

# **BioCure Pharmaceuticals**

**INVESTIGATIONAL PRODUCT: TCX-301**

## **A Phase III, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of TCX-301 in Subjects Neuropathic Pain Associated with Diabetic Peripheral Neuropathy**

Sponsor: BioCure Pharmaceuticals

This is a confidential document.

**INVESTIGATOR SIGNATURE PAGE:**

I have read and understand the **Phase III, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of TCX-301 in Subjects Neuropathic Pain Associated with Diabetic Peripheral Neuropathy** dated 15Jan2024. I am responsible for proper conduct of the study at my site. I will not deviate from or make changes to the protocol without written approval from IRB, except where necessary to eliminate an immediate hazard to subjects. I understand and will follow ICH GCP guidelines and code of federal regulations. I agree to adhere to the protocol and maintain confidentiality.

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Printed Name of Investigator

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Signature of Investigator

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Date

## Protocol

### **Introduction:**

Peripheral neuropathy is nerve damage caused by chronically high blood sugar and diabetes. It leads to numbness, loss of sensation, and sometimes pain in your feet, legs, or hands. It is the most common complication of diabetes.

About 60% to 70% of all people with diabetes will eventually develop peripheral neuropathy, although not all suffer pain. Yet this nerve damage is not inevitable. Studies have shown that people with diabetes can reduce their risk of developing nerve damage by keeping their blood sugar levels as close to normal as possible.

Chronically high blood sugar levels damage nerves not only in your extremities but also in other parts of your body. These damaged nerves cannot effectively carry messages between the brain and other parts of the body.

This means you may not feel heat, cold, or pain in your feet, legs, or hands. If you get a cut or sore on your foot, you may not know it, which is why it's so important to inspect your feet daily. If a shoe doesn't fit properly, you could even develop a foot ulcer and not know it. The consequences can be life-threatening. An infection that won't heal because of poor blood flow causes risk for developing ulcers and can lead to amputation, even death.

### **Number of Sites:**

80

### **Number of Patients:**

400

### **Phase:**

III

### **Primary Objective:**

To evaluate the efficacy of TCX-301 70mg BID versus placebo in treating neuropathic pain associated with diabetic peripheral neuropathy.

### **Secondary Objective:**

Protocol Version 1.0 dated 15Jan2024

## Protocol

To assess the effects of TCX-301 70mg BID versus placebo on pain characteristics and sleep disturbances.

### Study Design:

The study will be a 13 to 16 week study, including a 1 to 4 week screening period, followed by a 12 week double blind, randomized, placebo controlled treatment Period

### Inclusion Criteria

1. Must provide a written informed consent.
2. Subject is  $\geq 18$  and  $\leq 75$  years of age.
3. Diagnosis of Type 2 Diabetes for at least 1 year prior to screening visit.
4. At least moderate pain intensity over the last week as assessed by PGI-S at Visit 1.
5. Hemoglobin A1c (HbA1c)  $\leq 11\%$  (measured at Visit 1).
6. Presence of pain due to diabetic neuropathy for at least 6 months prior to screening.
7. Body mass index  $\leq 40$

### Exclusion Criteria

1. Diagnosis of Type 1 Diabetes
2. Current diagnosis of a major psychiatric disorder (including schizophrenia and/or bipolar disorder)
3. History of hypoglycemia that disturbed consciousness, or ketoacidosis requiring hospitalization within the past 3 months.
4. Pulse rate  $< 45$  bpm or  $> 90$  bpm
5. History of severe renal impairment defined by renal dialysis or peritoneal dialysis or has undergone renal transplant.

### Study Visits

#### Visit 1 (Screening):

Subjects will be asked to provide written informed consent for this study before any required procedures are performed. This study may employ electronic informed consent. Electronic or



## Protocol

digital signatures may be captured indicating the patient's willingness to participate in the clinical trial. Employees, contractors or site employees are not eligible to participate.

After providing informed consent, subjects will participate in a screening visit where medical history, concomitant medications, scales and eligibility will be assessed. Subjects who meet eligibility and are taking any analgesic medications for their pain related to diabetic neuropathy will then be required to discontinue the analgesic medication for two weeks and then continue screening. Subjects taking no concomitant analgesic medication for their painful diabetic neuropathy may continue screening.

Subjects will be dispensed acetaminophen to be used as a rescue medication (RM) and will be instructed to take no more than 2 g/day (one to two 500 mg tablets every 6 hours **as needed** up to 4 tablets total) for DPN related pain.

### Screening Procedures:

- Informed Consent
- Assess inclusion/exclusion criteria
- Demographic
- Medical History
- Height
- Body Weight
- Vital signs (blood pressure and pulse after sitting or lying supine for at least 5 minutes)
- Physical Examination
- Triplicate ECG (at least 2 minutes apart)
- Blood Collection (8 hour fast) - hematology, serum chemistry, hemoglobin A1c (HbA1c), urine sample for urinalysis
- Discontinue all concomitant medications
- Dispense rescue medication (acetaminophen)
- Brief Pain Inventory (BPI) - DPN
- Patient Global Impression of Severity (PGI-S)
- Concomitant Medications
- Adverse Events

### Baseline Visit: Week 0/Visit 2:

Study personnel will verify eligibility with the inclusion/exclusion criteria when subjects are on site and perform safety assessments prior to randomization.

## Protocol

The appropriate use of rescue medication will be assessed by inventory of the returned tablets, as well as by subject interview. Subjects will be asked non leading questions to assess potential adverse events. Use of concomitant medications will be documented.

Subjects that test positive for amphetamines, benzodiazepines, psychoactive cannabinoids, opiates, PCP, cocaine, or barbiturates, will not be allowed to continue in the study.

### Procedures:

- Vital signs (blood pressure and pulse after sitting or lying supine for at least 5 minutes)
- ECG (after at least 5 minutes in supine position)
- Blood Collection (8 hour fast) - hematology, serum chemistry, hemoglobin A1c (HbA1c), urine sample for urinalysis
- Re-dispense rescue medication (acetaminophen)
- Brief Pain Inventory (BPI) - DPN
- Randomization (Subjects will be randomized to 70 mg of TCX-301 or placebo)
- Dispense first dose of IP in clinic
- Dispense investigational product (IP)
- Return rescue medication and perform accountability
- Patient Global Impression of Severity (PGI-S)
- Concomitant Medication
- Adverse Events

### Treatment Period: Week 2/Visit 3:

Subjects will be contacted by the clinic study staff via telephone or videoconference at the end of Week 2 (Visit 3) for assessment of compliance with study drug, rescue medication use and diary entries by interview. Subjects will be instructed to continue to take one capsule of the study drug by mouth twice daily throughout the study.

The subject will be reminded not to exceed 2 g/day (one to two 500mg tablets every 6 hours as needed up to 4 tablets total) for DPN related pain.

### Procedures:

- Concomitant Medication
- Adverse Events



## Protocol

### Treatment Period: Week 4/Visit 4:

The appropriate use of rescue medication will be assessed by inventory of the returned tablets, as well as by subject interview. Subjects will be asked non leading questions to assess potential adverse events. Use of concomitant medications will be documented.

Subjects that test positive for benzodiazepines inconsistent with protocol specified allowed prescriptions, psychoactive cannabinoids inconsistent with reported use, opioids, PCP, cocaine, or amphetamines, will not be allowed to continue in the study.

#### Procedures:

- Vital signs (blood pressure and pulse after sitting or lying supine for at least 5 minutes)
- ECG (after at least 5 minutes in supine position)
- Blood Collection (8 hour fast) - hematology, serum chemistry, hemoglobin A1c (HbA1c), urine sample for urinalysis
- Re-dispense rescue medication (acetaminophen)
- Brief Pain Inventory (BPI) - DPN
- Dispense investigational product (IP)
- Return rescue medication and perform accountability
- Patient Global Impression of Severity (PGI-S)
- Concomitant Medication
- Adverse Events

### Treatment Period: Week 8/Visit 5:

The appropriate use of rescue medication will be assessed by inventory of the returned tablets, as well as by subject interview. Subjects will be asked non leading questions to assess potential adverse events. Use of concomitant medications will be documented.

Subjects that test positive for benzodiazepines inconsistent with protocol specified allowed prescriptions, psychoactive cannabinoids inconsistent with reported use, opioids, PCP, cocaine, or amphetamines, will not be allowed to continue in the study.

#### Procedures:

- Vital signs (blood pressure and pulse after sitting or lying supine for at least 5 minutes)
- ECG (after at least 5 minutes in supine position)
- Blood Collection (8 hour fast) - hematology, serum chemistry, hemoglobin A1c (HbA1c), urine sample for urinalysis
- Re-dispense rescue medication (acetaminophen)

## Protocol

- Brief Pain Inventory (BPI) - DPN
- Dispense investigational product (IP)
- Return rescue medication and perform accountability
- Patient Global Impression of Severity (PGI-S)
- Concomitant Medication
- Adverse Events

### Treatment Period: Week 12/Visit 6 or Early Termination Visit:

During week 12 (visit 6) or Early Termination Visit, subjects will return to the clinic for assessment of compliance with study drug and rescue medication use. The appropriate use of study drug and rescue medication, as well as by subject interview.

A safety follow-up telephone call will be made to the subject within 7-10 days and then approximately 30 days after Visit 6/Week 12 to assess for any AE/SAE closure and any newly reported SAEs.

### Procedures:

- Body Weight
- Vital signs (blood pressure and pulse after sitting or lying supine for at least 5 minutes)
- Physical Examination
- ECG (after at least 5 minutes in supine position)
- Blood Collection (8 hour fast) - hematology, serum chemistry, hemoglobin A1c (HbA1c), urine sample for urinalysis
- Brief Pain Inventory (BPI) - DPN
- Return rescue medication and perform accountability
- Concomitant Medication
- Adverse Events

### Investigational Product

TCX-301 70 mg oral capsules, single capsule twice daily by mouth

### List of Disallowed Analgesic Medications

Washout of the following disallowed analgesics should be completed during screening, with the last dose being at least 2 weeks prior to randomization.

- Amphetamines
- Benzodiazepines



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- Cannabinoid Metabolites
- Opiates
- Phencyclidine (PCP)
- Barbiturates
- Cocaine Metabolites
- Topical therapies: topical capsaicin, local anesthetic lidocaine

Schedule of Events (see attached)

Schedule of Events

| Study Period                                                                                                      | Screening      | Baseline  | Treatment Period |            |            |             |
|-------------------------------------------------------------------------------------------------------------------|----------------|-----------|------------------|------------|------------|-------------|
|                                                                                                                   | -1 to -4 Weeks | Week 0    | Week 2           | Week 4     | Week 8     | Week 12/E T |
| <b>Study Week (Day)</b>                                                                                           | (-28 to -1)    | (1 +/- 2) | (14 +/- 2)       | (28 +/- 4) | (56 +/- 4) | (84 +/- 4)  |
| <b>Study Visit</b>                                                                                                | Visit 1        | Visit 2   | Visit 3          | Visit 4    | Visit 5    | Visit 6     |
| Informed Consent (prior to any study procedure)                                                                   | X              |           |                  |            |            |             |
| Assess inclusion/exclusion criteria                                                                               | X              |           |                  |            |            |             |
| Demographic characteristics                                                                                       | X              |           |                  |            |            |             |
| Medical History                                                                                                   | X              |           |                  |            |            |             |
| Height                                                                                                            | X              |           |                  |            |            | X           |
| Body Weight                                                                                                       | X              |           |                  |            |            | X           |
| Vital signs (blood pressure and pulse after sitting or lying supine for at least 5 minutes)                       | X              | X         |                  | X          | X          | X           |
| Physical Examination                                                                                              | X              |           |                  |            |            | X           |
| Triplicate ECG (at least 2 minutes apart)                                                                         | X              |           |                  |            |            |             |
| ECG (after at least 5 minutes in supine position)                                                                 |                | X         |                  | X          | X          | X           |
| Blood Collection (8 hour fast) - hematology, serum chemistry, hemoglobin A1c (HbA1c), urine sample for urinalysis | X              | X         |                  | X          | X          | X           |
| Discontinue all concomitant analgesic medications                                                                 | X              |           |                  |            |            |             |
| Dispense/Re-dispense rescue medication (acetaminophen)                                                            | X              | X         |                  | X          | X          |             |
| Brief Pain Inventory (BPI) - DPN                                                                                  | X              | X         |                  | X          | X          | X           |
| Randomization (Subjects will be randomized to 70 mg of TCX-301 or placebo)                                        |                | X         |                  |            |            |             |
| Dispense first dose of IP in clinic                                                                               |                | X         |                  |            |            |             |
| Dispense investigational product (IP)                                                                             |                | X         |                  | X          | X          |             |
| Return rescue medication and perform accountability                                                               |                | X         |                  | X          | X          | X           |
| Patient Global Impression of Severity (PGI-S)                                                                     | X              | X         |                  | X          | X          |             |
| Concomitant Medication                                                                                            | X              | X         | X                | X          | X          | X           |
| Adverse Events                                                                                                    | X              | X         | X                | X          | X          | X           |

REFERENCES:

Introduction: <https://www.webmd.com/diabetes/peripheral-neuropathy-risk-factors-symptoms>