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| **Full Title:** | A Phase II, Placebo-, Real-World Data Controlled study of Beroclin in subjects with early Parkinson disease |
| **Trial Acronym:** | ReCoPaD |
| **Sponsor Protocol Identifier:** | CB0321 |
| **Version Number:** | Version 1.0 |
| **Version Date:** | 28 February 2025 |
| **Compound Code(s):** | B2513 |
| **Compound Name(s):** | Beroclin |
| **Sponsor Name and Address:** | ClinLine  Van der Valk Boumanweg 15  2352 JA Leiderdorp  The Netherlands |
| **Regulatory Agency Identifier Number(s):** | *This is a test protocol an not used for actual study execution. It is based on a number of publicly available Parkinson example study protocols and is not intended to resemble a specific existing drug or a study.* |
| **Sponsor Approval:** | Not applicable |

Table of Contents

[1 Protocol Summary 9](#_Toc199945011)

[1.1 Protocol Synopsis 9](#_Toc199945012)

[1.1.1 Primary and Secondary Objectives and Estimands 9](#_Toc199945013)

[1.1.2 Overall Design 9](#_Toc199945014)

[1.2 Trial Schema 9](#_Toc199945015)

[1.3 Schedule of Activities 10](#_Toc199945016)

[2 INTRODUCTION 12](#_Toc199945017)

[2.1 Purpose of Study 12](#_Toc199945018)

[2.2 Assessment of Risks and Benefits 12](#_Toc199945019)

[3 STUDY Objectives and Associated Estimands 13](#_Toc199945020)

[3.1 Primary Objective(s) and Associated Estimand(s) 13](#_Toc199945021)

[3.2 Secondary Objective(s) and Associated Estimand(s) 13](#_Toc199945022)

[3.3 Exploratory Objective(s) 13](#_Toc199945023)

[4 STUDY Design 14](#_Toc199945024)

[4.1 Description of Study Design 14](#_Toc199945025)

[4.2 Rationale for Study Design 14](#_Toc199945026)

[4.3 Trial Stopping Rules 14](#_Toc199945027)

[5 Study Population 14](#_Toc199945028)

[5.1 Inclusion Criteria 14](#_Toc199945029)

[5.2 Exclusion Criteria 15](#_Toc199945030)

[6 StUDY Intervention And Concomitant Therapy 15](#_Toc199945031)

1. Protocol Summary
   1. Protocol Synopsis
      1. Primary and Secondary Objectives and Estimands

Primary objective:

* To evaluate the effect of intravenous infusions of Beroclin administered once daily on motor symptoms in subjects with early stage Parkinson’s disease.

Secondary objective:

* To evaluate the safety and tolerability of intravenous infusions of Beroclin administered once daily in subjects with early stage Parkinson’s disease.
  + 1. Overall Design

This is a open-label phase 2 study to assess efficacy and safety of multiple infusions of Beroclin vs Placebo for the treatment of Parkinson’s disease.

The design for the interventional arm includes a screening period of up to 4 weeks, a 12-week treatment period, and a safety Follow-up period of 8 weeks after the last investigational product administration.

For the External Control arm, corresponding patients are selected from the MIMIC data source. Patient are included in the external control cohort when all eligibility criteria are met and sufficient number of visits and data is available to match the interventional arm.

The interventional arm will be open to enroll 24 eligible participants diagnosed with Parkinson’s disease. Eligible external Control arm subjects will be matched to interventional control arm subjects based on propensity score weighting (PSW) in a ratio of 3 to 1. This results in a total of 96 subjects are expected to be included in the final analysis.

* 1. Trial Schema

12 weeks

8 weeks

4 weeks

Interventional arm

Follow-up

Weekly Beroclin infusion

Screening

External control arm

Observational data collection

Screening

* 1. Schedule of Activities

**Schedule of Activities: Interventional Arm**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Period | Screening | Treatment1) | | | | Follow-up2) |
| Timing /  Activities | D-28 to  D-1 | Week 1 | Week 2-4 | Week 6 | Week  7-11 | Week 12, 16, 20 |
| **Administrative** |  |  |  |  |  |  |
| Informed Consent | X |  |  |  |  |  |
| Demographics | X |  |  |  |  |  |
| Eligibility | X |  |  |  |  |  |
| Medical History | X |  |  |  |  |  |
| Previous and   concomitant   medication | X | X | X | X | X | X |
| adverse events | X | X | X | X | X | X |
| **Safety** |  |  |  |  |  |  |
| Hematology/  Biochemistry | X | X |  | X |  | X |
| Vital Signs | X | X |  | X |  | X |
| *Assessments to be added* |  |  |  |  |  |  |
| **Efficacy** |  |  |  |  |  |  |
| UPDRS3) | X | X |  | X |  | X |
| Epworth   Sleepiness Scale | X | X |  | X |  | X |
| C-SSRS4) | X | X |  | X |  | X |
| PDQ-395) | X | X |  | X |  | X |
| **Study Medication** |  |  |  |  |  |  |
| Beroclin Infusion6) |  | X | X | X | X |  |
| Dose management  log |  | X | X | X | X |  |

1) Infusion of study medication and corresponding assessments on Day 1 (+/- 1 day) of every week.

2) Assessments at Day 1 (+/- 3 Days) of planned weeks.

3) UPDRS: Unified Parkinsons Disease Rating Scale

4) C-SSRS: Columbia Suicidality Severity Rating Scale

5) PDQ-39: Parkinson’s disease Questionnaire

6) The required dose of Beroclin will be dissolved in 100 mL and will be administered over 2h while patients are in semi-posine position.

**Schedule of Activities: Observational Arm**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Period | History | | Observation period | | |
| Timing /  Activities | ScreeningWithin last 3 years | Baseline  Within last 3 months | Index Visit | Week 6 1) | Week 12, 16, 20 2) |
| **Administrative** |  |  |  |  |  |
| Demographics |  |  | X |  |  |
| Eligibility |  |  | X |  |  |
| Medical History | X |  |  |  |  |
| Previous and   concomitant   medication3) | X |  | X | X | X |
| adverse events3) |  |  | X | X | X |
| **Safety** |  |  |  |  |  |
| Hematology/  Biochemistry |  | X | X | X | X |
| Vital Signs |  | X | X | X | X |
| *Assessments to be added* |  |  |  |  |  |
| **Efficacy** |  |  |  |  |  |
| UPDRS4) |  | X | X | X | X |
| Epworth   Sleepiness Scale |  | X | X | X | X |
| C-SSRS5) |  | X | X | X | X |
| PDQ-396) | X |  | X | X | X |

1) All observations between index date and week 10 (Day 70 inclusive) will be collected for review and potential analysis. The closest value will be used for analysis. Imputation will be considered if values are outside the time window of +/- 4 days.

2) All observations between week 10 and week 24 (Day 168 inclusive) will be collected for review and potential analysis. Imputation will be considered if values are outside the time window of +/- 7 days of week 12, 16 and 20.

3) All observations for the complete history period as well as the observation period will be collected.

4) UPDRS: Unified Parkinsons Disease Rating Scale, if available

5) C-SSRS: Columbia Suicidality Severity Rating Scale, if available

6) PDQ-39: Parkinson’s disease Questionnaire, if available

1. INTRODUCTION
   1. Purpose of Study

This is a proof of concept study which mimicks a study on a new intervention for Parkinsons disease. This proof of concept aims to show:

* the alignment of an real-world data external control arm with an internal arm in the design,
* the downstream connectivity of parameterized data in USDM with real-world data sources,
* and the lineage from real-world data source to submissible datasets.
  1. Assessment of Risks and Benefits

The intervention and corresponding interventional arm are virtual and will not be the focus of this study. Therefore, no risks and benefits are to be noted for this arm. The Real-World data control arm will be selected from the MIMIC data source which is publicly available. Patients with the indication for Parkinsons disease will be selected from this source. Although, this data is based on real-US patients, all data is anonymized which minimizes the risk of identification. The arm is non-interventional and therefore, no health risks are expected for these patients.

1. STUDY Objectives and Associated Estimands
   1. Primary Objective(s) and Associated Estimand(s)

Primary objective:

* To evaluate the effect of intravenous infusions of Beroclin administered once daily on motor symptoms in subjects with early stage Parkinson’s disease.
  1. Secondary Objective(s) and Associated Estimand(s)

Secondary objective:

* To evaluate the safety and tolerability of intravenous infusions of Beroclin administered once daily in subjects with early stage Parkinson’s disease.
  1. Exploratory Objective(s)

Not applicable

1. STUDY Design
   1. Description of Study Design

This is a open-label phase 2 study to assess efficacy and safety of multiple infusions of Beroclin vs Placebo for the treatment of Parkinson’s disease.

The design for the interventional arm includes a screening period of up to 4 weeks, a 12-week treatment period, and a safety Follow-up period of 8 weeks after the last investigational product administration.

For the External Control arm, corresponding patients are selected from the MIMIC data source. Patient are included in the external control cohort when all eligibility criteria are met and sufficient number of visits and data is available to match the interventional arm.

The interventional arm will be open to enroll 24 eligible participants diagnosed with Parkinson’s disease. Eligible external Control arm subjects will be matched to interventional control arm subjects based on propensity score weighting (PSW) in a ratio of 3 to 1. This results in a total of 96 subjects are expected to be included in the final analysis.

* 1. Rationale for Study Design
  2. Trial Stopping Rules

1. Study Population

This clinical study is designed to include adult male and female outpatients with Parkinson’s disease. Study participants who fulfil all of the inclusion criteria and none of the exclusion criteria are eligible for participation in the clinical trial. See below eligibility criteria:

* 1. Inclusion Criteria

1. Male and female participants 18 – 75 years of age.

2. Diagnosed with early and/or moderate Parkinson's disease at least 6 months before study participation.

3. Able to read, understand and to provide written consent.

4. Female study participants should not be pregnant or plan to become pregnant during study participation and for 6 months after last investigational product administration.

5. Male participants if their sexual partners can become pregnant should use a method of contraception during study participation and for 6 months after the last administration of the investigated product.

6. Study participant is able and willing to comply with the requirements of this clinical study.

7. Parkinson’s disease subjects deemed appropriate for treatment of motor symptoms

with a MDS-UPDRS Part III score >10.

8. Treatment naïve or history of prior incidental treatment with dopaminergic agents (including L-Dopa and dopamine receptor agonist medications) for no more than 28 days and not within at least 7 days prior to Visit 1 (Randomization).

9. Willing and able to refrain from any Parkinson’s disease medication not permitted by the protocol (including dopaminergic agents) throughout participation in the study.

* 1. Exclusion Criteria

1. Any active malignancy, including evidence of cutaneous basal, squamous cell carcinoma or melanoma.

2. Study participant has 1 or more significant concurrent medical conditions (verified by medical records), including poorly controlled diabetes mellitus (PCDM), chronic kidney disease (CKD) diagnosis, Class III/IV heart failure during screening visit, any medical history of myocardial infarction, history of uncontrolled high blood pressure, medical history of inherited thrombophilias, recent major general surgery, (within 12 months before the Screening), lower extremity paralysis due to spinal cord injury, fracture of the pelvis, hips or femur, cancer of the lung, brain, lymphatic, gynecologic system (ovary or uterus), or gastrointestinal tract (like pancreas or stomach), and history of brain surgery for Parkinson’s disease.

3. A laboratory abnormality during screening

4. Any other laboratory abnormality or medical condition which, in the opinion of the investigator, poses a safety risk or will prevent the subject from completing the study.

5. Known concurrent acute or chronic viral hepatis B or C or human immunodeficiency virus (HIV) infection.

6. Study participant with any systemic infection requiring treatment with antibiotics, antivirals, or antifungals within 30 days prior to first dose of the investigational product.

1. StUDY Intervention And Concomitant Therapy

| **Arm Name** | **Arm Type** | **Intervention Name** | **Intervention Type** | **Pharmaceutical Dose Form** | **Dosage Strength(s)** | **Dosage Level(s)** | **Route of Administration** | **Regimen/Treatment Period/Vaccination Regimen** | **Use** | **IMP/NIMP** | **Sourcing** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Interventional | Active Comparator | Beroclin | Pharmacologic Substance | Tablet | 20 MG | 20 MG | Oral | BID | Experimental Intervention | IMP | Centrally |

IMP=Investigational Medicinal Product; NIMP=NonInvestigational/Auxiliary Medicinal Product.

**NOTES:**

*Assessments in CDISC terminology*

UPDRS

Epworth Sleepiness Scale

C-SSRS

*Assessments not in CDISC terminology*

PDQ-39

*Assessments from example protocols*

Changes in MDS-UPDRS Part II from Baseline to Week 52. Motor Aspects of

Experiences of Daily Living (M-EDL), including speech, saliva and drooling, chewing

and swallowing, eating tasks, dressing, hygiene, handwriting, doing hobbies and other

activities, turning in bed, tremor, getting out of bed, a car, or a deep chair, walking and

balance and freezing.

Unified Parkinson’s Disease Rating Scale (UPDRS) (PART I – V)

Epworth Sleepiness Scale

Change from baseline in 2-day average ON time without troublesome dyskinesia at Day 27

as recorded in the Patient Motor Diary

Perform the Columbia Suicidality Severity Rating Scale (C-SSRS)

Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease–Rating Scale (QUIP-RS);

Changes in MDS-UPDS Part I, III, IV, or total score.

• Changes Neuro-Quality of Life Assessments, including Communication, Ability to

Participate in Social Roles and Activities, Anxiety, Depression, Emotional and

Behavioral Dyscontrol, Fatigue, Lower Extremity Function (Mobility), Positive Affect

and Well-Being, Sleep Disturbance, Upper Extremity Function (Fine Motor, ADL),

Stigma, Satisfaction with Social Roles and Activities and Cognition Function.

• Changes in Parkinson’s disease fatigue scale (PFS-16). Score of ≥8 indicates the presence

of significant fatigue.

• Changes in Parkinson’s disease Questionnaire (PDQ-39), assessing how often patients

experience difficulties across the 8 quality of life dimensions of functioning of wellbeing.

• Changes in Visual Analog Scale for Pain and muscle spasms.

• Changes in Dosage of medications taken to treat Parkinson’s disease.

• Incidence of treatment-

Columbia Suicide Severity Rating Scale (C-SSRS)

 Vital Signs (blood pressure, heart rate, temperature, weight)

 Unified Parkinson’s Disease Rating Scale (UPDRS) – Parts I, II and III. Only com-plete UPDRS Part IV if symptomatic therapy has been initiated.

 Assess Need for Symptomatic Therapy (completed only if subject has not reached need for symptomatic therapy)

 Modified Hoehn & Yahr Scale

 Modified Schwab & and England Activities of Daily Living

 Dispense and Titrate study drug (Visit 02 ONLY; see Section 5.2.7)

 Dose Management Log

 Adherence Assessments (see Section 6.3.13)

 Drug Dispensing/Return Log (pill counts)

 Adverse Event Log