TECHNICAL RESOURCES INTERNATIONAL, INC.

PROTOCOL SUMMARY

Title	Evaluation of Efficacy and Safety of rapid hormonal cycling (RHC) vs RHC + EndroCream for the treatment of Severe Empathy Withdrawal
Description of Study Design	This is a Phase I, 2-arm open-label clinical trial of standard of care rapid hormonal cycling (RHC) vs RHC + EndroCream as treatment for IGR-confirmed Severe Empathy Withdrawal
Objectives	**Primary:** 1. To evaluate the safety and efficacy of the rapid hormonal cycling as evidenced by Response, per Empathy Specific Antigen (ESA) levels. 2. To assess safety and reactogenicity to investigational VS standard of care combination therapies. **Secondary:** 1. To assess changes in pre to post-treatment immune levels **Additional / Correlative:** 1. To assess correlates in population sample statistical data, per questionnaire (regarding demographic, medical history, mood and sex & gender criteria), both before/after rapid hormonal cycling and monthly during active treatment.
Population	300 males or females, between 13 and 70 years old, with IGR-confirmed Severe Empathy Withdrawal who are otherwise healthy (not immunocompromised)
Sites	15 Sites (9 in United States, 3 in United Kingdom, 2 in France, & 1 in Singapore)
Study Duration	Participants will receive combination therapy for a period of 6 months, and then must return to clinical site for study follow-up visits at 3, 6 and 12 months after intervention has ended. Expected total duration of study participation is 18 months. Enrollment is expected to complete within 36 months of study initiation. Note each intervention cycle = 28 days long (4 weeks), and equal to one "month".
Randomization	Participants in Arm A will receive monthly rapid hormonal treatment for 6 months. Participants in Arm B will receive RHC + EndroCream for 6 months. **Both arms require participants return to clinical site for study follow-up visits at 3, 6 and 12 months after intervention has ended.*
Ages Eligible for Study	Participants between 13 and 70 years of age (teenagers, adults, seniors).
Genders Eligible for Study	All; note there is an additional statistical (*optional to all participants and based on questionnaire response*) endpoint regarding gender identification.

Inclusion Criteria:

1. Males and/or females between the ages of 13-70.
2. Confirmed Severe Empathy Withdrawal, per IGR-assessment of depleted Empathy Specific Antigen (serum-ESA) levels in the bloodstream.
    a. Severe Empathy Withdrawal in this study is limited to confirmed, severe (Stage III-IV) diagnosis, per International Golden Rule (IGR) assessment
    b. Screening IGR-assessment must be confirmed first by local site PI, and second by central medical monitor, prior to subsequent randomization and enrollment.
    c. Please include a (site PI verified/signed) completed "IGR Confirmation Assessment form" (located in Protocol Appendix A) with completed Eligibility Checklist and accompanying source documentation submitted to the medical monitor (MedicalMonitor@Sponsor.com) during screening.
3. The effects of the Rapid Hormonal Cycling combined with this study's investigational agent, on the developing human fetus in subjects with Severe Empathy Withdrawal are unknown. For this reason and because there have been no adequate and well-controlled studies RCH + EndroCream in pregnant women, women who are able to become pregnant must have a confirmed negative pregnancy test result prior to enrollment and must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation.
4. Axillary temperature ≤37℃.
5. Adult participants and the parent(s) or guardians of pediatric participants are able to understand and sign informed consent.
6. Willing and able to comply with trial protocol and follow-up.
7. Screening ALT within lab normal limits.

Exclusion Criteria:

1. Previous treatment with rapid hormonal cycling, or EndroCream, for any indication.
2. Medical History associated with endocrine system determined as clinically significant by treating physician and confirmed by study monitor. This includes history of allergic reactions.
3. Use of commercially available endocrine gel or testosterone supplement within 180 days preceding first dose
4. Prior use, or participation in a clinical trial, of an investigational agent that blocks androgen synthesis
5. Absolute neutrophil count < 1,000/µL, or platelet count < 50,000/µL, or hemoglobin<8 g/dL) at the Screening visit

6. Gastrointestinal disorder affecting absorption (e.g., gastrectomy, active peptic ulcer disease within last 3 months)
7. Active and acute (currently requiring concomitant medication or other clinically-significant intervention) respiratory system diseases, acute infection or active chronic, cardiovascular diseases, liver and kidney diseases, skin diseases, HIV.
8. History of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke, significant brain trauma) at any time in the past. Also, history of loss of consciousness or transient ischemic attack within 12 months of Day 1 visit;
9. Pregnant or intention to get pregnant. Pregnant women are excluded from this study because the safety and effectiveness of Rapid Hormonal Cycling (RCH), both alone or in combination with EndroCream, has not been established in pregnant women.

Treatment

1. Standard of Care – Rapid Hormonal Cycling (RHC)
    a. GnRH: Goserelin is a gonadotropin-releasing hormone analogue, and the LHRH analogue therapy in this trial
        i. goserelin (Other Names: ZOLADEX)
            1. Dosing: standard dose of Zoladex for Severe Empathy Withdrawal is 3.6 mg every 4 weeks (28 days)
            2. Implant: implant is designed to slowly release the medicine over either a 4-week period. It is inserted just beneath the skin on the stomach, and releases the medicine as it dissolves in the body.
    b. Bicalutamide
        i. Bicalutamide tablets 50 mg daily is indicated for use in combination therapy with a luteinizing hormone-releasing hormone (LHRH) analog for the treatment of Stage D 2 metastatic carcinoma of the prostate.
        ii. Dosing: one 50 mg tablet once daily (morning or evening), with or without food. It is recommended that Bicalutamide tablets be taken at the same time each day. Treatment with Bicalutamide tablets should be started at the same time as treatment with an LHRH analog. If a dose of Bicalutamide is missed, take the next dose at the scheduled time. Do not take the missed dose and do not double the next dose.
        iii. Drug Diary: a drug diary is located in the protocol appendix, for use in determining and maintaining subject compliance to taking oral drug at home

2. Investigational Product (IP)
    a. EndroCream
        i. Dosing: EndroCream is a topical cream, applied to specific areas of the body B.I.D. (twice daily, separated by 12 hours).
        ii. Background: EndroCream is a is a topical estradiol replacement therapy. 17-beta estradiol (estradiol) is a form of oestrogen, a female sex hormone produced mainly in the ovaries. Males produce estradiol as well, but at much lower levels and non-cyclically. In females, estradiol aids in the formation of secondary sex characteristics such as breast development and regulation of the menstrual cycle. In males, it helps govern sperm maturation and on a much smaller scale, reproductive function. While primarily viewed as a female hormone, estradiol has many nonreproductive influences on various physiological systems including brain development, blood coagulation and bone growth. The 17-beta estradiol (estradiol) in EndroCream (0.3%) is the same as the that which the humanody makes naturally.
        iii. IP Storage
            1. EndroCream will be stored in secure temperature monitored pharmacy environments at room temperature (20–25 °C / 68–77 °F) until needed.
            2. The temperature of the storage unit must be monitored during the duration of the trial. In the event of any temperature excursions, study IP should not be administered/given to patient, and the investigator (or the responsible study team delegate) should notify each of the 3 following:
                a. Sponsor: (EndroCreamCoordinator@sponsor.com)
                b. Medical Monitor / Coordinating Center PI: (medicalmonitor@coordinatingcenter.edu)
                c. Coordinating Center Representative: (mainsitecoordinator@coordinatingcenter.edu).

Laboratory Evaluations

Instructions for packaging and shipment (including acceptable windows) of all laboratory procedures are included in the Pharmacy Manual (Appendix X) and pharmacist training will be documented at SIV, prior to activation

Clinical Laboratory Evaluations

One screening lab, ALT, performed by the site laboratory. At screening or on the day of, but prior to, first vaccination, ALT [SGPT] will be assessed and the value must be confirmed as within normal limits of the site laboratory reference ranges prior to randomization and vaccination. Approximately 4 mL of venous blood will be collected.

Urine or serum pregnancy tests will be performed within 24 hours prior to each monthly administration of Rapid Hormonal Cycling. For all female subjects of childbearing potential, results must be negative and known prior to study treatment. Females found to become pregnant while on study must have treatment stopped and taken off study.

Safety labs will be performed by sponsor-approved local (to site) laboratory. Safety labs will include white blood cell (WBC) count, neutrophils and lymphocytes, platelets, prothrombin time (PT) and partial thromboplastin time (PTT), and sodium, potassium, creatinine, ALT [SGPT], total protein, and albumin. Approximately 17 mL of venous blood will be collected.

Clinical laboratory evaluations for safety will be performed at screening visit, and at the start of each treatment cycle at C1D1 (Month1/Day1), C2D1(Month2/Day29), C3D1 (Month3/Day57), C4D1 (Month4/Day85), C5D1(Month5/Day113), C6D1 (Month6/Day131). Clinical lab evaluations for safety will have a +/- 5day acceptable window.

Follow-up lab evaluations will be performed after end of study intervention at 3 (90days), 6 (180days) and 12 (360days) months post-intervention. Post-treatment follow-up lab evaluations will have a +/- 30day acceptable window.

Special Assays or Procedures

Antibody assays (Immunity PK samples), to determine presence of active immunosuppression while on study, will be performed by a central laboratory (Central Lab USA in New York, New York). Blinded samples will be provided to the central lab for analysis, per lab manual instruction.

Optional / Correlative Study Participant Evaluations

For enrolled participants who agree to participate in this study's optional questionnaire (regarding demographic, medical history, mood and sex & gender criteria), Questionnaire will be collected at each protocol study visit only for enrolled subjects who sign or initial (per local IRB regulation), and date, the "Optional Correlative Study" agreement ***on page X in the ICF***.

Adverse Events Common Side Effects of RHC and/or EndroCream

This is a Phase I study, and all toxicities (including out of range labs) should be collected and assessed by local site PI, for grading and causality to both standard of care (RHC) and study IP (EndroCream). *Please contact medical monitor for clarification*.

Response

Response is measured per confirmed serum Empathy Specific Antigen (serum-ESA) levels measured in the blood at C1D1 (Month1/Day1), C2D1(Month2/Day29), C3D1 (Month3/Day57), C4D1 (Month4/Day85), C5D1(Month5/Day113), C6D1 (Month6/Day131) timepoints.

- Complete Response:
  Normalization of serum-ESA (< or = to 500 for patients with IGR-confirmed Severe Empathy Withdrawal) as confirmed by central lab
- Partial Response:
  Decrease in serum-ESA value by > or = to 30% from baseline value (without normalization)
- Stabilization:
  Patients who do not meet the criteria for PR or PROG for at least 90 days will be considered stable.
- Progression:
  Worsening of serum-ESA by > or = to 10% from baseline value

<u>Removal of subjects for progression:</u>

Subjects with confirmed progression will be taken off study immediately, and follow-up assessment schedule will be subsequently initiated per protocol, as long as subject does not withdraw consent.

Monitoring

External review (on-site or remote) of clinical sites will be conducted by two subcontracted CROs: *Pro Pharma CRO* will monitor USA sites on behalf of the sponsor, while *Worldwide CRA, Inc* will conduct monitoring at sites outside the USA. Site PI and delegated staff must ensure monitors access to physical site, affiliated Pharmacy and any/all relevant internal database containing relevant, study-specific source documentation during site visits and review visits. If site not contacted within 6 months of study activation by study monitor, please contact coordinating center or medical monitor.