



Arab Republic of Egypt
Egyptian Drug Authority
Central Administration of
Biological and Innovative
Products and Clinical Studies
GA of Clinical Trials

جمهورية مصر العربية
هيئة الدواء المصرية
الإدارة المركزية للمستحضرات الحيوية
والمبتكرة والدراسات الإكلينيكية
إ.ع. الدراسات الإكلينيكية

CT Application(s) Summary Report

- **Protocol title:** Adhesion and Safety of Rotigexole Compared to Neupro®: A Non-Inferiority Open-Labelled Crossover Randomized Controlled Trial.
- **Protocol code number:** START24042025
- **Public Registry Number:** NCT07015346
- **Version:** 4.0
- **Date:** 16 October 2026

• Investigational Medicinal Product being tested:

Biological ☐ Pharmaceutical ☐ Innovative ☒
Herbal medicine ☐ Medical device ☐

• Sponsor: EVA Pharma, Egypt

- **Indication:**
Early-Stage Parkinson's Disease
- Advanced-Stage Parkinson's Disease
- Restless Legs Syndrome
(the study population is limited to patients with Parkinson's Disease, RLS is a product-level indication that is not being investigated in this study)

• Investigator's brochure (IB)

Version: 2.0
Date: 26/8/2024

• Name of all Sites:

- 1- Ain Shams Specialized Hospital, Neurology department
- 2- El-Manial Specialized Hospital, Neurology department
- 3- MARC CRC

• Name of PI(s):

- 1- PI: Prof. Dr. Ali Shalash.
- 2- PI: Prof. Dr. Hatem Samir.
- 3- PI: Prof. Dr. Ahmed Farag

• EDA approval date: 12 November 2025

• Summary of pre-clinical studies:

Since the product is a generic patch with the same qualitative formula of the reference product

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“Neupro 2 mg/24 h transdermal patch “, therefore related information to this section is not required.

As per SMPC of the reference product (Neupro transdermal patch (UCB Pharma S.A., Belgium):

➤ **In repeated dose and long-term toxicity studies:**

- The major effects were associated with the dopamine agonist related pharmacodynamic effects and the consequent decrease of prolactin secretion.
- After a single dose of rotigotine, binding to melanin-containing tissues (i.e., eyes) in the pigmented rat and monkey was evident, but was slowly cleared over the 14-day observation period.
- **Retinal degeneration was observed by transmission microscopy at a dose equivalent to 2.8 times the maximum recommended human dose on a mg/m² basis in a 3-month study in albino rats.** The effects were more pronounced in female rats.
- Additional studies to further evaluate the specific pathology have not been performed.
- Retinal degeneration was not observed during the routine histopathological evaluation of the eyes in any of the toxicology studies in any species used. **The relevance of these findings to humans is not known.**

➤ **In a carcinogenicity study:**

- Male rats developed Leydig cell tumors and hyperplasia. Malignant tumors were noted predominantly in the uterus of mid- and high-dose females. **These changes are well-known effects of dopamine agonists in rats after life-long therapy and assessed as not relevant to man.**

➤ **Reproductive studies:** The effects of rotigotine on reproduction have been investigated in rats, rabbits and mice:

- **Rotigotine was not teratogenic in all three species, but was embryotoxic in rats and mice at materno-toxic doses.**
- **Rotigotine did not influence male fertility in rats, but clearly reduced female fertility in rats and mice,** because of the effects on prolactin levels which are particularly significant in rodents.

➤ **Rotigotine did not induce gene mutations in the Ames test,** but did show effects in the in vitro Mouse Lymphoma Assay with metabolic activation and weaker effects without metabolic activation. This mutagenic effect could be attributed to a clastogenic effect of rotigotine. This effect was not confirmed in vivo in the Mouse Micronucleus Test in the rat Unscheduled DNA Synthesis (UDS) test. Since it ran more or less parallel with a decreased relative total growth of the cells, it may be related to a



cytotoxic effect of the compound. Therefore, the relevance of the one positive in vitro mutagenicity test is not known.

• **Summary of previous clinical studies:**

Since Rotigotine 4.5 mg (2 mg/ 24 hours) transdermal patch is a generic product, a pilot bioequivalence study has been performed sponsored by Eva pharma for pharmaceutical industries, Egypt:

- **Study title:** A randomized, blinded assessor, single dose two-way crossover bioequivalence study to determine the bioequivalence of the transdermal patch of Rotigotine from Test Product Rotigotine 4.5 mg (2 mg/ 24 hours) transdermal patch Eva pharma for pharmaceutical industries, Egypt versus Neupro 2 mg/24 h transdermal UCB pharma S.A., Belgium in healthy human volunteers under fasting conditions.
- **Objective:** To investigate the bioequivalence of Rotigotine from Rotigexole 4.5 mg Transdermal Patch (2 mg/24 hrs) (Eva Pharma for Pharmaceutical Industries, Egypt) versus Neupro 2 mg/24 hrs transdermal patch (UCB Pharma S.A., Belgium) in Healthy Human Volunteers Under Fasting Condition.
- **Study Design:** Randomized, blinded assessor, single dose, two sequence two-periods crossover
- **Diagnosis and Main Criteria for Inclusion:** Rotigotine is a non-ergoline dopamine agonist for transdermal delivery system. The bioavailability of Rotigotine is studied in Healthy Human Volunteers Under Fasting Condition.
- **Pharmacokinetic parameters:**
 - **Primary Pharmacokinetic Parameters:** C_{max} , $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$
 - **Secondary Pharmacokinetic Parameters:** K_e , t_{max} and $t_{1/2e}$.

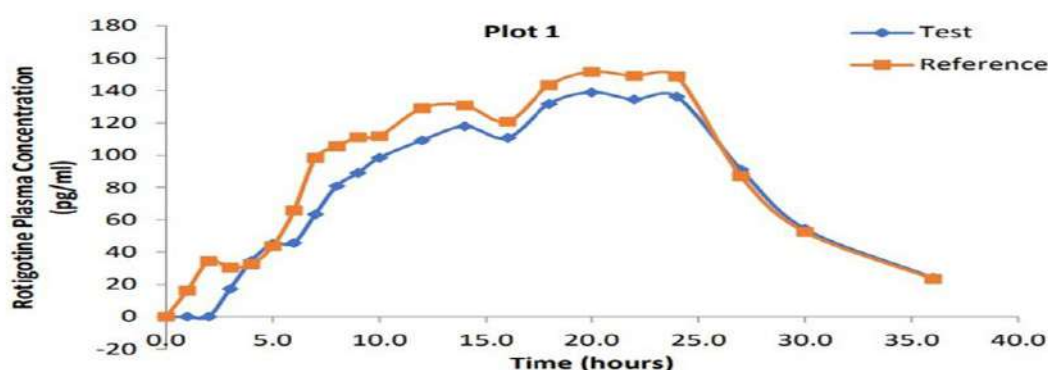
Results:

Table I: Bioequivalence confidence intervals of Rotigotine after single dose administration of Treatment T TEST Product Rotigexole 4.5 mg Transdermal Patch (2 mg/24 hrs) (Eva Pharma for Pharmaceutical Industries, Egypt) and Treatment R REFERENCE Product Neupro 2 mg/24 hrs transdermal patch (UCB Pharma S.A., Belgium.)

	Point estimate %	90% confidence intervals of parametric means	
		Lower limit %	Upper limit %
C_{max}	94.12	86.68	102.21
$AUC_{0 \rightarrow t}$	92.34	85.74	99.45
$AUC_{0 \rightarrow \infty}$	93.42	86.56	100.83

As presented in Table I, the point estimates for the test/reference ratios were 94.12% for C_{max} , 92.34% for AUC_{0-T} , and 93.42% for $AUC_{0-\infty}$. The corresponding 90% confidence intervals were 86.68%–102.21% for C_{max} , 85.74%–99.45% for AUC_{0-T} , and 86.56%–100.83% for $AUC_{0-\infty}$. All confidence intervals are fully contained within the predefined bioequivalence acceptance range of 80.00%–125.00%, demonstrating that both the rate (C_{max}) and extent (AUC_{0-T} and $AUC_{0-\infty}$) of absorption of the test product are comparable to those of the reference product. **These results support the conclusion that the test and reference products are bioequivalent under the studied conditions.**

Figure 1: Linear presentation (Plot 1) for Rotigotine mean plasma concentration after single dose administration of Treatment T TEST Product Rotigexole 4.5 mg Transdermal Patch (2 mg/24 hrs) (Eva Pharma for Pharmaceutical Industries, Egypt) and Treatment R REFERENCE Product Neupro 2 mg/24 hrs transdermal patch (UCB Pharma S.A., Belgium).



As illustrated in Figure 1, the mean plasma concentration–time profiles of rotigotine following administration of the test and reference transdermal patches show a comparable pattern over the entire sampling period. Both treatments exhibit a gradual increase in plasma concentrations, reaching peak levels at approximately the same time, followed by a similar decline phase. Although slightly higher concentrations are observed for the reference product at certain time points, the overall profiles remain closely aligned, with no marked divergence in the absorption or elimination phases. **This similarity in the concentration–time curves further supports the comparable rate and extent of absorption between the test and reference products, consistent with the bioequivalence results.**

Efficacy Results:

Point estimates and the 90% confidence intervals for the log-transformed ratios (TEST/REFERENCE) were **within the predefined acceptance limits (80.00% – 125.00%)** for C_{max} , AUC_{0-T} , and $AUC_{0-\infty}$.

∞ , indicating that the rate and extent of absorption of the test product Rotigotine from Rotigexole 4.5 mg Transdermal Patch (2 mg/24 hrs) are comparable to those of the reference product Neupro 2 mg/24 hrs transdermal patch. Accordingly, these results demonstrate that the bioequivalence criteria have been met for all primary pharmacokinetic parameters.

Safety results:

The tolerability of the two formulations, each given in a single administration, was acceptable as no adverse events have occurred during the administration of both treatments. All the clinical laboratory investigations were normal, or clinically insignificant as evaluated by the principal investigator.

Conclusion:

This study was single center, randomized, blinded assessor, single dose study with two-way crossover design to compare the bioavailability of Rotigotine between two products, in 47 healthy, adult volunteers.

The results of this bioequivalence study showed the equivalence of the two studied products in terms of the rate of absorption as indicated by C_{max} and in terms of the extent of absorption as indicated by $AUC_{0 \rightarrow T}$ AND $AUC_{0 \rightarrow \infty}$. The parametric 90% confidence intervals of the mean values for the TEST / REFERENCE ratio were in each case well within the bioequivalence acceptable boundaries of 80.00-125.00% for C_{max} , $AUC_{0 \rightarrow T}$ AND $AUC_{0 \rightarrow \infty}$.

ANOVA analysis on the log-transformed data, C_{max} , $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$. and untransformed data for C_{max} , $AUC_{0 \rightarrow t}$ and $AUC_{0 \rightarrow \infty}$, K_e , $t_{1/2e}$ and T_{max} showed that sequence effect, product or period effect for all these parameters did not significantly influence the outcome of the study. The mean plasma curve of both products are almost super imposable suggesting that not only C_{max} and AUC but also the time course of plasma levels over the whole sampling period are identical.

Since plasma levels are a meaningful surrogate for pharmacodynamics action and adverse events, this demonstrates that an equivalent therapeutic activity and tolerance is to be expected from TEST and REFERENCE product.

Absorption and Bioavailability

When single doses of 8 mg/24 hours are applied to the trunk, there is an average lag time of approximately 3 hours until drug is detected in plasma (range 1 to 8 hours). T_{max} typically occurs between 15 to 18 hours post dose but can occur from 4 to 27 hours post dose. However, there is no characteristic peak concentration observed. Rotigotine displays dose-proportionality over a daily dose range of 1 mg/24 hours to 24 mg/24 hours. When studying Rotigotine effectiveness, the transdermal system application site was rotated from day to day (abdomen, thigh, hip, flank, shoulder, or upper arm) and the mean measured plasma concentrations of rotigotine were stable over the six months of

maintenance treatment. Relative bioavailability for the different application sites at steady-state was evaluated in subjects with Parkinson's disease.

In a single trial conducted in patients with early-stage Parkinson's disease differences in bioavailability ranged from less than 1% (abdomen vs hip) to 46% (shoulder vs thigh) with shoulder application showing higher bioavailability. Because rotigotine is administered transdermally, food should not affect absorption, and the product may be administered without regard to the timing of meals.

In a 14-day clinical study with rotigotine administered to healthy subjects, steady-state plasma concentrations were achieved within 2 to 3 days of daily dosing.

Distribution

The weight normalized apparent volume of distribution, (V_d/F), in humans is approximately 84 L/kg after repeated dose administration. The binding of rotigotine to human plasma proteins is approximately 92% in vitro and 89.5% in vivo.

Metabolism and Elimination

Rotigotine is extensively metabolized by conjugation and N-dealkylation. After intravenous dosing the predominant metabolites in human plasma are sulfate conjugates of rotigotine, glucuronide conjugates of rotigotine, sulfate conjugates of the N-despropyl-rotigotine and conjugates of N-desthienylethyl - rotigotine. Multiple CYP isoenzymes, sulfotransferases and two UDP-glucuronosyltransferases catalyze the metabolism of rotigotine. After removal of the patch, plasma levels decreased with a terminal half-life of 5 to 7 hours. The pharmacokinetic profile showed a biphasic elimination with an initial half-life of 3 hours. Rotigotine is primarily excreted in urine (~71%) as inactive conjugates of the parent compound and N-desalkyl metabolites. A smaller proportion is excreted in feces (~23%). The major metabolites found in urine were rotigotine sulfate (16% to 22% of the absorbed dose), rotigotine glucuronide (11% to 15%), and N despropyl-rotigotine sulfate metabolite (14% to 20%) and N-desthienylethyl-rotigotine sulfate metabolite (10% to 21%). Approximately 11% is renally eliminated as other metabolites. A small amount of unconjugated rotigotine is renally eliminated (<1% of the absorbed dose).

As per SMPC of the reference product (Neupro transdermal patch (UCB Pharma S.A., Belgium) to support rotigotine clinical evidence:

➤ Clinical Efficacy:

- The efficacy of rotigotine was evaluated in 5 placebo-controlled trials with more than 1,400 patients with idiopathic Restless Legs Syndrome (RLS).
- Efficacy was demonstrated in controlled trials in patients treated for up to 29 weeks. The effect

was maintained over a 6 months period. The changes from baseline in the International RLS Rating Scale (IRLS) and CGI-item 1 (severity of illness) were primary efficacy parameters. For both primary endpoints statistically, significant differences have been observed for the doses 1 mg/24 h, 2 mg/24 h and 3 mg/24 h in comparison to placebo. **After 6 months of maintenance treatment in patients with moderate to severe RLS, the baseline IRLS score improved from 30.7 to 20.7 for placebo and from 30.2 to 13.8 for rotigotine. The adjusted mean difference was -6.5 points (CI95% -8.7; -4.4, $p < 0.0001$). CGI-I responder rates (much improved, very much improved) were 43.0% and 67.5% for placebo and rotigotine respectively (difference 24.5% CI 95%: 14.2%; 34.8%, $p < 0.0001$).**

In a placebo-controlled, 7-week trial polysomnographic parameters were investigated. Rotigotine significantly reduced the periodic limb movement index (PLMI) from 50.9 to 7.7 versus 37.4 to 32.7 for placebo ($p < 0.0001$).

- **Augmentation:** In two 6-month, double-blind, placebo-controlled studies, clinically relevant augmentation was observed in 1.5% of rotigotine-treated patients versus 0.5% of placebo treated patients.
- In two open label, follow-up studies over a subsequent 12 months, the rate of clinically relevant augmentation was 2.9%. None of these patients discontinued therapy because of augmentation.
- In a 5-year open-label treatment study, augmentation occurred in 11.9% of patients treated with the approved dosages for RLS (1-3 mg/24 h), and 5.1% were considered clinically significant. In this study, the majority of augmentation episodes occurred in the first and second years of treatment. Furthermore, in this study a higher dose of 4 mg/24 h that is unapproved in RLS was also used and led to higher rates of augmentation.

➤ **Pharmacokinetics:**

- **Absorption:** Rotigotine is continuously released from the transdermal patch and absorbed through the skin.
 - Steady-state concentrations are reached after one to two days of patch application and are maintained at a stable level by once daily application in which the patch is worn for 24 hours.
 - Rotigotine plasma concentrations increase dose-proportionally over a dose range of 1 mg/24 h to 24 mg/24 h. Approximately 45% of the active substance within the patch is released to the skin in 24 hours.
 - The absolute bioavailability after transdermal application is approximately 37%. Rotating the site of patch application may result in day-to-day differences in plasma levels. Differences in bioavailability of rotigotine ranged from 2% (upper arm versus flank) to 46% (shoulder versus

thigh). However, there is no indication of a relevant impact on the clinical outcome.

- **Distribution:** The in vitro binding of rotigotine to plasma proteins is approximately 92%. The apparent volume of distribution in humans is approximately 84 l/kg.
- **Biotransformation:** Rotigotine is metabolised to a great extent. Rotigotine is metabolised by N-dealkylation as well as direct and secondary conjugation. In vitro results indicate that different CYP isoforms are able to catalyse the N-dealkylation of rotigotine. Main metabolites are sulfates and glucuronide conjugates of the parent compound as well as N-desalkyl-metabolites, which are biologically inactive. The information on metabolites is incomplete.
- **Elimination:** Approximately 71% of the rotigotine dose is excreted in urine and a smaller part of about 23% is excreted in faeces. The clearance of rotigotine after transdermal administration is approximately 10 l/min and its overall elimination half-life is 5 to 7 hours. The pharmacokinetic profile shows a biphasic elimination with an initial half-life of about 2 to 3 hours.
- **Food effect:** Because the patch is administered transdermally, no effect of food and gastrointestinal conditions is expected.
 - **Special patient groups:** Because therapy with Neupro is initiated at a low dose and gradually titrated according to clinical tolerability to obtain the optimum therapeutic effect, adjustment of the dose based on gender, weight, or age is not necessary.
 - **Hepatic and renal impairment:** in subjects with moderate hepatic impairment or mild to severe renal impairment, no relevant increases of rotigotine plasma levels were observed. Neupro was not investigated in patients with severe hepatic impairment. Plasma levels of conjugates of rotigotine and its desalkyl metabolites increase with impaired renal function. However, a contribution of these metabolites to clinical effects is unlikely.
 - **Paediatric population:** limited pharmacokinetic data obtained in adolescent patients with RLS (13-17 years, n=24) following treatment with multiple doses of 0.5 to 3mg/24h showed that systemic exposure to rotigotine was similar to that observed in adults. Efficacy/safety data is insufficient to establish a relation between exposure and response.
- **Summary of the safety profile:**

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 748 Neupro and 214 placebo-treated patients, 65.5% of the patients on Neupro and 33.2% of patients on placebo reported at least one adverse reaction. At the beginning of therapy dopaminergic adverse reactions such as nausea and vomiting may occur. These are usually mild or moderate in intensity and transient even if treatment is continued. Adverse drug reactions (ADRs) reported in more than 10% of patients treated with Neupro are nausea, application site reactions, asthenic conditions and headache

➤ **Tolerability:**

In trials where the application sites were rotated as reflected in the instructions provided in the SmPC and package leaflet, 34.2% of 748 patients using Neupro, experienced application site reactions. The majority of application site reactions were mild or moderate in intensity, limited to the application areas and resulted in discontinuation of Neupro in 7.2% of subjects.

➤ **Discontinuation rate:** The discontinuation rate was studied in 3 clinical trials ranging up to 3 years in duration. The percentage of subjects discontinuing was 25-38% over the first year, 10% in the second year, and 11% in the third year. Periodic assessment of efficacy should be performed, along with evaluation of safety, including augmentation.

• **Protocol:** Adhesion and Safety of Rotigexole Compared to Neupro®: A Non-Inferiority Open-Labelled Crossover Randomized Controlled Trial.

• **Phase:** IV

• **Objective(s):**

The objective of this study to evaluate the adhesion and local safety of Rotigexole compared to Neupro®

1.Primary Objective

Establish non-inferiority of Rotigexole (test) and Neupro® transdermal patch adhesiveness in patients with Parkinson's disease.

2.Secondary Objectives

- 1- Evaluate application site reactions for Rotigexole (test) and Neupro® transdermal patches in patients with Parkinson's disease
- 2- Patient's satisfaction towards the adhesiveness of Rotigexole (test) compared to Neupro® transdermal patches in patients with Parkinson's disease.

• **Evaluation Criteria**

Primary Endpoint:

The cumulative mean percentage adhesion of the transdermal patch over the 24-hour dosing interval for two treatment periods, compared between Rotigexole (Test) and Neupro® (Reference) using a mixed-effects model adjusted for period and sequence effects, with subject as a random effect.

Secondary Endpoints (comparative):

1. Proportion of participants achieving more than 90% adherence at 4, 8, 12, 16, 20 and 24 hours at each period as assessed by the investigator/designee as per modified EMA scale for adhesion.
2. Adjusted Mean adhesion percentage at each assessment time (4, 8, 12, 16, 20 and 24 hours).
3. Proportion of participants with a meaningful degree of detachment (more than half of the patch lifting off the skin or falling off) at 4, 8, 12, 16, 20 and 24 hours.
4. Number of patches that are completely detached at 4, 8, 12, 16, 20 and 24 hours.

5. Number of participants with cold flow in each treatment period (Cold flow is defined as dark ring formed around the patch).
6. Number of participants with patch movement/displacement in each treatment period.
7. Number of participants with patch wrinkling in each treatment period.
8. Number of participants with patch residue formation in each treatment period (Patch residue formation is assessed at patch application on the release liner and at patch removal on the skin).
9. The incidence, seriousness and severity of adverse events (AEs) including application site reactions, and discontinuations because of AEs.

Exploratory endpoints:

1. Ease of Patch Application and Removal: Assess how easy it is for patients to apply and remove each patch using a 5-point Likert scale.
2. Impact on Daily Activities: Assess how patch adhesion affects patients' ability to perform daily activities using 5-points Likert scale.
3. Overall Satisfaction with Patch Wear: Evaluate overall patient satisfaction with wearing each patch type using 5-points Likert scale.

Rationale:

The present study for **submission to EMA** is undertaken to evaluate the test product Rotigexole transdermal patch, manufactured by EVA Pharma, Egypt [hereafter referred to as **Rotigotine-test (T)**] is non-inferior in adhesion to the reference product Neupro® Transdermal Patch [hereafter referred to as **Rotigotine-reference (R)**]. Both formulations will undergo comparative adhesion and local safety evaluation.

As per EMA "Guideline on quality of transdermal patches" Section: 5.3.2.

To support a **generic or abridged application**, bioequivalence with the reference product and also non-inferiority (absence of statistically significant difference) with respect to **in vivo skin adhesion** should be demonstrated.

As per EMA "Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms" (EMA/CHMP/EWP/280/96 Rev. 1) Appendix II: in vivo skin adhesion

1. Applications for a TDDS of a new chemical entity or a known active substance newly developed as TDDS, **the investigation of in vivo adhesive performance will be usually part of the efficacy studies**. The robustness of the product to normal human behaviors' (e.g. moisture resistance to washing, showering, saunas, use of moisturizers and risk of removal during exercise and/or sleeping, possible transfer to partners or family) should be evaluated, as appropriate, based on risk analysis and the instructed conditions of use for the individual products. Accidental transfer of a patch to the skin of a non- patch wearer has to be prevented as well as other poor-adhesion related risks have to

be minimized by ensuring acceptable adhesion characteristics by the patch.

2. The adhesion should be measured as the percentage of area that remains adhered at the end of the dosing interval.

In general, it is expected that the 90% confidence interval of mean adherence for the test product at the end of the dosing interval should lie above 90%. Any deviation from this requirement has to be justified considering all potential risks associated with the incomplete attachment of the patch.

Design:

This is a non-inferiority, open-label, randomized, multicenter, four-period, two-sequence (TRTR or RTTR), cross over, comparative study to evaluate the patch adhesion of the test product Rotigotine Transdermal Patch (Rotigexole) 8mg/24 hrs as compared with reference product Neupro® (Reference) Transdermal Patch 8mg/24 hrs in adult male and female participants with Parkinson's disease.

• **Study Population:** Male or Female patients aged ≥ 30 years at screening diagnosed with Idiopathic Parkinsonism Disease.

• **The total duration of study participation including preparatory phase, intervention phase and post-intervention phase for each participant will be:** approximately 7 Weeks and 5 days (54 days)

- Screening phase of 2 weeks (14 days)
- Run-in phase of 3 weeks (21 days) with a window period of – 1 to 2 days
- Intervention phase for five days.
- Follow up phase of 2 weeks $\pm$ 1 week (14 days $\pm$ 7 days)

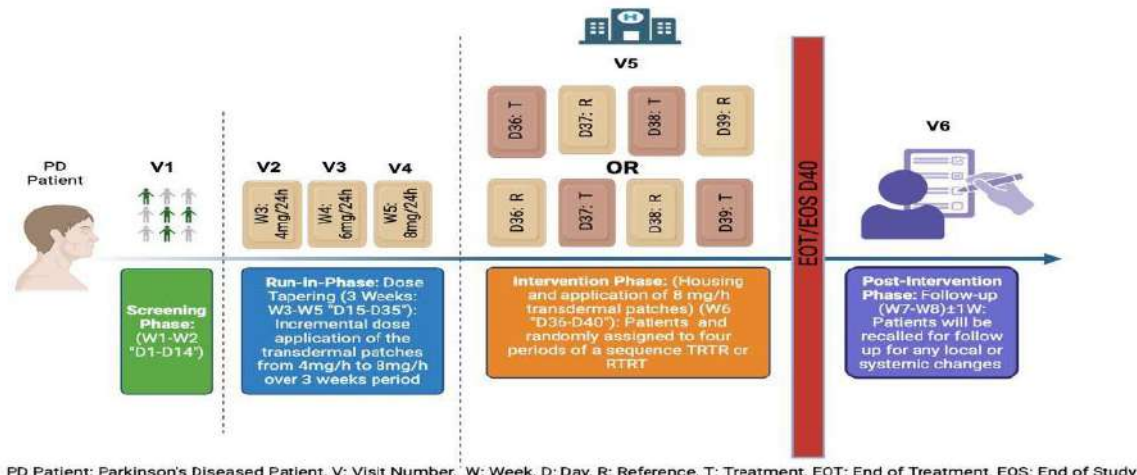


Figure 1: Study Schema

• Recommendation &/ or Questions & Answers:

Query 1. Regarding Institutional Review Board (IRB) Meeting Minutes and Decision For “Why Rotigotine transdermal patch 2 mg/24 h is subjected to routine bioequivalence study, while Rotigexole (Rotigotine 8 mg/24 hours transdermal patch) is subjected to clinical trial, given that both Neupro 2 mg and 8mg/24 h transdermal patches are available in the market abroad?” the answer of the above mentioned question is required to be clarified.

Response 1. During the committee meeting it was clarified to the committee members as follows During the committee meeting, the following clarification was provided to the members regarding this inquiry: The 2 mg/24 h rotigotine patch is the reference strength recommended by regulatory authorities (e.g., FDA) for conducting routine bioequivalence studies in healthy volunteers. This strength allows pharmacokinetic comparison and, if formulation proportionality is demonstrated, bioequivalence can be extrapolated to other strengths. In contrast, the 8 mg/24 h patch (Rotigexole) involves a higher drug load and larger patch size, which may affect adhesion and local skin tolerability. Therefore, a dedicated clinical trial in the target Parkinson's patient population is necessary to assess adhesion and local safety under real-world, multiple-dose conditions. These evaluations cannot be fully addressed by routine bioequivalence studies alone. This approach aligns with regulatory expectations to ensure that the higher strength patch performs safely and effectively in its intended clinical setting.

Query 2. Regarding exclusion criteria “Patients who have not received dopamine agonists in the past 30 days or are willing to discontinue current dopamine agonist therapy for the duration of the study” Clarification is required on whether the drug is prohibited 30 days prior to the study or must be discontinued for the study duration only.

Response 2. We thank the reviewer for this comment. This eligibility point is an inclusion criterion, not an exclusion. The intent is that enrolled patients must be free from dopamine agonist therapy before participation. Therefore, the criterion has been revised to: “Patients who have not received dopamine agonists in the past 30 days.” This ensures that prior dopamine agonist exposure will not confound study outcomes and that all participants enter the intervention phase after an appropriate washout. **The point has been reviewed, edited in the Subject Selection Criteria of the protocol synopsis, in inclusion criteria in section 4.1 and in CRF.**

Query 3. “willing to refrain from swimming, bathing or sauna use on assessment days.” According to “Assessment of Adhesion for Topical and Transdermal Systems Submitted in New Drug Applications “guidance draft. Section B: Inpatient Clinical Wear Trial Design:” “For products with a wear period of 24 hours or more, subjects should be permitted to bathe or shower routinely during the trial. The TDS should not be protected (e.g., do not apply a water-resistant covering over 148 the product) or wholly excluded from direct exposure to water (e.g., do not restrict bathing to only a sponge bath) during such routine activities. Activities that are thought to potentially impact adhesion, including bathing or showering, should be recorded for each subject (i.e., activity, duration, and timing relative to TDS application).” Update the protocol to follow the aforementioned guideline, or alternatively, submit other guidelines that support your design.

Response 3. We thank the reviewer for this comment. The restrictive statement requiring participants to refrain from bathing, swimming, or sauna use on assessment days has been removed. In accordance with FDA guidance, subjects will be permitted to bathe or shower routinely during the trial, without protecting the patch from water exposure. To ensure proper documentation, the study procedures section has been updated to capture activities that may affect adhesion (e.g., bathing, swimming, sauna), including the type of activity, duration, and timing relative to patch application.

Query 4. “Participants should be using a reliable method of contraception (e.g., intrauterine device, barrier methods, condoms) throughout the study and for at least 30 days after the last dose of study medication” As per SMPC of the reference product (Neupro), “In animal studies, rotigotine was shown to have adverse effects on embryofetal development when administered during pregnancy at doses similar to or lower than those used clinically” and the above mentioned Barrier methods, such as condoms, are not always sufficient or reliable as sole methods of contraception.”,

Clarification is required.

Response 4. Correct examples of reliable contraceptive methods were added with their corresponding references in the protocol synopsis and in the inclusion criteria section 4.1, CRF and ICF.

Query 5. Regarding question no.10: it was stated that “Introduced central photo review by site PIs to ensure consistency and quality across sites, more clarification regarding central review procedure is required.

Response 5. We thank the reviewer for the valuable comment. The central photo review process will be conducted through multiple levels of verification to ensure consistency and quality across all study sites:

- First level: The study coordinator will perform a daily review of the retrieved assessments and archived photographs to verify consistency. Any discrepancies identified will be immediately reported to the site Principal Investigator (PI).
- Second level: The site PI will conduct a central review after the completion of the intervention phase at each site to confirm accuracy and consistency of the assessments.
- Third level: The Clinical Research Associate (CRA) will perform a final quality control review during the Source Data Verification (SDV) process to confirm data consistency and address any outstanding discrepancies.

All involved personnel will undergo comprehensive training prior to study initiation to ensure standardization and calibration across all sites. This multi-stage review and training process ensures better data quality, consistency, and adherence to regulatory expectations.

Query 6. “Recent exposure to monoamine oxidase type A inhibitors, amphetamines, dopamine depleting antihypertensive agents, neuroleptics, or antiemetic that block central dopamine activities Page 37 table 5” It was mentioned that those medications are Prohibited 21 days prior to baseline till EOS. However, it was mentioned in the study manual Page.5 section 4. Contraindications (Exclusion criteria) it was mentioned that “ Intake of MAO inhibitors within 2 weeks prior to first study drug administration”, Unify the discrepancy through the whole study documents.

Response 6. The protocol was updated in section 4.2. Exclusion criteria as well as the ICF and CRF

Query 7. “Justify with reference to the following exclusion criteria is required “Presence of hepatitis B surface antigen (HBsAg) or positive for total hepatitis B core antibody (HbcAb), or positive hepatitis C (HCV) at screening”.

Response 7. We thank the reviewer for this comment. According to the SmPC of Neupro® (reference

product), Section 4.2 (“Posology and method of administration”), patients with hepatic impairment are considered a special population for whom Neupro® has not been systematically investigated. Since the primary objective of this study is to evaluate patch adhesion, not pharmacokinetics or systemic safety in special populations, the study investigators and PIs have determined that patients with hepatic conditions should not be enrolled. This decision ensures:

- Alignment with the reference product SmPC.
- Protection of patient safety in a population for which there is limited clinical data.
- Consistency in evaluating adhesion under controlled, comparable conditions.

Query 8. “Regarding secondary endpoints: Point 9. “Ease of Patch Application and Removal: Assess how easy it is for patients to apply and remove each patch. • Clarify if patch application will be done via participant or investigator during admission period & Clarify the methodology for assessing the easiness of batch application”

Response 8. We thank the reviewer for this comment. We confirm that during the in-clinic study period, patch application and removal will be performed by the investigator or a designated study staff member to ensure consistency and reliability of data collection. The ease of patch application and removal will be assessed by the investigator using a structured 5 point Likert scale that evaluates smoothness of application, adhesion during placement, and difficulty of removal. The detailed scale has been included in the revised protocol for clarity. It should be noted that this endpoint is not required by either FDA or EMA guidance for adhesion studies. However, it has been added as an exploratory endpoint (rather than secondary) in order to explore patient and investigator experience with both patch application and removal, and to maintain consistency across the endpoint hierarchy. Ease-of-Removal — 5-point Likert scale:

- Very difficult / painful: required help; sharp pain on removal; >60 seconds to remove.
- Difficult / uncomfortable: needed some assistance; unpleasant/stinging; 31–60 seconds.
- Neither easy nor difficult: removed independently but with effort; mild tugging; 11–30 seconds.
- Easy: removed independently with little effort; brief tugging; 5–10 seconds.
- Very easy / no discomfort: removed independently, no discomfort; <5 seconds.

Query 9. Point 11. “Impact on Daily Activities: Assess how patch adhesion affects patients' ability to perform daily activities and Point12 Overall Satisfaction with Patch Wear: Evaluate overall patient satisfaction with wearing”. • Clarify the methodology for assessing those secondary endpoints.

Response 9. The Impact on Daily Activities and Overall Satisfaction with Patch Wear will be assessed using brief patient-reported outcome (PRO) questionnaires incorporated into the case report form. For Impact on Daily Activities, participants will rate the degree of interference caused by the patch on a 5-point Likert scale ranging from “no interference” to “unable to perform usual

activities.” For Overall Satisfaction, participants will rate their satisfaction with patch wear on a 5 point Likert scale ranging from “very dissatisfied” to “very satisfied.” These assessments are not required by FDA or EMA guidance for adhesion studies. They have therefore been classified as exploratory endpoints rather than econdary endpoints, to explore the usability and acceptability of the patches from a patient perspective. Responses will be analyzed descriptively. Updated wording from the instruments:

- Impact on Daily Activities: “During the time you wore the patch, how much did it interfere with your ability to carry out your usual daily activities (e.g., walking, sitting, working, sleeping, personal care)?” Response options (5-point Likert):

No interference at all

Slight interference (noticeable but did not limit activities)

Moderate interference (some limitation of activities)

Severe interference (major limitation; required adjusting activities)

Unable to perform usual activities

Overall Satisfaction with Patch Wear: “Overall, how satisfied were you with wearing the patch?”

Response options (5-point Likert):

Very dissatisfied

Dissatisfied

Neither satisfied nor dissatisfied

Satisfied

Very satisfied

Query 10. Regarding Page.17 As per schedule of activities, ECG will be done on screening only & will not be repeated neither in the EOS visit nor in the follow up visit.

- ECG should be done at the end of trial to evaluate the safety of patient especially the ADR of drug include cardiovascular disease.

Response 10. We thank the reviewer for this important comment. The protocol was updated to include an ECG at the End of Study (EOS) visit to ensure participant safety and to capture any potential cardiovascular adverse events associated with the study intervention.

- ECG will continue to be performed at screening to identify participants with underlying cardiac conditions that contraindicate study participation.

• A repeated ECG at EOS will provide a safety assessment after the study intervention period.

- This addition aligns with good clinical practice and the known cardiac risk profile of the study drug. The Schedule of Activities (SoA) and relevant protocol sections were updated to reflect this change.

Query 11. Regarding Ramixole starting time: Page.12/Page. 21 of the protocol

-It was stated in Page.12 that *“At the final assessment of the 2nd transdermal patch application, the patient will be prescribed an alternative medicament (Ramixole) to stabilize the patient’s conditions”* while it was stated in Page.21 that *“Upon the patient’s dismissal, the patient will be prescribed Ramixole (1 mg) tablets (available in the Egyptian market) as a comparable substitute of Rotigotine patches (Studied Drug)”*. There is discrepancy in time of starting ramixole, clarification is required.

Response 11:

The wording has been harmonized to avoid discrepancy regarding the timing of Ramixole initiation. Ramixole will be prescribed at the time of patient dismissal, following the final assessment after the last transdermal patch application. This ensures both statements are aligned and consistently reported across the protocol.

Query 12: Regarding section 4.3.2 Activity page.27 It was stated that *“Participant should be informed regarding the risk of abrupt withdrawal of the study intervention. They may develop symptoms like pain, fatigue, depression, sweating, and anxiety if they abruptly withdraw the study intervention, therefore, they should inform to the Investigator or designee in case they do not want to continue the study intervention”*

➤ As per As per SMPC of the reference product (Neupro), it was stated in section warnings and precautions that *“Hyperpyrexia and Confusion: A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, rhabdomyolysis, and/or autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian therapy. Therefore, it is recommended that the dose be tapered at the end of NEUPRO treatment”*

➤ Reference As per ICH E6 R 3 Section 2.3 *“The informed consent process should take into consideration relevant aspects of the trial, such as the characteristics of the participants, the trial design, the anticipated benefits and risks of medical intervention(s).”*

• There is not any clarification in the informed consent regarding the risk of sudden prompt of the drug; Description as per the SMPC & the protocol is required to be added to the ICF.

Response 12. We acknowledge the need to clarify the risk of abrupt withdrawal of rotigotine (Neupro®) in the participant information. While the SmPC (Attachment #4) recommends tapering, in this study participants will be transitioned directly to an alternative dopaminergic treatment (Ramixole, available in the Egyptian market) at the time of study drug discontinuation. Accordingly, the Informed Consent Form (ICF) will be updated to include:

• Abrupt withdrawal of rotigotine may cause withdrawal symptoms (e.g., pain, fatigue, depression, sweating, anxiety) or, rarely, a serious syndrome resembling neuroleptic malignant syndrome (fever,

muscle stiffness, confusion, rhabdomyolysis, autonomic instability).

- To avoid these risks, participants will not discontinue rotigotine without medical oversight; instead, at the end of treatment or upon discontinuation, they will be switched to Ramixole as replacement therapy.
- Participants will be instructed to inform the investigator or study team before discontinuing study medication and to report any concerning symptoms immediately. This ensures participant safety, reflects the SmPC (Attachment #4) safety considerations, and maintains compliance with ICH E6(R3). Risk Associated with abrupt withdrawal of the study intervention section has been added in the ICF.

Query 13. Regarding Treatment compliance: Page. 35 it was stated that “A Participant will be considered compliant with study intervention if 70%-130% of the assigned dose is taken since previous visit. Compliance below 70% will require counselling of the participant by study site personnel

- Clarification is required regarding the upper limit 130 %
- specify the minimum compliance percentage required, below which participants will be deemed non-compliant and subject to discontinuation from the study.

Response 13. The compliance range of 70–130% was a general rule applied in oral medication protocols and is not applicable in this study, since a transdermal patch delivers a fixed dose and cannot exceed 100%.

Accordingly, the compliance definition has been revised as follows:

- A participant will be considered compliant if at least 70% of scheduled patch applications are completed within the prescribed time window.
- Compliance <70 % will be considered non-compliance; in such cases, participants may be discontinued from the study at the investigator discretion after appropriate counseling.
- The concept of compliance >100% has been removed entirely, as it does not apply to a fixed-dose patch intervention.

This revision ensures accuracy, eliminates carry over text from oral drug studies, and aligns compliance criteria with the design of a transdermal patch trial.

Query 14. Regarding Page.39/Page.43

➤ Page 39: Study Assessments it was stated that “Procedures conducted as part of the participant’s routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA”.

➤ Page 43: Chest X-ray The CXR will not be required if the participant had a previous normal CXR (posterior-anterior views) within 12 weeks of Screening provided all source documentation is available at the site as outlined below and provided nothing has changed in the participant’s medical history to warrant a repeat test

- The Schedule of Activities (SoA) does not specify whether previous assessments are acceptable. However, it has been clarified that a normal chest X-ray (posterior-anterior view) performed within 12 weeks prior to the Screening visit may be utilized. Clarify in the protocol if this is the only prior assessment that the Principal Investigator (PI) is permitted to use during the Screening period.

Response 14. We thank the reviewer for this comment and the opportunity to clarify. In line with the protocol and study manual, most baseline assessments (e.g., hematology, chemistry, ECG, urinalysis) must be conducted within the defined screening window to ensure consistency and minimize risk of missing evolving conditions. These tests are relatively simple, inexpensive, and routinely available in clinical practice; repeating them at screening is important to confirm eligibility and establish baseline values. The chest X-ray (CXR), however, is different. Requiring a new CXR for every participant—even when a recent, valid result is available—can lead to unnecessary radiation exposure, increased burden, and ethical concerns. Therefore, the protocol allows the use of a recent normal CXR performed within 12 weeks prior to screening, provided that:

- It is posterior-anterior (PA) view and of acceptable technical quality.
- Source documentation is available and verifiable at the site.
- There has been no change in the participant's clinical history or symptoms that would justify a repeat CXR.

This approach balances scientific rigor, patient safety, and ethical principles:

- Rigor is maintained by ensuring every participant has a documented normal CXR within an appropriate timeframe.
- Safety is preserved because any subject with new or worsening respiratory symptoms will still require a repeat CXR at screening.
- Ethical standards are respected by avoiding unnecessary radiation exposure, consistent with good clinical practice.

Accordingly, the Schedule of Activities and study text have been clarified to state explicitly that:

- A prior normal CXR (PA view) conducted within 12 weeks of screening may be used.
- If unavailable or if clinical changes are suspected, a new CXR must be performed at screening. This explains why CXR is the only assessment where prior results may be accepted. Other investigations are simpler, pose no radiation risk, and are more appropriately repeated within the screening window.

Query 15. Routine CXR for adhesion study may not be necessary; Clarify clinical justification or limit to clinically indicated cases; otherwise remove to reduce unnecessary exposure

Response 15. We acknowledge that in a typical adhesion study with healthy volunteers, a routine chest X-ray (CXR) may not be strictly necessary. However, the current study involves patients with Parkinson's disease, who may have an increased burden of comorbidities, particularly age-related cardiopulmonary conditions that could impact both study conduct and safety monitoring. The rationale for retaining the CXR requirement is as follows:

- Patient population: Unlike healthy volunteer adhesion trials, this study includes Parkinson's patients, who are generally older and may have undiagnosed pulmonary or cardiovascular comorbidities. A baseline CXR helps identify underlying issues that could complicate participation or confound safety signals.
- Clinical judgment: The protocol places final responsibility on the Principal Investigator (PI), who will determine whether a screening CXR is required based on each participant's history and risk profile. This ensures an individualized, clinically appropriate approach. In summary, while a routine CXR is not essential in all adhesion studies, in this study population it serves as a safety safeguard. The decision is grounded in the clinical recommendation of the PI, ensuring both scientific rigor and protection of participant welfare.

Query 16. Regarding Interim Analysis Page. 55/Page.57: In Page 55 section 8.2 Interim Analysis, it was stated that "No interim analysis is planned for this study". While in Page 57 section 9.4 Archival of Data) it was stated that "At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures".

- General examples that could lead to inconsistencies in the protocol should be avoided. All statements should be specific and accurately represent the protocol's status.

Response 16. We thank the reviewer for this observation. We confirm that no interim analysis is planned for this study as mentioned in the study protocol section 8.2 Interim Analysis. The reference to "production of interim reports" in Section 9.4 was a general template statement and has been removed to avoid inconsistency. The section now specifies only that data will be locked and cleaned at the time of the final analysis in accordance with established procedures.

Query 17. Regarding Page. 48 Special Reporting Situations: Exposure to the investigational intervention from breastfeeding . Clarify How exposure to the investigational intervention could occur through breastfeeding, given that breastfeeding is listed as one of the exclusion criteria.

Response 17. Breastfeeding is listed as an exclusion criterion, and therefore exposure to the investigational intervention through breastfeeding cannot occur in this study population. The reference to "exposure from breastfeeding" in the Special Reporting Situations section was a standard template statement not applicable to this clinical study and has now been removed to avoid inconsistency.

Query 18. Regarding Sample size assumptions inconsistent Page.54-55, the text cites within-subject variability 20% yet uses a within subject SD of 30% in Power TOST code; also, a comment says 'CV=30 # SD=10%'. • Harmonize assumptions: choose a single variance assumption and correct the Power TOST code comments; include a sensitivity analysis for dropout and variability.

Response 18. The sample size section has been clarified to remove the confusing code annotation and to harmonize assumptions.

- The within-subject variability was conservatively set at 30% for the power calculation. Although earlier text referred to 20%, the final assumption applied in the PowerTOST calculation was 30%, consistent with the code and outputs.
- The comment in the code suggesting “CV = 30% # SD = 10%” has been removed, as it was misleading.
- With these assumptions, the sample size required for 90% power at a one-sided 5% significance level (non-inferiority margin = -10%) was 36 patients, which already includes an allowance for ~10% dropout. The protocol therefore targets 40 randomized patients to ensure evaluable data.
- Variability is properly accounted for in the mixed-effects ANOVA model that includes treatment, sequence, and period as fixed effects, with subjects as a random effect.

We therefore confirm that the protocol text has been corrected to consistently reflect these assumptions.

Query 19. Regarding Model covariates and structure Page.55, Mixed-effects model includes treatment period, sequence; skin application region/side is not included though it can affect adhesion. Pre-specify application site/region (and possibly reader) as covariates; consider subject-by-treatment interaction if relevant.

Response 19. The primary analysis will use a mixed-effects ANOVA model with treatment, period, and sequence as fixed effects, and subject as a random effect. Least squares adjusted means will be compared between treatments, consistent with EMA/FDA guidance for non-inferiority adhesion studies. Adding additional covariates (e.g., site/region, subject-by-treatment interaction) would increase model complexity and could hinder interpretation. The subject-by-treatment interaction effect is already accounted for by using a conservative within-subject variability estimate in the sample size calculation. Application region will be rotated, and within a region, the application site will be changed once across the whole assessment phase on each side, thereby minimizing potential site effects. If deemed necessary by the regulatory authority at the time of study results submission, a sensitivity analysis may be conducted to explore additional covariates (e.g., application region or reader effect).

Query 20. Regarding Randomization details – generation and concealment Page. 15, Randomization schedule described but method (block size, stratification) and allocation concealment are not detailed.

- State who generates the sequence, block sizes, any stratification (site), and how concealment is maintained until assignment.

Response 20. We thank the reviewer for this comment. The following clarifications are provided:

- Randomization method: Block randomization with a fixed block size of 4 (2 allocations per sequence) will be used to maintain balance between the two sequences (TRTR, RTTR).
- Stratification: Randomization will be stratified by site. No additional stratification factors or covariates will be applied, as the study sample size is limited and this is consistent with adherence study design.
- Generation of list: The study statistician, independent from the enrollment team, will generate the randomization lists separately for each site.
- Implementation: The site study coordinator will assign the next available randomization code by entering the patient's site-ID, which is generated by site staff, and retrieving the corresponding allocation from the pre-specified list.
- Concealment: Allocation concealment will be maintained until the moment of assignment by using sequentially numbered, sealed, opaque envelopes (or equivalent secured procedure) at each site. Investigators and site staff will not have prior access to future assignments.

Query 21. Regarding Run-in phase with Neupro® – potential conditioning of skin Page.31-35, Three- week run-in with reference patch may condition skin and influence subsequent adhesion during intervention.

- Provide rationale and consider balancing/alternating application sites by sequence; document any pre-existing irritation before intervention starts.

Response 21. We thank the reviewer for this important observation. The potential for skin conditioning during the three-week run-in phase with Neupro® has been carefully considered. To minimize any influence on subsequent adhesion assessments:

- Application sites will be alternated in accordance with recommended practice to reduce local conditioning effects.
- Balancing by sequence (TRTR or RTTR) ensures that any residual conditioning effects are distributed evenly across treatment arms.
- Pre-existing skin irritation or dermatological findings will be carefully documented prior to the start of the intervention phase and considered in the analysis set.

Query 22. Regarding Definition of meaningful/complete detachment in Endpoints assessment Page. 27, Definitions are provided qualitatively; ensure quantitative translation into % adhesion and decision rules.

- Add clear mapping from categorical detachment grades to numeric % adhesion for analysis and reporting.

Response 22. To ensure clarity and consistency, the protocol has been updated to provide a direct mapping between qualitative detachment descriptions and quantitative percent adhesion values used for

analysis.

- Adhesion scoring scale: The FDA and modified EMA-recommended adhesion scale will be applied:
- $\geq 90\%$ adhered: essentially no lift off
- $\geq 75\%$ to $< 90\%$ adhered: some edges lift-off
- $\geq 50\%$ to $< 75\%$ adhered: less than half lifts off
- 0% to $< 50\%$ adhered: more than half lifts off without falling off
- 0% adhered: patch completely detached
- These categorical grades will be translated into numeric % adhesion ranges for both descriptive summaries and statistical analysis. This approach ensures that definitions of partial or complete detachment are standardized, reproducible across sites, and aligned with EMA guidance. Clear mapping as categorical detachment grades and numeric % adhesion was clarified under clinical assessments: Sections 7.1- Modified EMA scale for adhesion

Query 23. Regarding post-intervention/Follow-up visit; post-study dopamine agonist (Ramixole) prescription, starting pramipexole/ropinirole immediately post intervention could confound attribution of AEs during follow-up.

- Clarify timing vs follow-up safety window and ensure AE attribution rules consider concomitant DA initiation.

Response 23. We thank the reviewer for this important comment. We would like to clarify that the present study is designed to evaluate the local safety and adhesion of the investigational transdermal system, rather than systemic safety outcomes.

- As per the SmPC of the reference product (Neupro®), abrupt discontinuation of rotigotine is contraindicated due to the risk of withdrawal symptoms; therefore, transition to another dopamine agonist (Ramixole/pramipexole/ropinirole) immediately post-intervention is mandatory and cannot be avoided.

- Since the study endpoints are limited to local tolerability at the application site, initiation of post-study dopamine agonist therapy does not confound the primary or secondary outcomes.

Nevertheless, for completeness, the initiation of Ramixole will be captured in the concomitant medications log, and any adverse events reported during the follow up will be documented in the CRF in accordance with GCP requirements, even though attribution to systemic therapy is outside the study's primary scope.

• **Abbreviation:**

ADR: Adverse Drug Reaction

AE: Adverse Event

ANOVA: Analysis of Variance

AUC_{0→t}: Area Under the Plasma Concentration–Time Curve from Time Zero to the Last Measurable



Arab Republic of Egypt
Egyptian Drug Authority
Central Administration of
Biological and Innovative
Products and Clinical Studies
GA of Clinical Trials

جمهورية مصر العربية
هيئة الدواء المصرية
الإدارة المركزية للمستحضرات الحيوية
والمبتكرة والدراسات الإكلينيكية
إ.ع. الدراسات الإكلينيكية

Concentration

AUC_{0→∞}: Area Under the Plasma Concentration–Time Curve from Time Zero to Infinity

C_{max}: Maximum Observed Plasma Concentration

CGI: Clinical Global Impression

CRO: Contract Research Organization

CT: Clinical Trial

DA: Dopamine Agonist

EMA: European Medicines Agency

EU: European Union

GLP: Good Laboratory Practice

GMP: Good Manufacturing Practice

IB: Investigator's Brochure

ICF: Informed Consent Form

IRB: Institutional Review Board

IRLS: International Restless Legs Syndrome Rating Scale

PD: Parkinson's Disease

PI: Principal Investigator

R: Reference Product

RLS: restless leg syndrome

SmPC: Summary of Product Characteristics

T: Test Product

TDDS: Transdermal Drug Delivery System

V_d: volume of distribution

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