CT application(s) summary report

- **Protocol title:** A prospective, Multicentre, Open-label, Single-arm Interventional Study of Bisoprolol (Nerkardou) (Between Low Dose and High Dose) 5 and 10 mg ODF Treatment In Egyptian Patients with Essential Hypertension
- **Protocol code number:** GRC/NE-CV/EG/39/IV
- **Eudra-CT:** NCT no: NCT05880056
- **Version:**2
- **Date:** 05-Feb-2024

- **Investigational Medicinal Product being tested:**

Biological ☐ **Pharmaceutical** ☐ **Innovative** ■

Herbal medicine ☐ **Medical device** ☐

- **Sponsor:** Nerhadou International
- **CRO:** Genuine Research Center (GRC)

- **Indication:** Essential Hypertension

- **Investigator's brochure (IB)**

Version: 1.0
Date: June 2023

- **Name of all Sites:** Beni suef university Hospital,Fayoum university Hospital)
- **Name of PI(s):**

Prof. /Heba Hamdy (Beni suef university)
Prof. /Khaled El-Khashab (Fayoum university)

- **EDA approval date:**10/03/2024

- **Summary of pre-clinical studies:**

Nonclinical Pharmacology

For **Bisoprolol** non clinical data reveal **no special hazard** for humans based on conventional studies of **safety pharmacology**, **repeated dose toxicity**, **genotoxicity** or **carcinogenic** potential.

Like other betablockers, bisoprolol caused maternal **(decreased food intake and decreased body weight)** and embryo/foetal toxicity **(increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development)** at high doses, but was **not teratogenic.**

Toxicology

Toxicology studies in animals have established that bisoprolol fumarate has a **wide margin of safety.**

In **multiple-dose studies** in the **rat and dog**, findings were related to pharmacologic effects and/or were class effects known to occur with other **β-blockers** and thus were not specific to **bisoprolol fumarate.**

In the rat, at **high multiples of human therapeutic doses**, **increased serum triglycerides**, **focal myocardial necrosis, increased heart weight/size,** and **pulmonary phospholipidosis** were observed.

In the dog, the tolerance threshold for bisoprolol fumarate was determined by its pharmacologic actions **(i.e. hypotension)** which resulted in **lethality**. Increases in serum **triglycerides** and **hepatocyte**

inclusion bodies were also seen in dogs

- **Summary of previous clinical studies:**

Pharmacokinetics and Product Metabolism in Humans

***Absorption**

Bisoprolol is absorbed and has a biological availability of about **90 %** after oral administration.

*** Distribution**

The plasma protein binding of bisoprolol is about **30%.** The distribution volume is **3.5 L/kg.**

***Biotransformation and Elimination**

Total clearance is approximately **15 L/h**., half-life in plasma of **10-12 hours** gives a **24-hour** effect after dosing **once daily.** Bisoprolol is excreted from the body by **two routes**, **50%** is metabolized by the liver to inactive metabolites which are then excreted by **the kidneys,** the remaining **50%** is excreted by the kidneys in an unmetabolized form.

* **Linearity/non-linearity**

The kinetics of bisoprolol are **linear** and **independent of age.**

***Special Population**

- The pharmacokinetics in patients with **stable chronic heart failure** and with **impaired liver** or r**enal function has not been studied**.
- In patients with **chronic heart failure (NYHA stage III)** the plasma levels of **bisoprolol** are **higher** and the **half-life** is prolonged compared to the **healthy volunteers.**
- **Maximum plasma concentration at** steady state is **64+21 ng/ml** at a daily dose of **10 mg** and the half-life is **17+5 hours.**

***Pediatric Population**

There is no experience with bisoprolol in children and adolescents, therefore its use cannot be recommended for children.

***Elderly persons**

It is recommended to start with the lowest possible dose.

***Renal or hepatic impairment**

- In patients with liver or kidney function disorders of mild to moderate severity, no dosage adjustment is normally required as the elimination takes place in the kidneys and the liver to the same extent.
- ln patients with **severe renal impairment (creatinine clearance< 20 ml/min)** and in patients with severe liver function disorders it is recommended that a daily dose of **10 mg is not exceeded.**
- Experience with the use of bisoprolol in **renal dialysis patients is limited**. However, there is no evidence that the dosage regime needs to be altered.

*** Pregnancy and Breast Feeding**

- Bisoprolol has pharmacological effects that **may cause harmful effects** on pregnancy and/or the fetus/newborn.
- In general, beta-adrenoceptor blocking agents **reduce placental perfusion**, which has been associated with **growth retardation, intrauterine death, abortion** or **early labor.**
- Adverse effects **(e.g., hypoglycemia and bradycardia)** may occur in the **fetus and newborn infant.**

- If treatment with beta-adrenoceptor blocking agents is necessary, **beta 1 -selective adrenoceptor blocking agents are preferable.**
- **Nerkardou is not recommended during pregnancy unless clearly necessary.**
- If treatment with bisoprolol is considered necessary, monitoring of the uteroplacental blood flow and the fetal growth is recommended.
- In case of harmful effects on pregnancy or the fetus consideration of alternative treatment is recommended. The newborn infant must be closely monitored.
- Symptoms of **hypoglycemia** and **bradycardia** are generally to be expected within the **first 3 days.**

It is not known whether this medicinal product is excreted in human milk. Therefore, **breastfeeding is not recommended during the administration of Nerkardou.**

Safety and Efficacy:

***Summary of the safety profile**

Adverse events are listed below by system organ class and frequency.

very common (≥1/10), common (≥1/100 to1/10), uncommon (≥1/1000 to<1/100), Rare (≥1/10,000 to<1/1000), and very rare (<1/10,000), Not Known (cannot estimated from the available data).

Psychiatric disorders	Uncommon: **sleep disorders, depression Rare: nightmares, hallucination.**
Nervous system disorders	Common: **dizziness, Headache. Rare: Syncope**
Eye disorders	Rare: **reduced tear flow (to be considered if the patient uses lenses)** Very rare: **conjunctivitis**
Ear and labyrinth disorders	Rare: **hearing disorder**
Cardiac disorders	Very common: **bradycardia in patients with chronic heart failure** Common: **worsening of pre-existing heart failure in patients with chronic heart failure** Uncommon: **AV-conduction disturbance, worsening of pre-existing heart failure** (in patients with hypertension or angina pectoris), **bradycardia** (in patients with hypertension or angina pectoris)
Vascular disorders	Common: **feeling of coldness or numbness in the extremities**, **hypotension** (especially in patients with heart failure) Uncommon: **Orthostatic hypotension.**
Respiratory, thoracic and mediastinal disorders	Uncommon: **bronchospasm** in patients with bronchial asthma or a history of obstructive airways disease Rare: allergic rhinitis
Gastrointestinal disorders	Common: gastrointestinal complaints such as **nausea, vomiting, diarrhea, constipation**
Hepatobiliary disorders	Rare: **hepatitis**
Skin and subcutaneous tissue disorders	Rare**: hypersensitivity reactions such as itching, flush, rash and angioedema** Very rare: beta-blocking agents may **provoke or worsen psoriasis or induce psoriasis-like rash, alopecia**
Musculoskeletal and connective tissue disorders	Uncommon: **muscular weakness, muscle cramps**

Reproductive system and breast disorder	Rare: **erectile dysfunction**
General disorder and administration site conditions	Common: **fatigue, asthenia (patient with chronic heart failure)** Uncommon: **asthenia (in patient with hypertension or angina pectoris**)
Investigations	Rare: **Increased triglycerides, increased liver enzymes (ALAT, ASAT)**

- **Protocol:**

Phase: I ☐ II III ☐ IV ■

Objective(s):

Primary Safety Objectives		
Objectives	**Outcome Measures**	**Timepoint(s)**
1-The frequency of the first dose hypotension	The frequency of occurrence of the first dose hypotension, which is defined as a fall in systolic blood pressure of 20 mm Hg or more, or to a systolic blood pressure of less than 100 mm Hg, with or without associated symptoms.	At day 1 (week 1) within 1-4 hours of the first administration of 5& 10 mg doses
Secondary Safety Objectives		
Objectives	**Outcome Measures**	**Timepoint(s)**
1. Identifying Bradycardia manifestation Assess the safety of Nerkardou ODF.	Identify the number of patients with bradycardia manifestation, which is defined as heart rate reduction < 60 (bpm) after drug administration	At day 14±2 (week 2), day 28±2 (week 4), day 42± 2 (week 6), day 56±2 (week 8), day 70±2 (week 10), and day 84±2 (week 12)
2.Assess the safety of Nerkardou ODF.	Number of reported AEs, concomitant medications, vital signs, electrocardiograms, Clinical lab measurements, physical examination and dose interruptions or premature discontinuations.	At day 14±2 (week 2), day 28±2 (week 4), day 42±2 (week 6), day 56±2 (week 8), day 70±2 (week 10), and day 84±2 (week 12)
Secondary Efficacy Objectives		
Objectives	**Outcome Measures**	**Timepoint(s)**
1-Investigate the efficacy of (Nerkardou) in treating patients with hypertension	Measuring the response rate for a patient's BP response, which is defined as a ≥20mmHg decrease in sitting through SBP and a ≥10mmHg decrease in sitting through DBP, or a sitting through SBP of<130 mmHg and a sitting through DBP of <80mmHg	At day 14±2 (week 2), day 28±2 (week 4), day 42±2 (week 6), day 56±2 (week 8), day 70±2 (week 10), and day 84±2 (week 12)
2. Investigate the response of (Nerkardou) in treating patients with hypertension	The change of blood pressure from baseline will be measured.	At the end of day 84±2 (week 12)
3. Measuring Patients'	Doses returned will be counted at	At day 14±2 (week 2), day

compliance to this dosage form, especially being easy to carry and easy to use.	each visit	28±2 (week 4), day 42±2 (week 6), day 56±2 (week 8), day 70±2 (week 10), and day 84±2 (week 12)

Rationale:

The protocol was designed for the first bisoprolol fumarate oral dissolvable film **(ODF),** and the investigation of the **safety** and **efficacy** of this dose looks **mandatory**.

Also, the claim that this is a **new galenic** form might increase the compliance and hence the responder take it with to investigate. The use of **ODF** offers several benefits. Firstly, the ease of administration making it more convenient for patients with difficulty swallowing of oral tablets and no need to water for swallowing. Secondly, the size of bisoprolol fumarate ODF and its flexibility can be easily handled and carried by patients to avoid missing their doses accordingly it will improve patient's compliance.

Design:

The trial is designed to **assess the safety** and **investigation of the efficacy** of a **single oral dose** of **bisoprolol (Nerkardou - Nerhadou)** oral dissolvable film **(ODF) 5 & 10 mg** & patients' compliance in the treatment of essential hypertension.

This is a Phase **IV**, open-label, single-arm, prospective trial where subjects will receive:

The subject will initially administer once daily **5 mg bisoprolol (Nerkardou)** oral dissolvable film **(ODF)** for 2 weeks.

After the assessment of the subject being a responder, study medication will be maintained till **week 12.**

Response will be assessed for each patient **every 2 weeks** and dose-titration will be done based on the response and **PI decision** at any visit.

Then, for responders, **once daily 5 mg bisoprolol (Nerkardou)** oral dissolvable film (ODF will be administered for the subsequent **2 weeks.**

For non-responders once daily **10 mg bisoprolol (Nerkardou**) oral dissolvable film (ODF) will be administered for the subsequent **2 weeks**.

For those who are still not responding to the higher dose will be shifted to other alternatives according to their merit and they will be included to intention to treat.

A responder is defined by BP response, which is represented in the form of a **≥20 mmHg** decreases in sitting through SBP and a **≥10 mmHg** decreases in sitting through DBP, or a sitting through SBP of **<130 mmHg** and sitting through **DBP< 80 mmHg**

- **Questions & Answers:**

  <u>EDA Question 1</u>

  The following are required according to *(EMA Guideline on clinical investigation of medicinal products in the treatment of hypertension.*

  - A detailed section regarding blood pressure measurements in trial subjects should be written precisely as efficacy is one of the study objectives so measurements should be precise for obtaining reliable results including the following:
    - Measurements with a **calibrated sphygmomanometer.**
    - Time of measurement at each site visit, **BP** should be measured frequently with emphasis on the maximum and minimum effects of the drug **(peak-trough ratio).**
    - All measurements should be performed under **standardized conditions** and with the patient in the office.
    - **BP** at **trough** is defined as the **residual effect** at the end of the dose interval.
    - The peak effect is the **maximum BP reduction** (at steady state)

- If the first **two readings** of **SBP** differ by more than **5 mmHg**, additional readings should be obtained **until stabilization** has occurred with difference between these **two readings** within this limit

Applicant Response

A detailed section about the method and precautions for the measurement of blood pressure among study participants was added in page **22** of protocol documents.

EDA Question 2

Regarding trial design in protocol clarify what will happen to subjects who are not responders to **bisoprolol (Nerkardou) oral dissolvable film (ODF) 10 mg** regarding the statistical analysis plan for their data.

Applicant Response

Detailed procedures were provided in the protocol design. Section 14.4 "**Analysis Populations"**

EDA Question 3

Regarding safety objectives:

A. **The following measurements should be covered**: number of reported TEAEs/SAEs, AESIs, concomitant medications, vital signs, ECGs, Clinical lab measurements, physical examination.
B. It was mentioned in protocol that "Identifying Bradycardia manifestation as a secondary efficacy objective, **it should be shifted to secondary safety objectives**.
C. First dose hypotension should be mentioned as the only primary safety objective, Justification regarding the referenced measurement values that will be used to assess the first dose hypotension is required as the submitted paper not considered as a valid reference

Applicant Response

A. The safety objectives were updated and the measurements of adverse events, concomitant medications, vital signs, ECGs, Clinical lab measurements, physical examination.
B. Bradycardia manifestation were shifted to the **secondary safety objectives**.
C. The study design and frequency of measurement of first-dose hypotension was updated accordingly. This was modified in the synopsis, objectives, study procedures, statistical analysis, and informed consent form.
D. There are scarce studies regarding this point, and the submitted paper was the one of the initial studies to investigate the first dose hypotension among patients administered bisoprolol therefore, it was referenced, and our work is expected to provide more evidence regarding this point

EDA Question 4

In section 8.19.1 "Premature Termination of the Trial", it was mentioned that *Investigator may discontinue a participant from the trial treatment in case of Significant non-compliance with study drug*" & **in section 9.1.4. Compliance with Trial Treatment, it was mentioned that** "*Treatment compliance that is < 80% will be considered to be non-compliant*",

Clarification regarding the definition of significant non-compliance & procedure of study discontinuation for non-compliant subjects e.g (tapering, follow up … etc.)

Be notified that this statement not considered as "Premature Termination of the Trial", it is considered as Early Discontinuation & **should be shifted to item 9.18 " Early Discontinuation/Withdrawal of Participants from Trial Therapy.**

Applicant Response

- Significant non-compliance definition was added **(less than 80% for 2 subsequent visits)** the actions taken for non-compliant patients were clarified. Moreover, the **title Premature Termination of the Trial was corrected to be "Early Discontinuation"**, and noncompliance criteria was mentioned in this section
- Early Discontinuation/Withdrawal of Participants from Trial Therapy" The drug should be **tapered** slowly over **1-2 weeks** based on the investigator's schedule and under close monitoring by the investigator; this was clarified in all relevant sections in the protocol

EDA Question 5

According to **ESH 2023 Hypertension guidelines,** " Beta blockers **are not the first line** for hypertension management except in certain patients; it was mentioned in your reply that " initial reports demonstrated that **bisoprolol** could be a safe and effective therapy for newly diagnosed patients with high response rate" ,Kindly be notified that the submitted evidence **is not satisfactory** as it is an observational study with low quality of evidence in specific population & study design should follow the most updated international guidelines for disease management.

Applicant Response

There are **scarce studies** investigating the **efficacy and safety** of bisoprolol among patients newly diagnosed with hypertension, which is why that was the only study cited and the drug was not recommended as a first-line drug among those patients till now.

We believe our study would be able to increase our understanding of the efficacy and safety of the drug among newly diagnosed hypertension. Additionally, ESH recommended that beta-blockers among the 5 first-line antihypertensive medications which are recommended in certain patients, including those with heart rate more than 80 beats per minute which is a major point in our inclusion criteria.

EDA Question 6

Regarding the **exclusion criteria:**

- **Justification** is required for not mentioning these cases in the exclusion criteria section of the **protocol & ICF**: "Patients with AV Block, patients with untreated pheochromocytoma, patients with sick sinus syndrome, and patients with acute decompensated heart failure shouldn't use beta blocker, according to **Nerkardo package insert**.
- **It is required to add the following as per EMA guideline clinical investigation medicinal products treatment hypertension revision 4) (** *BP should be checked simultaneously in both arms, at least once. BP should be recorded in the arm with the higher pressure; if differences between arms greater than 20 mmHg for SBP and 10 mmHg for DBP are present on 3 consecutive readings, the patient should be* ***excluded from participating the study*** *and the reason for the observed difference should be examined further)*

Applicant Response

- Exclusion Criteria Number was updated to be consistent with Nerkardo package insert " 4.4 special warning and precaution for use"
- Blood pressure measurement was updated as per EMA guideline in section **7.6** in the protocol

EDA Question 7

Regarding the following section" 4.3. Trial Rationale" more clarification regarding the added value for using this dosage form (ODF) in comparison to the conventional film oral tablets is required to be added to this section.

Applicant Response

Section (4.3. Trial Rationale) in protocol was updated to includes the following clarification "The use of **ODF** offers several benefits. Firstly, the ease of administration making it more convenient for patients with difficulty swallowing of oral tablets and no need to water for swallowing, Secondly, the size of **bisoprolol fumarate ODF** and its flexibility can be easily handled and carried by patients to avoid missing their doses accordingly it will **improve patient's compliance".**

EDA Question 8

Regarding the sample size calculation based upon **Biostatistician expert comments :**

- The choice of **Median time of response** that is based on previous studies is not a good choice, on the contrary, the shortest or preferably the longest times should be used instead.
- the secondary recruitment of some more subjects during the study course is not clear, (Dropout calculation), More clarification is required.

Applicant Response

Our study employs the **median response time** as it aligns with our objective to reflect a **typical patient experience**, as seen in similar efficacy studies, notably referenced by Davidov, E. et al.
Unlike non-inferiority or superiority trials, where extreme response times might be more relevant, our choice is driven by the need to capture an accurate two-directional response.
To ensure statistical robustness without ethical compromise, we've carefully calibrated our sample size to **406 (10% dropout rate),** considering potential dropouts from the initial **369.**
This size is crucial: a smaller sample would risk underpowering our study, while a larger one could inflate confidence intervals and expose more participants to potential risks without proportional scientific gain.
This approach underscores our commitment to a study that is scientifically valid and ethically sound.

EDA Question 9

Regarding the following criteria mentioned in both submitted protocols & ICF " *Participants can withdraw completely from the study and withdraw the data and samples collected up until the point of withdrawal",*
kindly be notified that, as per FDA *"Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials ":*
FDA recognizes that a subject **may withdraw** from a study; however, the withdrawal does not extend to the data already obtained during the time the subject was enrolled,
The rationale behind this approach is the following reasonable & convincing justifications:
The **importance of maintaining complete clinical study data**, including information such as adverse events experienced by the subject.
The **validity** of the study might be affected by removal of data Non processing of subjects' personal information after withdrawal would hide important safety information regarding the studied IMP and posing risks for other participants in the study and for future beneficiaries of the results.
There is a risk that certain participants are **incentivized** by interested parties to withdraw, in order to artificially improve the results of the study. .

Applicant Response

Section **7.9.1** in protocol *(Early Discontinuation of the Trial)* was updated : Participants can withdraw from the study at any time while data and samples obtained up until the point of withdrawal **will be retained** for use in the study analysis.
No further data or samples would be collected after withdrawal, **ICFs were updated accordingly.**

- **Abbreviation:**

AEs: Adverse events
AESIs: Adverse events of special interest
AV: Atrioventricular
DBP: Diastolic blood pressure
HTN: Hypertension
mmHg: millimetres of mercury
NYHA: New York Heart Association (NYHA) Classification of heart failure
ODF: Oral dissolvable film
SAEs: Serious adverse events
SBP : Systolic blood pressure
TEAEs: Treatment-Emergent Adverse event