may be offered enrollment in the long-term extension study (SCOUT-016).

8. STUDY DRUG MATERIALS AND MANAGEMENT

8.1. Description of Investigational Product

RAD011 is an oral CBD solution in which CBD is solubilized in MCTs. Cannabidiol is classified as a phytocannabinoid with a low affinity for the cannabinoid receptors CB1 and CB2. Although CBD has a low affinity for CB1 receptors (Petitet, 1998; Thomas, 1998), it has demonstrated antagonism for CB1 receptor agonists (Pertwee, 2002; Zuardi, 1981). Table 8 presents an overview of the IP. Cannabidiol Oral Solution 100 mg/mL formulation contains vitamin E (DL-alpha-tocopherol) as an antioxidant, saccharin as a sweetener, strawberry flavor, and MCTs.

Refer to the Investigator's Brochure for a detailed description of RAD011. Refer to the Pharmacy Manual for detailed instructions on preparation, handling, storage, and accountability of RAD011.

Table 8: Investigational Product

	Investigational Product	
Product Name:	RAD011	Placebo
Dosage Form:	Oral solution	Oral solution
Unit Dose	30 mL vial at a concentration of 100 mg/mL	30 mL vial with vehicle
Route of Administration	Orally	Orally
Physical Description	Clear, colorless to pale yellow to pinkish brown solution, free of visible particles. Medium chain triglycerides (Miglyol 812N) are used as the vehicle to dissolve cannabidiol Saccharin concentration of 0.24 mg/mL	Clear, colorless to pale yellow to pinkish brown solution, free of visible particles. Medium chain triglycerides (Miglyol 812N) are used to formulate the placebo formulation Saccharin concentration of 0.24 mg/mL
Manufacturer	Benuvia Manufacturing	Benuvia Manufacturing

8.2. Study Drug Packaging and Labeling

RAD011 (100 mg/mL) finished drug product is filled into 30 mL amber-colored screwcap glass bottles and capped with a 20-mm child resistant white polypropylene cap. The placebo will be provided in identical, amber-colored screwcap, child-resistant glass bottles.

Investigational product will be released to the site upon receipt of all required essential documents. All medication provided to the study site will be prepared, packaged, and labeled by the Sponsor according to Standard Operating Procedures (SOP), Good Manufacturing Practices (GMP), and applicable local laws and regulations.

8.3. Study Drug Storage

The IP is shipped to the site at 2 to 8°C (36 to 46°F). While at the site, IP must always be stored in a refrigerated (2 to 8°C [36 to 46°F]) secure location with limited access. To ensure adequate storage in the home setting, IP is recommended to be stored in the caregiver's refrigerator. Additional information on stability is provided in the Pharmacy Manual.

8.4. Study Drug Preparation

Investigational product will be obtained from the vial using a plastic syringe provided by the Sponsor. The dose will be ejected from the plastic syringe into a dosing cup. Investigational product must be administered orally directly and not mixed with food or other liquids prior to administration. Patients should take the IP with food.

8.5. Study Drug Accountability

The Investigator is required to maintain adequate records of the disposition of the IP, including kit numbers, the date and quantity of drug received, the time, date, and volume to whom it was dispensed, and a detailed accounting of any drug accidentally or deliberately destroyed.

Drug accountability will be measured at every in-person visit by weighing and counting the number of bottles returned by the patient at each visit. Patients will be required to retain and return all empty and partially filled bottles at each study visit. Additional details on drug accountability are provided in the Pharmacy Manual.

Records for storage, preparation, and dispensing of IP must be available for inspection by the Sponsor throughout the study.

8.6. Study Drug Handling and Disposal

Unused IP will be returned to the Sponsor at the conclusion of the study, or destroyed according to the site's SOPs, as mutually agreed between the Sponsor and the Site.

Bottles of IP returned by patients may be destroyed per the site's SOPs once accountability has been completed.

9. ASSESSMENT OF EFFICACY

Questionnaires completed by the patients, or their caregivers are used to assess primary, secondary, and other endpoints. The same caregiver should complete the questionnaires with the patient every time the questionnaires are administered.

9.1. Primary Efficacy Endpoint (HQ-CT Questionnaire)

The primary efficacy endpoint for this study is the change in HQ-CT scores from Baseline through End of Study/Week 34 Visit for RAD011 compared to placebo. The HQ-CT questionnaire is a tool that was developed specifically for use in patients with PWS and was validated in this population as a 13-item questionnaire (Dykens, 2007). The original tool was further refined and validated and now consists of 9 items, with a 2-week recall period. Each question is rated on a scale of 0 to 4, therefore providing a maximum score of 36. An HQ-CT score of 13 is associated with moderate to severe hyperphagia (Fehnel, 2015).

The HQ-CT questionnaire was selected as the primary endpoint since it has been validated in patients with PWS and is the gold standard outcome measure in studies evaluating hyperphagia-related behavior (Allas, 2018; McCandless, 2017). Additionally, this tool has recently been reported to have a strong correlation to caregiver burden, further supporting the clinical relevance of the HQ-CT questionnaire in this study (Kayadjanian, 2021).

9.2. Secondary Efficacy Endpoints

9.2.1. Change in Irritability (Irritability subscale of the ABC Questionnaire)

A secondary endpoint of this study is to evaluate the change in PWS-associated irritability from Baseline through End of Study/Week 34 Visit using the irritability subscale of the ABC questionnaire. In patients with PWS, anxiety manifests as irritability. The ABC questionnaire is an informant-rated questionnaire assessing severity of behavioral symptoms, is one of the few empirically developed scales designed to measure psychiatric symptoms and behavioral disturbance exhibited by individuals with developmental disabilities (intellectual disability, autism spectrum disorder, cerebral palsy, epilepsy). According to factor analyses, there are five subscales: (a) irritability and agitation, (b) lethargy and social withdrawal, (c) stereotypic behavior, (d) hyperactivity and noncompliance, and I inappropriate speech (Aman, 1987). The ABC originally was developed to assess the effectiveness of psychotropic medication, and has been used extensively in pediatric, as well as adult behavioral and psychiatric research due to its high reliability and validity. The Irritability subscale of the ABC covers symptoms such as agitation, aggression, meltdowns, and self-harm. An extensive psychometric assessment of the ABC has indicated that the subscales have high internal consistency, good reliability, and established validity. For this reason, the Irritability subscale of the ABC questionnaire is being proposed to evaluate PWS-associated anxiety, manifesting as irritability, as a secondary outcome. Anxiety and irritability associated with PWS is of significant concern to patients and to their caregivers and represents an unmet medical need (Aman, 1995; Aman, 1987; Aman, 1985; Aman, 1985).

Overall, the ABC contains 58 items divided in 5 subscales, and the Irritability subscale contains 15 items. Each item is scored as 0 (never a problem), 1 (slight problem), 2 (moderately serious problem), or 3 (severe problem). Items load onto one of five empirically derived subscales: Irritability, Agitation, & Crying (15 items); Lethargy/Social Withdrawal (16 items); Stereotypic Behavior (7 items); Hyperactivity/Noncompliance (16 items); and Inappropriate Speech (4 items). In addition, a Total Score can be calculated. The ABC questionnaire has a recall period of 1 month, and has also successfully been used in patients with PWS (Clarke, 1996; Consoli, 2019; Ishii, 2017; Salehi, 2018).

9.2.2. Change in Clinician Global Impression of Change in Hyperphagia (CGI-C Questionnaire)

A secondary endpoint of this study is to evaluate the change in hyperphagia as defined by the CGI-C in Hyperphagia response through End of Study/Week 34 Visit. The CGI scales have been found to be valid as an external criterion in symptom improvement and to correlate significantly with self-rated and other valid scales of symptom severity (Khan, 2002; Leon, 1993). Clinical Global Impression scales have also been used successfully in evaluating therapeutic responses in patients with PWS (Avrahamy, 2015; Consoli, 2019; Dykens, 2018).

9.2.3. Change in Clinician Global Impression of Severity of Hyperphagia (CGI-S Questionnaire)

A secondary endpoint of this study is to evaluate the change in severity of hyperphagia as defined by the CGI-S response from Baseline through End of Study/Week 34 Visit.

9.3. Other Endpoints

9.3.1. Change in Caregiver Global Impression of Change in Hyperphagia, Change in Caregiver Global Impression of Severity of Hyperphagia, Change in Caregiver Global Impression of Change in Irritability

Caregiver global impression scales of severity and change specific to hyperphagia and change in irritability will be other endpoints in this study. They will be assessed through the End of Study/Week 34 visit.

9.3.2. Change in Overall Behavior (ABC)

Change in overall behavior from Baseline through End of Study/Week 34 Visit in response to RAD011 compared to placebo will also be considered an endpoint in this study. The remaining ABC subscales (described in Section 9.2.1) will be used to assess overall behavior.

9.3.3. Change in Sleep (ESS-CHAD Questionnaire)

An other endpoint is the change in the ESS-CHAD questionnaire from Baseline through End of Study/Week 34 Visit. The ESS-CHAD is an 8-question scale with a 1-month recall period that has been validated in school-attending children and adolescents to evaluate daytime sleepiness (Janssen, 2017). Each question is rated on a 0 to 3 scale, with a maximum score of 24, and a score above 10 is considered to represent mild excessive daytime sleepiness.

9.3.4. Change in Body Mass Index and Weight

Changes in BMI and weight through End of Study/Week 34 Visit will be evaluated as an other endpoint. Change in age-normalized BMI z-scores (USPSTF, 2017; Wei, 2020) will be used for patients aged 8 to 19 years inclusively, whereas percent change in weight will be used for patients aged 20 to 65 years.

9.3.5. Change in Skin-Picking Behavior

An other endpoint in this study is to evaluate the change in skin-picking behavior between scale values across time points using the Skin Picking questionnaire from Baseline through End of Study/Week 34. The Skin Picking questionnaire is a 6-item questionnaire of skin picking symptoms, with scores ranging from 0 to 24 (Keuthen, 2001). A score of ≥7 is considered highly suspicious for a skin picking disorder.

9.3.6. Change in Muscle/Fat Composition (DEXA Scan)

Change in muscle/fat composition using a DEXA scan from Visit 5 through End of Study/Week 34 visit will also be an other endpoint. The assessment of change in muscle/fat composition will be performed at a selected number of US sites only. All attempts should be made to have both DEXA scans performed at the same site using the same DEXA scanner, and DEXA scans of children and adolescents should be interpreted only by providers experienced in scoring DEXA scan in this patient population. Results of the DEXA scan will be reported as percentage body fat. The DEXA scan may be performed within ± 7 days of Visits 5 and 14.

9.4. Pharmacokinetic Endpoints

Throughout the study, plasma samples will be collected to establish the PK profile of CBD and 2 metabolites, 7-OH-CBD and 7-COOH-CBD in patients with PWS. Furthermore, an exposure-response analysis using CBD and 7-OH-CBD concentrations as well as a population PK model will be derived from the data. Details on sample collection are provided in Section 10.1.13 and in the Laboratory Manual.

9.5. Biomarkers assessments (Phase 3 exploratory)

For Phase 3 patients: If the patient/legal guardian consents, samples will be collected for exploratory assessment of biomarkers. Blood samples will be collected at Visit 1 and Visit 14 and stored for potential exploratory analysis of biomarkers (including but not limited to inflammation). Details on sample collection are provided in the Laboratory Manual. No genetic or DNA analysis will be conducted on the samples.

10. ASSESSMENT OF SAFETY

10.1. Safety Parameters

10.1.1. Demographics and Medical/Surgical/Seizure History

Demographic characteristics will be collected during the Screening Visit (Visit 1). A full medical/surgical history (including seizure history) will also be documented at the Screening Visit (Visit 1). Evaluation of seizure history and Seizure Patient Impression are provided in Appendix 2.

10.1.1.1 Seizure Patient Impression

Patients with a history of seizure who are randomized will be evaluated for potential changes in seizure activity at the End of Study/Week 34 Visit as detailed in Appendix 2.

10.1.2. Vital Signs

Vital signs to be collected include BP, HR, RR, oxygen saturation, and temperature. Blood pressure and pulse measurements may be assessed using an automated device or by manual techniques. Vital signs should be collected after the patient has rested (per standard of care) and prior to blood draws for laboratory tests.

10.1.3. Weight and Height

Height and weight will be collected as identified in the Schedule of Assessments tables (Table 6 and Table 7). Both height and weight must be collected per the Schedule of Assessments as BMI Z-scores will be computed for children and change from baseline will be computed for adults (see the SAP for additional information). Efforts should be made to use the same scale throughout the project when possible.

10.1.4. Physical Examination

A full physical examination will be performed at Screening Visit 1 (Visit 1) and at Visit 5 (Week 7). All other physical examinations should be abbreviated, symptom directed physical examinations. The Investigator is responsible for conducting the exams, determining findings, assessing abnormalities, and evaluating clinical significance.

10.1.5. Electrocardiogram

A 12-lead ECG will be performed after the patient has rested in a supine position.

10.1.6. Columbia Suicide-Severity Rating Scale

The C-SSRS is a broadly validated scale aimed at assessing suicidal risk in a variety of children and adult populations. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. Administration of the C-SSRS should occur after nonleading AE collection, and findings from the C-SSRS should not be included as an AE unless it leads to study discontinuation. The first time the C-SSRS questionnaire is administered, on Visit 5 (Week 7), the Baseline/Screening questionnaire (Posner, 2008) should be used, and the "Since Last Visit" questionnaire should be used for all subsequent assessments.

The standard C-SSRS scale should be used for patients aged 6 and over and the Children's C-SSRS scale should be used in patients aged less than 6 years. However, the Children's version may be used in patients aged 6 years or older when the Investigator or designee determines that the patient is unable to understand the first couple of questions in the standard version. The same C-SSRS scale should be used for a given patient throughout the study.

If a suicidal behavior is identified during the study, the Investigator must provide immediate care and refer the patient to additional care as needed.

10.1.7. Laboratory Assessments

Laboratory assessments will be performed per the Schedule of Assessments (Table 6 and Table 7). All laboratory assessments are to be performed centrally unless otherwise specified. The Investigator must review results from these laboratory assessments (performed locally and centrally) and determine the clinical significance of any results outside the reference range. This review must be documented, and laboratory values considered clinically significant during this study be recorded as an AE. On the days where a dose of IP is administered, all laboratory assessments should be performed prior to dosing unless otherwise specified. A list of analytes is presented in Table 9.

10.1.8. Hepatic Function Testing

Patients presenting with elevated liver function tests should be closely monitored. Any patient with an elevation of ALT or AST ≥3 × ULN, alkaline phosphatase ≥2 × ULN, or total bilirubin ≥2 × ULN should have their liver function tests repeated within 3 days. If the repeat results remain above these thresholds or higher, the Investigator should conduct additional testing and consult the Sponsor Medical Monitor. Monitoring of liver function tests should continue until results stabilize or return approximately to their level prior the initial elevation.

10.1.9. Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate will be calculated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey, 2009) for patients aged ≥18 years. For patients aged ≤17 years, the "Bedside Schwartz" equation (Schwartz, 2009) will be used to calculate eGFR.

10.1.10. Urine Drug Screen

Urine drug screen for drugs of abuse will be performed locally via dipstick testing on urine and may be repeated at the Investigator's discretion. Testing kits will be provided by the central laboratory. Urine drug screens should test for the following drugs of abuse: THC, cocaine, opiates, methamphetamine, amphetamines, phencyclidine (PCP), benzodiazepine, barbiturates, methadone, tricyclic antidepressants, ecstasy, and oxycodone.

10.1.11. Follicle-Stimulating Hormone

Menopausal status of women must be confirmed by testing for FSH levels at the Screening Visit (Visit 1). To be considered menopausal, FSH level must be ≥30 mIU/mL and the patient must not have had a menstrual period in ≥1 year. Follicle-stimulating hormone testing must only be performed in women reporting menopause.

10.1.12. Pregnancy Screen

A serum pregnancy test will be performed centrally at Screening (Visit 1) in women of childbearing potential (WOCBP). All other pregnancy tests will be performed locally using dipstick testing on urine in women of childbearing potential only. Testing kits will be provided by the study site. A positive urine pregnancy test must be confirmed by sending a serum sample to the central laboratory. Women with a confirmed positive serum pregnancy test should be withdrawn from the study. The Investigator should refer the patient for appropriate care. Details on reporting and following pregnancies are provided in (Section 10.2.9).

10.1.13. Pharmacokinetic Sampling

On Visits 5 (Week 7), 8 (Week 10), 12 (Week 27), and 14 (End of Study [EOS]/Week 34), patients will have a blood sample collected for PK at the same time as their laboratory blood samples. The time of sampling will be recorded, with the exception of Visit 8 (Week 10). Pharmacokinetic sampling on Visit 8 should occur within 6 ± 2 hours of dose. The dose preceding Visit 8 PK sampling may be taken at home in order to comply with the PK sampling window. Pharmacokinetic samples at Visits 5, 12, and 14 can occur without regards to the time of dosing, as long as dosing and PK sampling times are accurately recorded.

Table 9: Laboratory Analytes

Renal Panel (10-hour fasting[a])	**Hematology**	HbA1c
Sodium	Hematocrit	
Potassium	Hemoglobin	**Coagulation**
Chloride	MCV	PT-INR
Calcium	MCH	**Appetite Hormones**
Bicarbonate	MCHC	Insulin
Glucose	RDW	Circulating ghrelin[b]
Phosphorus	RBC	Leptin
BUN	WBC	**Urinalysis**
Creatinine	Platelets	Color
eGFR	Differential (% and absolute	Appearance
Liver Function Panel	Count)	pH
ALT	Neutrophils	Specific gravity
AST	Eosinophils	Protein
Albumin	Basophils	Glucose
Alkaline phosphatase	Lymphocytes	Ketones
Direct and indirect bilirubin	Monocytes	Bilirubin
Total bilirubin	**Urine tests**	Blood
Total protein	Drug screen including THC[c,d]	Urobilinogen
Serologies	Pregnancy test[c,e,f]	Nitrites
HIV	**Other test**	Microscopic examination if
Hepatitis B surface antigen	FSH[g]	blood, protein, or leukocyte
Hepatitis C antibody	Quantitative serum pregnancy test[h]	esterase is abnormal in urine

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; FSH = follicle stimulating hormone; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cells; RDW = red cell distribution width; THC = tetrahydrocannabinol; WBC = white blood cells.

All tests to be performed centrally unless otherwise specified

[a] Fasting is preferred, if possible. If obtained in a non-fasting state, will not be considered a protocol deviation.

[b] Includes acylated ghrelin and des-acyl ghrelin

[c] Performed locally via dipstick testing and provided by the central laboratory. Must include testing for THC, cocaine, opiates, methamphetamine, amphetamines, PCP, benzodiazepine, barbiturates, methadone, tricyclic antidepressants, ecstasy, and oxycodone

[d] May be repeated at any time at the Investigator's discretion

[e] To be performed in females of childbearing potential only. Testing kits to be provided by the study site

[f] If positive, a confirmatory pregnancy test at the central laboratory is required

[g] To be performed in postmenopausal females only

[h] To be performed centrally at Screening (Visit 1) and if a local urine pregnancy test is positive.

10.1.14. Food Diary

A food diary will be distributed to all patients on Visits 4, 7, 11 and 14 but can be distributed at the site's or patient's convenience. This food diary will be collected as per Table 7. The food diary will collect time of food consumption, type and amount of food consumed, date and time of evening and morning dose, and support the pharmacokinetic analysis.

10.2. Adverse and Serious Adverse Events

10.2.1. Evaluation of Safety

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients and is mandated by Regulatory Agencies worldwide. All clinical studies sponsored by Radius will be conducted in accordance with SOPs that have been established to conform to regulatory requirements worldwide to ensure appropriate reporting of safety information.

Where possible, a diagnosis rather than a list of symptoms should be recorded. All AEs should be captured on the appropriate AE pages in the electronic case report form (eCRF) and in source documents.

All AEs will be collected from the time of consent/assent until the following time points:

- For patients who are not enrolled: until time of screen failure
- For enrolled patients:
  - For patients continuing in the long-term extension study SCOUT-016: through Visit 14 (Week 34) inclusively
  - For patients entering the follow-up period with IP tapering: through Visit 16 (Week 38).

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study or 30 days after the last dose of IP, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE.

All patients will be queried using non-leading questions about the occurrences of AEs at each study visit. Adverse events spontaneously reported by the patient and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. When possible, a constellation of signs and/or symptoms should be identified as one overall event or diagnosis. All AEs for enrolled patients will be recorded in the eCRF and the patient's source documents. Any AEs for patients who are screened but not subsequently enrolled in the study will be recorded only in the patient's source documents. The following data should be documented for each AE by the Investigator:

- Description of the event term as diagnosis, in standard medical terminology when possible
- Classification of "serious" or "not serious"

- Date and time of the onset and resolution (if applicable)
- Severity
- Causal relationship to study drug
- Action taken with study drug
- Outcome (as applicable)
- Concomitant medication or other treatment given
- Whether or not it caused the patient to discontinue the study.

10.2.1.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH, 1995). This includes any newly occurring event which occurs during the study, having been absent at Screening, or any previous condition, if present at Screening, that appears to worsen (i.e., increased in severity or frequency) after the administration of study drug.

Study assessments including laboratory tests, ECGs, physical examinations, and vital signs should be performed and those deemed a clinically significant worsening from Screening will be documented as an AE. When possible, a clinical diagnosis for the study assessment should be provided rather than the abnormal test result alone (e.g., urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself should be listed as the AE (e.g., bacteria in urine or decreased hemoglobin).

Investigators will be requested to evaluate abnormal study assessments for clinical significance.

This would include:

- Worsening from Screening (change in nature, severity, or frequency) of conditions present at Screening
- Concomitant signs or symptoms related to the abnormal study assessment
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- Further diagnostic testing or medical/surgical intervention is required
- Abnormal laboratory values (this includes significant shifts from Screening within the range of normal that the Investigator considers to be clinically significant)
    - An abnormal laboratory value will not be assessed as an AE unless it requires a therapeutic intervention or is considered by the Investigator to be clinically significant
- Clinically significant abnormalities in physical exam, vital signs, or weight
- A change in the dose of study drug, if study drug is withheld, or discontinuation from study drug occurs.

Hyperphagia or decreased appetite will not be considered an AE in this study unless it significantly worsens or warrants reporting in the opinion of the Investigator.

10.2.1.2 Determination of Clinical Significance Must be Made by the Investigator.

Events that do not meet the definition of an AE or SAE include:

- Planned hospital admissions or surgical procedures that are elective or for a condition that existed before the patient signed the ICF are not considered an AE unless the condition deteriorates in an unexpected manner during the study (e.g., surgery had to be performed earlier than planned)
- Anticipated day-to-day fluctuations of pre-existing disease(s), condition(s), and signs or symptoms present or detected prior to the start of the study that are not more severe than expected for the patient's condition.

10.2.1.3 Definition of a Serious Adverse Event

An SAE is defined (21CFR 312.32) as any adverse experience that suggests a significant hazard, contraindication, side effect, or untoward medical occurrence that, in the view of the Investigator or Sponsor, results in any of the following criteria:

- Death
- Is immediately life threatening
    - An AE or suspected adverse reaction that places the patient, in the view of either the Investigator or the Sponsor, at immediate risk of death. It does not include an

AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death

- Requires in-patient hospitalization or prolongation of existing hospitalization
    - Admittance to an emergency room for observation without being admitted to the hospital may be considered to be an AE but is not considered as an SAE unless other serious criteria is met. In addition, complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization the event is considered serious
- Results in persistent or significant disability or incapacity
    - Defined as a substantial disruption in a person's ability to conduct normal life functions
- Results in a congenital abnormality or birth defect
    - A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the IP
- Other medically important event
    - An AE that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgement, the event may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed in the definition of an SAE
    - Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms "serious" and "severe" since they **are not** synonymous. The term "severe" is often used to describe the intensity (synonym: severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself may be of relatively minor medical significance (such as a severe headache). This is **not** the same as "serious", which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

In cases of events meeting serious criteria due to hospitalization, the onset date is the date of admission into the hospital and the stop date is the date the patient was discharged. Note that a SAE can meet more than one serious criterion (ie, medically important event) and therefore, event onset date and event stop date may not be the same as hospitalization dates, based on the Investigator's assessment of the event(s).

10.2.1.4 Unexpected Adverse Events

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure within the section "Reference Safety Information" for Assessment of Expectedness of Serious Adverse Reactions.

10.2.1.5 Adverse Events of Special Interest (AESI)

An AESI is an adverse event (AE) that is designated to be of special medical or scientific interest to the Sponsor. All AEs within the category of AESIs should be reported promptly, following the reporting procedures for abnormal laboratory, AEs or SAEs as appropriate.

1. Suicide ideation and behavior AESI

Included in this AESI are adverse events following administration of RAD011 that are assessed by the Investigator to be any of the following: suicidal ideation, suicidal behavior, suicide attempt, and completed suicide.

2. Hepatic dysfunction AESI

Included in this AESI are abnormal laboratory findings or adverse events suggestive of hepatic dysfunction following administration of RAD011 such as greater or moderate elevation of liver enzymes (AST, ALT, ALP, gamma-glutamyl transferase [GGT]) and bilirubin; or adverse events of right upper quadrant abdominal pain, chronic fatigue, loss of appetite, unexplained nausea and vomiting, yellowing of skin or eyes, itching, dark urine, and light-colored stools.

10.2.2. Collection and Recording of Adverse Events

All patients will be monitored closely for AEs/SAEs during study participation. Sources for AE/SAE notification include patient self-reports, abnormalities found on physical assessments, imaging, or other clinical investigations, clinical laboratory exam results, and other sources relating to the patient's health that becomes available to the Investigator. The Investigator should take all appropriate measures to ensure the safety of patients and should follow up the outcome of all AEs (clinical, laboratory values, or other, etc.) until the return to normal or until the patient's condition has stabilized. In the event of an SAE, the Investigator should follow up for the outcome until the clinical recovery is complete and laboratory results have returned to normal or until progression has been stabilized.

All AEs/SAEs will be entered into the electronic database. All AEs/SAEs will be collected from the time of ICF signature up to completion of the EOS/Week 34 Visit for patients enrolling in the long-term extension study (SCOUT-016) or up to Week 38Visit for patients entering the Taper and Follow Up Periods. Patients who discontinue prematurely from the study will be encouraged to return for assessment of safety. Follow up safety information may also be obtained from a patient's physician or medical records.

All AEs/SAEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures must be recorded in the source document and on the appropriate page of the eCRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the appropriate pages of the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Documentation of time of onset, time of resolution, seriousness assessment, maximal severity assessment, relationship assessment, action taken, treatments administered, and outcomes must be provided on the AE CRF and SAE form.

All SAEs that occur during the course of the study, as defined by the protocol, must be reported by the Investigator to Radius by completing and emailing the SAE Form within 24 hours of the

Investigator or site's study staff first becoming aware of the SAE to [redacted] (see Section 10.3 for additional details). In addition, all SAEs including deaths, which occur up to and including 30 days after administration of the last dose of study drug, must be reported to Radius within 24 hours of the first awareness. All SAEs and deaths must be reported whether or not considered causally related to the study drug. SAE forms will be provided to the clinical study site. The information collected will include a minimum of the following:

- Patient number
- A narrative description of the event
- An assessment by the Investigator as to the relatedness to study drug
- Intensity of the event.

Note: Any SAE that occurs at any time after the completion of the study which the Investigator considers to be related to study drug, must be reported to the Sponsor or its designee.

Planned or elective hospital admissions for treatment/procedures for a condition/disease that existed prior to signing the ICF and did not worsen from Screening will not be captured as SAEs. However, complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization the event is considered serious.

10.2.3. Follow-up of Adverse Events

All AEs/SAEs will be followed up with appropriate medical management until resolved or before study end (database lock).

Follow-up information on the SAE may be requested by the Contract Research Organization (CRO) or the Sponsor Medical Monitor. Contact information for reporting SAEs to the Medical Monitor will be provided in a separate document.

Reasonable attempts should be made by the Investigator to obtain follow up and outcome information for unresolved AEs. The Sponsor may request additional information at the end of the study if necessary for unresolved AEs.

For patients whose status is unclear or "lost to follow-up" because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his scheduled end of study visit would have occurred.

10.2.4. Intensity

For both SAEs and non-SAEs, the Investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Intensity for each AE will be defined according to the following criteria as noted in Table 10. If the intensity of an AE changes within a day, the maximum intensity should be recorded. If the intensity changes over a longer period of time, the changes should be recorded as separate events (having separate onset and stop dates for each intensity).

Table 10: Intensity Classification and Definition of Adverse Events

Intensity	Definition
Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with normal daily activities
Severe	Inability to perform normal daily activities

10.2.5. Relationship to Study Drug

Every effort should be made by the Investigator to assess the relationship (causality) of the AE, if any, to the IP.

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to study drug, indicating on the eCRF that an AE is either related or not related. The following guidance should be taken into consideration when determining the relationship of an AE to study drug:

- Temporal relationship of event onset to initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or environment, or use of concomitant medications known to be associated with the event
- Presence of treatment-unrelated factors that are known to be associated with the occurrence of the event
- Whether there is a reasonable alternative explanation for the event

10.2.6. Study Drug Action taken

The Investigator will determine the study drug action taken with regard to the AE. The action taken should be classified according to the categories shown in Table 11.

Table 11: Classification for Study Drug Action Taken with Regards to an Adverse Event

Classification	Definition
Dose Not Changed	Study drug dose or frequency not changed in response to the AE
Dose Reduced	Study drug dose or frequency reduced in response to the AE
Drug Interrupted	Study drug administration interrupted in response to the AE
Drug Withdrawn	Study drug administration permanently discontinued in response to the AE
Not Applicable	Action taken regarding study drug administration does not apply. "Not applicable" should be used in circumstances such as death or when the investigational treatment had ended before the AE began or the event occurred prior to investigational product administration.

10.2.7. Adverse Event Outcome

The outcome of an AE describes the status of the AE. An AE should be followed until the Investigator has determined and provided the outcome. The outcome should be classified according to the categories shown in Table 12. Resolution of AEs will be monitored throughout the study, and will be classified as resolved, resolved with sequelae, or ongoing.

Table 12: Classifications for Outcome of an Adverse Event

Classification	Definition
Recovered/Resolved	Resolution of an AE with no residual signs or symptoms
Recovered/Resolved with Sequelae	Resolution of an AE with residual signs or symptoms
Recovering/Resolving (Ongoing)	Improvement of an AE
Not Recovered/Not Resolved (Ongoing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing.
Fatal *	Outcome of an AE is death. "Fatal" should be used when death is at least possibly related to the AE.
Unknown	Outcome of an AE is not known (e.g., patient lost to follow-up).

*Only event(s) resulting in the fatal outcome, should report "fatal" as an outcome. All other events that were ongoing at the time of death should be reported as "not resolved."

10.2.8. Abuse, Misuse, and Overdose

Abuse, misuse, and overdose (as defined below) must be assessed by the investigator and should be reported regardless of resulting in an adverse event. Any adverse event that meets seriousness criteria, as defined by the protocol, must also be reported by the Investigator to Radius by completing and emailing the SAE Form within 24 hours of the Investigator first becoming aware of the SAE to [redacted] (see Section 10.3 for additional details).

- Abuse: Persistent or sporadic intentional intake of investigational medicinal product at a higher dose than prescribed per protocol (e.g., but below the dose defined for overdose) or when used for non-medical purpose (e.g., altering one's state of consciousness)

- Misuse: Intentional or unintentional use of investigational medicinal product other than as directed or indicated at any dose. Note: this includes a situation where the test article is not used as directed at the dose prescribed by the protocol
- Overdose: Administration of a quantity of a medicinal product greater than the dose defined in the protocol for the investigation product.

10.2.9. Pregnancy

Any pregnancy that occurs in a study participant during the study or within 30 days after the last study dose must be reported within 24 hours to the Radius Pharmacovigilance Department using the Pregnancy Report Form. Every effort should be made to gather information regarding the pregnancy course and outcome. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 days postpartum.

Pregnancy is neither an AE nor an SAE, unless a complication relating to the pregnancy occurs. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The course of all pregnancies, including perinatal and neonatal outcome, regardless of whether the patient has discontinued participation in the study, will be followed until resolution, including follow up of the health status of the newborn to 6 weeks of age. Congenital abnormalities/birth defects in the offspring of patients should be reported as an SAE if conception occurred during this study.

The effects of administration of the IP in pregnant females is unknown. Fetal development studies in female mice exposed to CBD suggest that perinatal CBD exposure in males may interfere with long term androgen mediated processes of differentiation, testicular function including spermatogenic and steroidogenic components, and endocrine functions. Therefore, women of childbearing potential are required to use effective contraception from Screening through 30 days after IP administration.

In patients who have partners of child-bearing potential, the patient and his partner should use contraceptive approaches as mentioned in Inclusion Criterion 5 and Inclusion Criterion 6, and for at least 30 days after the last dose of IP.

10.2.10. Study Completion and Post-Investigational Product Treatment

The Investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study due to an AE or must refer them for appropriate ongoing care.

10.3. Reporting of Serious Adverse Events

Prompt notification of SAEs by the Investigator is essential so that legal obligations and ethical responsibilities toward the safety of patients are met. Documentation of submissions for all unexpected events must be retained in the site study file.

All SAEs must be reported to the Sponsor within 24 hours of the Investigator's awareness of the event. The Investigator must complete, sign and date the SAE Report Form and verify the accuracy of the information recorded on the SAE form with the corresponding source

documents. The event should also be entered onto the AE CRF in the EDC. E-mail the completed SAE form to:

- **Email:** [redacted]
  - Report the SAEs to Radius by completing an SAE Report Form. All sections on the form are to be completed. Information that is not available at the time of initial reporting should be submitted as a follow up within 24 hours of the investigator's awareness. The date of receipt of an initial SAE Report Form will be considered as Day 0 for the purpose of determining the time for regulatory reporting of an expedited event and timelines of further study related activities
  - Do not attach documents (e.g., discharge summary, autopsy report, diagnostic test results, examinations, etc.) unless requested. All relevant information should be provided on the SAE form in English.

It is the PI's responsibility to notify the Institutional Review Board (IRB) or Institutional Ethics Committee (IEC) of all SAEs or other AEs that require reporting that occur at his or her site.

The Sponsor is responsible for notifying the relevant regulatory authorities of all suspected unexpected, serious, adverse reactions (SUSAR, 7/15 Day Safety Reports) that occur during the clinical study. Each site is then responsible for notifying its IRB or IEC of these additional SAEs. A copy of such SUSAR will be sent to the clinical CRO who will be responsible for notifying all clinical sites, central IRBs (if applicable), and IECs.

Any SAEs that occur at any time after completion of the study, which are considered by the Investigator to be related to IP, must be reported to the Sponsor or its designee via email [redacted].

An investigator who receives a safety report describing an SAE or other specific safety information from RADIUS will file it in their Investigator Site File (ISF) and will notify their IRB and independent EC, if appropriate according to local requirements.

10.4. Data Monitoring Committee

A DMC, composed of individuals not affiliated with the study and selected based on their scientific and clinical background and expertise in clinical studies, will be formed. The roles, responsibilities and additional details on DMC operations are provided in the DMC Charter.

After approximately 45 patients complete 4 weeks of the Maintenance Period of the Phase 2 part of the study, the DMC will meet to review the safety and tolerability data and to recommend 1 or 2 RAD011 dose level(s) for evaluation in the Phase 3 part of the study.

The DMC will also be available to assist in the review of aggregate safety events as requested by the Sponsor at any time during the study.

11. STATISTICAL CONSIDERATIONS

Statistical methods to assess study endpoints will be detailed in the final version of the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock and unblinding. All

analyses and tabulations will be performed using SAS® Version 9.4 or higher (SAS Institute, Cary, NC).

Efficacy analyses will be conducted on the ITT, mITT, and PP populations, safety analyses will be conducted on the Safety Population, and PK analyses will be performed on the PK Evaluable Population.

Data will be presented using tables by treatment group, unless otherwise specified. Continuous variable summaries will be summarized using the number of patients (n), mean, standard deviation, median, minimum, and maximum. Categorical variable summaries will be summarized as frequency counts and percentages. Figures and listings may be used to support the presentation of selected data.

Handling of missing and partial data will be described in the SAP.

11.1. Sample Size Determination

DMC Recommendation of Two RAD011 Doses

For the primary efficacy analysis, a total of 150 patients (50 patients per treatment group) aged 12 to 65 years will provide 90% power to compare each dose group vs. placebo with a two-sided alpha of 0.025. The study is powered to detect a difference in the HQ-CT from Baseline to Week 34 of 5 points with a standard deviation of 7 points. The 0.05 Type 1 error is split equally between groups (low dose and high dose). The low and high volume placebo groups will be combined for all comparisons to placebo. Assuming a 15% post-randomization dropout rate, approximately 180 patients (~60 patients per treatment group) will be evaluated for the primary efficacy analysis.

Thus, if the DMC recommends two RAD011 doses for Phase 3 of the study, approximately a total of 191 patients aged 12 to 65 years (approximate target of 200 patients) will be randomized in this study. The 191 reflects 176 patients required for primary efficacy analysis plus 15 patients randomized in the Phase 2 part of the study to the dose not selected for Phase 3 of the study.

Assuming a 20% pre-randomization eligibility failure rate (including HQ-CT eligibility criteria), approximately 240 patients will be enrolled into the Screening Period. An additional 10 patients per treatment group aged 8 to <12 years may be allowed to participate in Phase 3 of the study and will be randomized in a way to obtain a balanced number of patients on RAD011 (at dose levels recommended by the DMC) and placebo. Patients aged 8 to <12 will not be included in the primary efficacy analysis.

DMC Recommendation of One RAD011 Dose

For the primary efficacy analysis, a total of 100 patients (50 patients per treatment group) aged 12 to 65 years will provide 94% power to compare active vs. placebo with a two-sided alpha of 0.05. The study is powered to detect a difference in the HQ-CT from Baseline to Week 34 of 5 points with a standard deviation of 7 points. Assuming a 15% post-randomization dropout rate, approximately 118 patients (~59 patients per treatment group) will be evaluated for the primary efficacy analysis.

Thus, if the DMC recommends one RAD011 dose for Phase 3 of the study, approximately 148 patients aged 12 to 65 years (target approximately 150 patients) will be randomized in this study.

The 148 reflects 118 patients required for primary efficacy analysis plus 30 patients randomized in the Phase 2 part of the study to the two doses not selected for Phase 3 of the study.

Assuming a 20% pre-randomization eligibility failure rate (including HQ-CT eligibility criteria), approximately 185 patients will be enrolled into the Screening Period. An additional 10 patients per treatment group aged 8 to <12 years may be allowed to participate in Phase 3 of the study and will be randomized in a way to obtain a balanced number of patients on RAD011 (at dose level recommended by the DMC) and placebo. Patients aged 8 to <12 will not be included in the primary efficacy analysis.

11.2. Hyperphagia Questionnaire for Clinical Trials and Prader-Willi Syndrome Mean Score

In order to assess patient eligibility at the end of the Screening Period (Visit 2) and prior to initiating dosing of patients at Visit 2, patients/caregiver must complete the HQ-CT.

The EDC system will automatically calculate a mean HQ-CT score from Visit 1 and Visit 2. Patients must have a mean HQ-CT score ≥13 to be eligible to continue in the Tolerability Period. Patients with a mean score <13 will not be eligible to continue in the Tolerability Period and will be discontinued from the study.

At the end of the Tolerability Period (Visit 5), Investigators will review a patient's HQ-CT eligibility to be randomized and proceed to the Dose Escalation Period.

Patients/caregivers must first complete the HQ-CT. The EDC system will automatically calculate a mean HQ-CT score from Visit 3, Visit 4 and Visit 5. Patients must have a mean HQ-CT score ≥13 to be eligible to be randomized and proceed to the Dose Escalation Period. Patients with a mean score <13 will not be eligible for randomization and will not have the opportunity to participate in the long-term extension study (SCOUT-016).

11.3. Change in Hyperphagia Questionnaire for Clinical Trials During Tolerability Period Response Evaluation

In addition to the mean HQ-CT score requirement described in Section 11.2, the EDC system will also automatically calculate the change in HQ-CT score from the Tolerability Period to the Screening Period. This change is calculated as

Mean HQ-CT score (Visit 3, Visit 4, Visit 5) – Mean HQ-CT score (Visit 1, Visit 2)

Patients must also have a decrease in HQ-CT score ≤7 to be eligible for randomization and able to proceed to the Dose Escalation Period. Patients with a decrease HQ-CT score >7 will not be eligible for randomization.

11.4. Statistical Analyses

11.4.1. Populations for Analyses

The following patient populations will be defined for analysis:

- Safety Population: the Safety Population will include all randomized patients who were treated with at least one dose of IP

- Intent to Treat (ITT) Population: the ITT Population will include all randomized patients
- Modified ITT (mITT) Population: the mITT Population will include all patients aged ≥12 years who were randomized, received at least 1 dose of IP, had at least 1 post-randomization HQ-CT questionnaire completed, and were randomized to receive the dose level(s) recommended for development in Phase 3 of the study, including patients in the Phase 2 part of the study who received the chosen dose level(s)
- Per Protocol (PP) Population: the PP Population will include all patients aged ≥12 years who were randomized, received at least 1 dose of IP, completed Week 34 without significant protocol deviations that were prospectively defined to impact efficacy (see SAP) and received the dose level(s) recommended for development in Phase 3 of the study, including patients in Phase 2 of the study who received the chosen dose level(s)
- Pharmacokinetic Evaluable Population: the PK Evaluable Population will include all patients who received at least 1 dose of IP and underwent at least 1 PK sample collection.

11.4.2. Primary Endpoint

The primary endpoint, change in HQCT score from Baseline to End of Study (Week 34) will be analyzed for the mITT population based on the treatment policy estimand using a mixed model for repeated measures (MMRM) with change in HQCT score as the response variable and randomization assignment, Baseline HQ-CT score and stratification variables (age [≥16 or <16 years] at randomization and GH treatment at randomization [yes/no]) and time × treatment interaction as fixed effects. Patient will be included as a random effect with an unstructured covariance matrix. A multiple imputation will be used for missing data. Baseline will be defined as the mean HQ-CT score (Visit 1, Visit 2).

For the primary endpoint analysis at Week 34, multiple imputation will be used to assign a value to those cases with missing data. The full conditional specification method with predictive means matching as described in Berglund & Heeringa (Berglund, 2014) will be used. This method uses all of a patient's known primary outcome measures at Baseline, Weeks 10, 19, 27, and/or 34 weeks to impute any missing values for Week 34.

DMC Recommendation of two RAD011 Doses

The primary comparison will be mean change in HQ-CT as calculated via least square means comparing RAD011 low dose vs. placebo and RAD011 high dose vs. placebo at Week 34. Low dose and high dose groups will be compared to placebo at the two-sided 0.025 level so overall type 1 error is maintained at two-sided 0.05 level.

DMC Recommendation of one RAD011 Dose

The primary comparison will be mean change in HQ-CT as calculated via least square means comparing RAD011 vs. placebo at Week 34. RAD011 will be compared to placebo at the two-sided 0.05 level.

11.4.3. Secondary and Other Endpoints

All analyses of the secondary and other endpoints for continuous measures will be conducted analogous to the primary endpoint analysis, using, the baseline value of the relevant variable as a

covariate, and patient as a random effect. All analyses of the secondary and other endpoints will be described in the SAP.

11.4.4. Pharmacokinetic Analyses

All PK analyses will be described in the pharmacokinetic analysis plan prior to performing statistical analyses. A pharmacodynamic analysis may be completed to evaluate exposure with efficacy and safety.

11.4.5. Safety Analyses

The Safety Population will be used for all safety assessments. Safety assessments will be based on AEs, C-SSRS, vital signs, ECGs, and laboratory assessments. All analyses of safety will be described in the SAP.

All safety assessments will be descriptive, and no inferential statistics will be performed. All data listings will be provided for protocol specified safety data. The Medical Dictionary for Regulatory Activities will be used to classify all AEs with respect to System Organ Class (SOC) and preferred term. Adverse event summaries will include only treatment-emergent adverse events (TEAEs) by treatment group. Assessment of severity and relationship will also be presented. Adverse events leading to study discontinuation will also be summarized by SOC, PT, severity, and relationship.

The Columbia Suicide Severity Rating Scale will be used to evaluate suicidal ideation and intensity of ideation. Ideation and intensity will be grouped by categories, with separate groupings for the Baseline/Screening and the "Since Last Visit" questionnaires.

Clinical laboratory and vital signs will be summarized for the Safety Population for observed values and change from Baseline. Shifts from Baseline according to normal range criteria will also be presented for all patients in the Safety Population.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1. Study Monitoring

Monitoring and auditing procedures approved by the Sponsor will be followed, in order to comply with Good Clinical Practices (GCP) guidelines (ICH E6[R2]).

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal or remote visits from a representative or designee of the sponsor (site monitor) and will include review of the eCRFs for completeness and clarity, cross checking with source documents, and clarification of administrative matters will be performed. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Remote visits may require remote access to the patient's electronic medical record and other systems at the study sites. Deidentified and redacted source documentation may need to be provided to the Sponsor or its designee to complete remote monitoring activities.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, email, telephone, and fax).

Regulatory authorities, the IRB/IEC and other appropriate institutional regulatory bodies, and/or the sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its designee may conduct a quality assurance audit.

12.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IEC, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH-GCP, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

12.3. Institutional Review Board and Independent Ethics Committee

The PI must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent/assent form/process must be maintained by the Investigator and made available for inspection.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Ethics Review

This protocol was designed and will be conducted, recorded, and reported in compliance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, 1996; Guidelines for Clinical Safety Data Management, 1994; European Regulations and appropriate Ethics Committee, the Code of Federal Regulations (CFR 21 parts 50, 56, and 312) and any country specific regulations or laws.

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. If the Investigator directly submitted the protocol to an IRB or an IRC, he or she must submit written approval to the Sponsor or its designee before he or she can enroll any patient into the study. If the study protocol was submitted on behalf of the Sponsor or Investigator to local or central IRB or IEC, the Investigator must confirm IRB and/or IEC approval prior to enrolling patients in the study, in accordance with local laws and regulations.

The Investigator, or a Sponsor designee, will be responsible for submitting any amendment to the protocol or to the ICF to the IRB or IEC in accordance with local laws and regulations. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study and any written information to be provided to patients (e.g., food diaries). The protocol must be

re-approved by the IRB or IEC upon receipt of amendments and at the frequency required by local laws and regulations.

Initial IRB or IEC approval, and all materials approved by the IRB or IEC for this study, including the ICF and recruitment materials, must be maintained by the investigator and made available for inspection.

The PI at each study site is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the IP. The Sponsor or its designee will provide this information to the PI.

Progress reports will be provided to the IRB or IEC according to local laws and regulations.

13.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements.

The Investigator will be thoroughly familiar with the appropriate use of the IP as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. A TMF will be established at the beginning of the study, maintained for the duration of the study, and retained according to appropriate regulations.

13.3. Patient Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the patient to the patient’s physician or to other appropriate medical personnel responsible for the patient’s well-being.

Sponsor shall not disclose any confidential information on patients obtained during the performance of their duties in the clinical study without justifiable reasons.

Sponsor affirms the patient’s right to protection against invasion of privacy. Only a patient identification number and/or initials (where allowed by local or national regulations) will identify patient data retrieved by Sponsor. However, Sponsor requires the Investigator to permit Sponsor, designated representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

Sponsor will ensure that the use and disclosure of protected health information or of personal data obtained during a research study complies with the local federal and/or regional legislation related to the privacy and protection of personal information.

13.4. Written Informed Consent/Assent

Investigator(s) at each site will explain the nature of the study, answer all questions regarding the study, and ensure that the patient or their legally authorized representative is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study, in accordance with local regulations and GCP guidelines. Patients must also be notified

that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient or their legally authorized representative and the authorized person obtaining the informed consent must sign the ICF. The patient's signed and dated ICF must be obtained before conducting any study procedures. The investigator(s) must maintain the original, signed and dated ICF, and provide a copy the signed and dated ICF to the patient or their legally authorized representative.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study, as appropriate.

Investigators must document in the patient's medical record a statement that written informed consent was obtained before the patient was enrolled in the study, that no study procedures were performed prior to the patient signing the ICF, and the date the written consent was obtained. Investigators will also document in the patient's medical record a statement that patients were reconsented with new ICFs, and the time reconsent occurred, when reconsenting is required.

The Investigator obligations in this section are also be respected for patients providing assent.

13.5. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

14. DATA HANDLING AND RECORDKEEPING

14.1. Case Report Form Completion

The Sponsor or its designee will provide the clinical sites with access to the eCRFs for each patient. The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data reported in a patient's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

The investigator or designated representative should complete the eCRFs as soon as possible after information is collected. The Investigator must sign and date the eCRF to endorse the recorded data.

14.2. Inspection of Records

The Sponsor or its designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The PI agrees to allow the monitor to inspect the drug storage area, IP stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

14.3. Retention of Records

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation or according to applicable regulatory requirements.

If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

14.4. Substantial Amendments to the Protocol

A substantial amendment must be agreed to in writing by Sponsor and submitted to and approved by the respective regulatory authority and IRB/IEC before the amendment can be implemented. Written approval of a protocol amendment is not required prior to implementation of changes to the protocol which eliminate an immediate hazard to the study patient; however, approval must be obtained as soon as possible thereafter. Any amendments must also be signed by the PI.

15. PUBLICATION POLICY

All information regarding the IP is privileged and confidential information. The Investigator agrees to use this information to conduct the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee of Investigators participating in the study and representatives from the Sponsor may be formed to oversee the publication and presentation of the study results, which will reflect the experience of all participating clinical sites.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between the Sponsor and the Investigator and/or the Investigator's institution.

The Sponsor has full rights over any invention, discovery, or innovation, patentable or not, that may occur when performing the study.

16. DISSEMINATION OF STUDY DATA

Study results will be posted on the National Institutes of Health Protocol Registration and Results System website, ClinicalTrials.gov, to meet the FDAAA 801 and/or International Committee of Medical Journal Editors ICMJE requirements.

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18. APPENDICES

APPENDIX 1. SUMMARY OF PROTOCOL CHANGES

Table 13: Summary of Protocol Changes

Protocol Version (Date Issued)	Changes	Rationale
Version 1.0 (20 August 2021)	Original Protocol	Not applicable
Version 2.0 (13 September 2021)	Changed name of Sponsor from Radius Health, Inc. to Radius Pharmaceuticals, Inc.	To be in Alignment with the Radius IND filing
	Maintenance Period updated from 23 Weeks to 24 Weeks.	To align with study design.
	Arrow added to study schematic in both Phases between Tolerability Period and SCOUT-016 LTE study	Reflect potential participation of patients not eligible for randomization in the SCOUT-016 LTE study
	Section 5.7.2: added clarification of weeks during which dose reductions could be conducted	Clarify time frame for dose reductions during the Maintenance Period
	Section 5.8.4.1: added drug accountability assessment at Visit 5	dispensed during the Tolerability Period is returned to the site.
	Section 5.8.6: Modified Visits in Taper and Follow-Up Periods	Clarify and simplify assessments at visit time points
	Table 7: Changed visits in the Follow-Up Period to reflect changes in Section 5.7.2 and added assessments	Provide enhanced clarity on assessments to be performed
	Table 7: food diary reminder changed from Visit 4 to Visits 4, 7, 11, and 13.	To assist in proper food diary completion and collection.
	Table 7: added Drug accountability assessment at Visit 5	Confirm that all unused placebo dispensed during the Tolerability Period is returned to the site.
	Table 7: added Drug accountability assessment at Visit 15	Ensure that all IP is returned to site
	Section 7.1: updated language for IP administration to: “administered orally twice daily with food”, and removed “, within approximately 1 hour after a meal”	Clarify timing of administration of IP with regards to food
	Section 7.5: corrected dose administered during Tolerability Period.	Reflect dose to be administered of 0.1 mL/kg/day
	Section 8.3: Study Drug Storage updated to 2 - 8°C and added sentence to clarify additional information is provided in the Pharmacy Manual.	To ensure proper refrigerated storage at the site and recommend refrigeration in the home setting.
	Section 10.1: general formatting updates	

Protocol Version (Date Issued)	Changes	Rationale
	Section 10.2.2: changed start of AE collection from Visit 2 to Visit 1	Ensure full AE documentation
Version 3.0 (25Oct2021)	Section 5.8.2.1, specified that HQ-CT and ABC questionnaires must be completed a minimum of 14 days prior to visit 2	Clarify the exact time point
	Section 5.8.4.1, ABC-I will not be done at visit 5	Replaced by full ABC questionnaire
	Section 5.8.5.1, ABC will now be completed at visit 14	Replacing ABC-I questionnaire
	Sections 5.1, 5.8.3, 5.8.4.1, 6.4.1, 6.4.2, 11.2, specified that patient/caregiver completes HQ-CT	Consistency with other sections
	Section 6.1, Inclusion criterion 1 updated to read "Presence of a parent/legal guardian that is able to consent for their participation. Parent/caregiver/legal guardian can complete the required assessments throughout the study. Patient Consent/Assent will be obtained if the patient is 8 years of age or older and has the mental capacity to understand and sign a written consent/assent form and/or give verbal assent."	Clarify that a caregiver and/or legal guardian can assist in the consent/assent process
	Section 6.1, Inclusion criterion 2 updated to refer to age at time of consent	Age to be calculated at date of consent rather than screening
	Section 6.1, Inclusion criterion 5, updated timescale from "30 days" to "4 weeks" after the last dose	Consistency with other criteria
	Section 6.1, Inclusion criterion 6, updated IUD timescale to 12 weeks prior to dosing and continued used of approved contraceptive method to 4 weeks after last dose	Consistency with other criteria
	Section 6.1, Inclusion criterion 7, added "metabolic treatments that could affect appetite (including metformin), to list. Updated timescale from "at least 6 weeks prior to screening" to "at least 4 weeks prior to consent/ascent"	Clarify types of interventions and time frame
	Section 6.2, Exclusion criterion 2, within 4 weeks prior to consent/assent instead of screening	Clarify that time frame starts from the time of consent/assent
	Section 6.2, Exclusion criterion 5, removed reference to "drugs known to affect appetite or gastric emptying", update timing to within 4 weeks prior to consent/assent.	Clarify indication for weight loss and harmonized timelines with other criteria
	Section 6.2, Exclusion criterion 6, updated timescale to within 4 weeks of consent/assent	Harmonize timelines with other criteria

Protocol Version (Date Issued)	Changes	Rationale
	Section 6.2, Exclusion criterion 7, added "any significant", bullet a timeline updated to 4 weeks prior to consent /assent, bullet e updated to specify drugs taken orally	Clarify that comorbid conditions had to be clinically significant in the opinion of the investigator and harmonized timelines with other criteria
	Section 6.2, Exclusion criterion 9 updated to "At Screening, patients with age-matched hypertensive levels of systolic and/or diastolic blood pressure may be excluded at the Investigator's discretion if deemed to be in the best interest of the patient."	Clarify that blood pressure measurements should be evaluated using age-specific reference ranges, as needed
	Section 6.2, added Exclusion criterion 18 : "Participation in any other study involving an investigational product or device within 4 weeks or 5 half-lives (whichever is longer) of consent/assent or longer as required by local regulations"	Prevent patients from participating in multiple interventional studies at once
	Section 7.2.1, removed paragraph about concomitant treatment with valproate, valproic acid, or divalproex-containing products. Final paragraph updated to "patients who experience adverse events due to significant drug/drug interactions may have treatment discontinued while remaining on study"	Provide more general guidance to investigators
	Section 7.5, updated to read "To maintain the blind, multiple placebo groups were created to mimic the RAD011 groups: low volume (0.1 mL/kg/day), mid volume (0.2 mL/kg/day), and high volume (0.4 mL/kg/day). During the dose escalation period, the volume of blinded therapy for the mid volume and high volume placebo groups will increase in the same manner as the mid dose and high dose RAD001 groups, further ensuring blinding between RAD011 and placebo"	Clarify that only mid and high volume placebo groups would increase the administered volume
	Section 8.4, now specifies that IP should be taken with food	Clarify timing of administration of IP with regards to food
	Section 9.2.1, updated to refer to the irritability subscale of the ABC Questionnaire	To specify that the irritability measure is a subscale of the ABC and not a separate instrument
	Section 9.3.4, removed the sentence "Interpretation of DEXA scan results should include age, gender, and race-matched Z scores."	Interpretation to be performed per standard of care
	Section 10.1.9, cutoff age for the formulas updated to 17 years.	Alignment with central laboratory requirements
	Section 10.1.13.1, date and time of dosing will now be recorded in food diary.	Specify additional information to be documented

Protocol Version (Date Issued)	Changes	Rationale
	Section 10.2.1, AEs will be collected from time of consent/assent	Clarify the start of AE collection
	Section 13.4, title changed to "Written Informed Consent/Assent", added "The Investigator obligations in this section are also be respected for patients providing assent."	Clarify that the Investigator obligations that apply to consent also apply to assent.
	Table 6, footnote f added	Specify when the children's version of the C-SSRS should be used
	Table 7, footnote p added	Specify when the children's version of the C-SSRS should be used
Version 4.0 (10Feb2022)	Change logo of Radius and updated document version and date	Administrative change
	Synopsis	Consistency with other sections
	Section 4.1.2 edited secondary and other objectives to include CGI-S and CGI-C	Updated per FDA Comments of 26-Jan-2022 and 31-Jan-2022
	Section 5.1, 5.8.3, 5.8.4.1, Removed "However, patients not eligible for randomization for reasons other than a mean HQ CT score <13 may be offered participation in the long-term extension study (SCOUT 016)"	SCOUT-016 protocol requires patients complete SCOUT-015 to be eligible for participation in order to demonstrate long-terms safety for RAD011 and potential maintenance of efficacy
	Section 5.1, changed caretaker to caregiver	Administrative change
	Section 5.8.2.1, 5.8.5.1, added CGI-S Irritability	Updated per FDA Comments of 26-Jan-2022 and 31-Jan-2022
	Section 5.8.2.1, 5.8.4.1, added "Ghrelin samples will only be collected for Phase 3 patients at sites where proper collection is feasible"	DMC recommendation on dose will be made in Ph3. This allows testing of Ghrelin when it could potentially link to efficacy. It also accounts for operational complexity in obtaining samples at all sites.
	Section 5.8.2.1, 5.8.5.1, 9.5 added biomarker assessment	This will help to assess the potential anti-inflammatory effect of RAD011 on low grade inflammation (LGI) often present in subjects with PWS.
	Section 5.8.2.2, 6, removed method of diagnosis	Administrative change for clarity, updated to focus on the diagnosis
	Section 5.8.3.1, 5.8.5.1, added CGI-S Hyperphagia	Updated per FDA Comments of 26-Jan-2022 and 31-Jan-2022
	Section 5.8.5.1, added CGI-C Hyperphagia, CGI-C Irritability, and CaGI-C questionnaires	Updated per FDA Comments of 26-Jan-2022 and 31-Jan-2022
	Section 5.9, added COVID-19 impact assessment	Include flexibility for sites to conduct the trial during a pandemic
	Updated Table 6 and Table 7 and footnotes	Consistency with other sections

Protocol Version (Date Issued)	Changes	Rationale
	Section 6, removed abstinence and added double-barrier contraception	Updated per FDA Comments of 26-Jan-2022 and 31-Jan-2022
	Section 6.2, added neutropenia to exclusion	Updated per FDA Comments of 26-Jan-2022 and 31-Jan-2022
	Section 6.2, edited group home criteria	To allow patients living in a group home an opportunity to be eligible for participation while preserving the need for a consistent caregiver
	Section 6.3.2, added drug-induced liver injury	Updated per FDA Comments of 26-Jan-2022 and 31-Jan-2022
	Section 7.2, changed 6 weeks to 4 weeks for stable medication	Administrative change to correct typo
	Section 7.5.1, added breaking the blind	To ensure consistency with instructions provided to investigators within the Pharmacy Manual
	Section 9, 9.2.2, 9.3, 11.4.3, edited secondary and other objectives to include CGI-S and CGI-C. Editorial changes made for document consistency.	Updated per FDA Comments of 26-Jan-2022 and 31-Jan-2022. Administrative change
	Section 10.1.6, added clarity to C-SSRS scale for patients aged 6 and over.	Updated per FDA Comments of 26-Jan-2022 and 31-Jan-2022
	Section 10.2.1.5, added AESI for hepatic dysfunction and suicide ideation and behavior	Updated per FDA Comments of 26-Jan-2022 and 31-Jan-2022
	Section 10.2.9, added follow up for AE/SAE occurred during the course of all pregnancies.	To further substantiate safety follow-up in the event that a pregnancy occurs during the study
	Section 11.4.1 added “randomized”	Updated per FDA Comments of 26-Jan-2022 and 31-Jan-2022
	Section 11.4.2 specified the mITT will be analyzed based on the treatment policy estimand	Updated per FDA Comments of 26-Jan-2022 and 31-Jan-2022
Version 5.0 (10Mar2022)	Change of version and date	Administrative change
	Synopsis	Consistency with other sections

Protocol Version (Date Issued)	Changes	Rationale
	Section 4.1.2.2 Added the following secondary objectives: • Effect of RAD011 on Clinician Global Impression of Change (CGI-C) in Hyperphagia • Effect of RAD011 on Clinician Global Impression of Severity (CGI-S) of Hyperphagia Scale Removed the following secondary objective: • Effect of RAD011 on Caregiver Global Impression of Change (CaGI-C)	Updated per FDA Comments of 24-Feb-2022
	Section 4.1.2.3 Added the following other objective: • Effect of RAD011 on Caregiver Global Impression of Change (CaGI-C) in Hyperphagia Modified the Global Impression of change and severity in hyperphagia and irritability from clinical to caregiver assessments Removed the following other objective: • Effect of RAD011 on Clinical Global Impression of Change (CGI-C) in Hyperphagia Scale	Updated per FDA Comments of 24-Feb-2022
	Figures 2 and 3: updated figure to remove dotted line leading from the Tolerability Period to the SCOUT-016 LTE study	Patients who do not complete the Maintenance Period are no longer eligible to participate in the SCOUT-016 LTE study
	Sections 5.8.2.1, 5.8.4.1: changed CGI-S Irritability to CaGI-S Hyperphagia	Align with change in endpoints
	Section 5.8.5.1: changed CGI-S Irritability to CaGI-S Hyperphagia and CGI-C Irritability to CaGI-C Irritability	Align with change in endpoints
	Tables 6 and 7: updated Schedules of Assessments to reflect changes in endpoints and associated assessments	Align with change in endpoints
	Section 6.1, Inclusion criterion 7: changed stability period for GH, psychotropic therapy, metabolic treatments that could affect appetite, and other treatments including thyroid hormone from 4 weeks to 90 days	Updated per FDA Comments of 24-Feb-2022
	Section 6.1, Inclusion criterion 8: changed stability period for non-medical interventions from 4 weeks to 90 days	Updated per FDA Comments of 24-Feb-2022
	Section 6.2, Exclusion criteria 2, 5, and 6: changed exclusion period from 4 weeks to 90 days	Updated per FDA Comments of 24-Feb-2022

Protocol Version (Date Issued)	Changes	Rationale
	Section 6.2, Exclusion criterion 7a): removed the 4-week time prior to consent/assent period for diagnosis of a new respiratory, heart, or psychiatric disease	These comorbid conditions might interfere with patient care and patient assessments, regardless of the time of diagnosis
	Section 7.2: changed stability period from 4 weeks to 90 days	To align with inclusion criterion 7
	Section 9.2.2: updated wording in change in hyperphagia and changed CGI-C to CaGI-C. Removed text detailing CGI 7-point scale.	To align with change in endpoints
	Section 9.2.3: Moved CGI-S description to Section 9.2.3	To align with change in endpoints
	Section 9.3.1: updated wording for caregiver impression of change and severity scales	To align with change in endpoints
	Overall: formatting and administrative changes	To align with other protocol changes and ensure consistency

APPENDIX 2. EVALUATION OF SEIZURE HISTORY AND SEIZURE PATIENT HISTORY

Medical History Questionnaire

As part of the Medical History assessments, the following questions must be asked and documented in the eCRF:

- During the last 12 months did you experience any seizure that was medically documented? Yes/No
- What was/were the type/s of seizure you experienced during the last 12 months? Please list all types.
- Was/were the seizure(s) treated? Yes/No
- Are you currently receiving any seizure medications? Please list all.
- Has the dose for your anti-seizure medication changed during the last 6 months?

Seizure Patient Impression

At the End of Study/Week 34 Visit (Visit 14), patients with a seizure history must be asked the following questions and documented in the eCRF:

- Based on your study experience, has your impression of seizures changed in any way (occurrence, severity, etc.):
    - No change
    - Became better
    - Became worse

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