SYNOPSIS – ABBREVIATED REPORT

Sponsor: **Lundbeck LLC**	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: **Melperone HCl 5 mg/mL Oral Syrup**	**Volume:**	
Name of Active Ingredient: Melperone HCl	**Page:**	

Study Title:
Safety and Effectiveness of Open-Label Melperone in the Treatment of Patients with Psychosis Associated with Parkinson's Disease

Investigators and Study Centers:
Multicenter: 10 sites in the US, 2 sites in Italy, and 2 sites in India participated in the study (see Appendix 16.1.4)

Publication (reference): None

Studied Period:

13 October 2005 (first subject first dose) to
01 October 2008 (last subject last dose)

Study Phase: 2

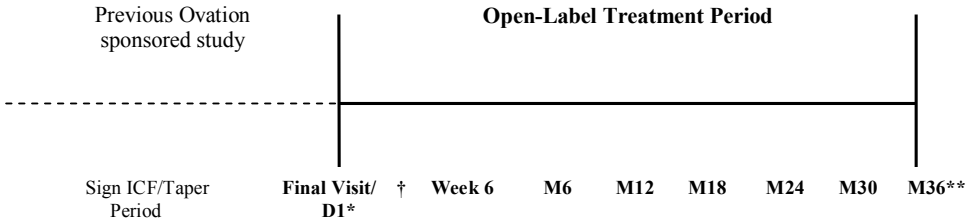
Objectives:
The objective of this study was to determine the long-term safety and effectiveness of open-label melperone in the treatment of patients with psychosis associated with Parkinson's Disease.

Methodology:

This multicenter, open-label study was designed to assess the long-term safety and effectiveness of melperone HCl 5 mg/mL oral syrup (melperone) in the treatment of psychosis associated with Parkinson's Disease (PD). Subjects previously enrolled in a Lundbeck-sponsored study OV-1003 (prior sponsor Ovation) of melperone for psychosis associated with PD who either completed the study or prematurely discontinued therapy during the study (subjects who prematurely discontinued due to a serious or severe adverse event that was probably or definitely related to melperone use in the Investigator's opinion were not eligible for enrollment) were given the option of continuing in the open-label study.

The Final/Day 1 Visit marked the end of the previous Lundbeck-sponsored study and the start of the open-label study. The Final Visit procedures outlined in the schedule of assessments of the previous study were performed and double-blind study drug was stopped and collected by site personnel. When all Final Visit procedures were completed, subjects were considered closed out of the study and formally entered the open-label study. The procedures for Day 1 in the open-label schedule of assessments were performed and open-label melperone syrup was dispensed to subjects and/or their caregivers.

Study Schematic:



*Denotes the end of the previous Lundbeck-sponsored study and the start of the open-label study.

†ECGs were performed between Week 2 and Week 3.

** US subjects were permitted to participate until melperone was commercially available or until Lundbeck discontinued research on melperone in this indication. Ex-US subjects were permitted to participate for up to 36 months or until Lundbeck discontinued research on melperone in this indication; continuation on melperone after 36 months for ex-US subjects was decided based on medical need, availability and access to melperone and other treatment options, and discussions with physicians in each country.

Beginning on Day 1, all subjects were initiated on open-label melperone 10 mg/day (equivalent to 2 mL/day) every night (QHS). During the first five weeks of the Treatment Period, the daily dose of melperone was increased by 10 mg increments on a weekly basis to therapeutic effect (total daily dose not to exceed 60 mg or 12 mL). If, in the Investigator's opinion, a subject was tolerating the titration schedule, the rate of titration may have been adjusted to allow the dose to more quickly reach the dose range that may have been effective in the previous Lundbeck-sponsored study. In addition, in the Investigator's opinion, a dose greater than 60 mg or 12 mL would benefit the subject, the Investigator contacted the medical monitor to discuss the possibility of increasing the dosage.

Titration Schedule for Open-Label Treatment Period

Study Days	1-7	8-14	15-21	22-28	29-35	36
Dose	10 mg/day	20 mg/day	30 mg/day	40 mg/day	50 mg/day	60 mg/day

On Day 14 of the Treatment Period, the Investigator contacted the subject or their caregiver via telephone to assess the subject's response to treatment. The Investigator may have requested additional office visits during the Treatment Period if clinically indicated. If a subject was unable to tolerate a particular dose of melperone at any time during the Treatment Period, the subject and/or caregiver notified the Investigator. In response to dose intolerance, the Investigator may have modified dosing by changing the frequency from QHS to twice daily (BID), and if intolerance continued, the total daily dose may have been decreased. Subjects who prematurely discontinued from the Treatment Period were tapered by 10 mg increments every 2-3 days until study drug was discontinued. Subjects remained off study drug for 2-3 days before returning to the site for final assessments.

During the Open-Label Treatment Period, subjects returned to the investigational site between Week 2 and Week 3 (ECG only), at Week 6, and at Months 6, 12, 18, 24, 30, and 36 for safety, psychiatric and motor function assessments. A telephone visit occurred on Day 14 to assess the subject's response to treatment. The Investigator may have requested additional office visits during the Treatment Period if clinically indicated. Subjects brought their study drug and dosing cards to the site at each visit. Site personnel performed study drug accountability and dispensed a sufficient supply of study drug (unfinished study drug bottles were re-dispensed from visit to visit) and medicine droppers to last until the next visit.

Number of Subjects (Planned and Analyzed):
Subjects enrolled in Lundbeck-sponsored studies of melperone for psychosis in Parkinson's Disease (PD), who either completed the study or prematurely discontinued therapy during the study, were able to continue in the open-label study.
A total of 28 subjects were enrolled and 28 subjects were analyzed for safety. The study was terminated due to lack of efficacy in Lundbeck-sponsored study OV-1003; efficacy analyses were not performed for the current study. Values for neuropsychiatric scales are provided by subject in the listings.

Diagnosis and Main Criteria for Inclusion:
A subject was eligible to participate in the study if all of the following criteria were met:

1. The subject or subject's legally authorized representative (LAR) signed and dated the IRB/IEC approved Informed Consent Form and HIPAA Authorization (applicable to US only) prior to study participation.
2. Previous participation in a Lundbeck-sponsored psychosis in Parkinson's Disease study with melperone.
3. If female:
   - Subject was either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or if of childbearing potential, had complied with a method of birth control acceptable to the Investigator during the study, for at least 1 month prior to study entry and for 1 month following completion of the study.
   - Subject was not breastfeeding.
   - Subjects of childbearing potential had a negative serum pregnancy test prior to study entry.
4. If subject received treatment with an antipsychotic agent other then melperone, he/she was washed out for 5 half-lives prior to study entry.
5. Subject was willing and able to comply with all study procedures

Main Criteria for Exclusion:

Subjects were excluded from the study if any of the following criteria were met:

1. Greater than 14 days had elapsed since the subject received his/her last dose of study medication in the previous Lundbeck-sponsored psychosis in PD study.
   a. Subjects who completed or prematurely discontinued from a previous Lundbeck-sponsored psychosis associated with Parkinson's disease study, but were unable to enroll in the open-label extension study within 14 days, were considered

for entry into the open-label extension study on a case-by-case basis. The Principal Investigator, Sponsor, and subject (and/or subject's LAR) consulted to determine whether entry into the open-label extension study outside the defined rollover window was in the best interest of the subject. The subject was required to review and re-sign the Informed Consent Form with an authorized site representative, and may have been asked to undergo repeat screening procedures to ensure that the subject remained eligible for study entry.

2. Subject had a serious or severe adverse event in the previous Lundbeck-sponsored psychosis in PD study that in the opinion of the Investigator was probably or definitely related to melperone use.
3. Subject had any systemic factor contributing to the psychosis such as urinary infection, liver disease, renal failure, anemia, infection or cancer.
4. Subject had Dementia with Lewy-bodies (DLB).
5. Subject had dementia or a major depressive disorder precluding accurate assessment on rating scales.
6. Subject had an acute depressive episode at the time of study entry.
7. Subject had used any investigational product during the 30 days prior to study entry, with the exception of melperone in a Lundbeck-sponsored psychosis in PD study.
8. Subject had a history of a serious respiratory, gastrointestinal, renal, hematologic or other medical disorder.
9. Subject had a history of a serious cardiovascular condition (including, but not limited to Class IV angina and Class IV heart failure and/or a history of risk factors for Torsade de pointes [Tdp] including, but not limited to, current treatment for hypokalemia or family history of long QT syndrome).
10. Subject had myocardial infarction within 6 months prior to screening
11. During the previous Lundbeck-sponsored psychosis in PD study, subject had an ECG with corrected QT interval by Bazett's correction formula (QTcB) of greater than 450 msec, if female, or 430 msec, if male. If subject had an ECG of greater than 450 msec, if female, or 430 msec, if male, he/she may have been eligible for enrollment providing that:
    a. Subject did not have a QTc value of >500 msec during the double-blind study
    b. Subject's QTc was ≤ 450 msec if female, or ≤ 430 msec if male at the Day 43 (for subjects currently receiving 4 mL study drug) or Final Visit of the double-blind study.
        i. Subjects who had a QTc >450 msec, if female, or >430 msec, if male, at the Day 43 or Final Visit may have been eligible if they tapered study drug to 0 mL, returned for a repeat ECG, and the repeat ECG had a QTc ≤ 450 msec, if female, or ≤ 430 msec, if male.
12. Subject required treatment with an α-agonist agent.
13. Subject had uncontrolled seizures, uncontrolled angina, or uncontrolled symptomatic orthostatic hypotension (or orthostatic hypotension that lead to a history of falls 3 months prior to screening), or other medical disorders which made the subject a poor candidate for a clinical trial.
14. Subject had a history of severe adverse reactions to antipsychotic medications.
15. Subject had clinically significant abnormal laboratory values, ECG, or findings on a physical exam.

16. Subject had a recent history or current evidence of substance dependence or abuse
17. Subject was unable to ingest oral medication.
18. Subject was being treated with Deep Brain Stimulation (DBS).

Test Product, Dose and Mode of Administration, Lot Number:
Melperone HCl (5 mg/mL) was provided in syrup formulation and measured in milliliters.

Melperone was dispensed by subjects or their caregivers directly into the subject's mouth using a 5 mL, graduated dropper.

Study Drug	Dosage Strength/ Dosage Form	Lot Number	Manufacturer
Melperone HCl	5 mg/mL syrup	VS-4279-00-A-E	Nordmark
		VS-7305-00-A-E	Nordmark

Duration of Treatment:

Subjects enrolled in the US were permitted to participate for up to 36 months, or until melperone was commercially available or Lundbeck discontinued research on melperone in this indication. Subjects enrolled outside the US were permitted to participate for up to 36 months or until Lundbeck discontinued research on melperone in this indication.

Reference Therapy, Dose and Mode of Administration, Lot Number:
No reference therapy was used for the study.

Criteria for Evaluation:

Efficacy:
The primary effectiveness endpoint was the change in the Scale for Assessment of Positive Symptoms (SAPS) score. Other effectiveness endpoints included other neuropsychiatric scales, such as the Neuropsychiatric Inventory (NPI) total score and relevant items and subscales, and the Unified Parkinson's Disease Rating Scale (UPDRS) and relevant subscales.
The study was terminated due to lack of efficacy in Lundbeck-sponsored study OV-1003 and efficacy analyses were not performed; values for neuropsychiatric scales are provided by subject in the listings.

Safety:
Safety assessments included analyses of adverse events (AEs), serious adverse events (SAEs), physical examination, Body Mass Index (BMI), laboratory values, vital signs and ECG intervals.

AEs that occurred from the time of first dose of investigational product through 30 days post-treatment were collected. AEs that occurred after the Informed Consent and HIPAA Authorization (applicable to US only) were signed through Day 1 prior to dosing, unless judged to be serious adverse events, were captured as medical history.

Statistical Methods:

Efficacy:
All subjects who provided informed consent, took at least 1 dose of melperone and had at least 1 efficacy measurement in the open-label study were to be included in the analysis of efficacy. The short-term efficacy analysis was to use double-blind data in a historical comparison.

The goal of the short-term analysis of efficacy was to compare the effect of initiation of

melperone therapy on subjects who received placebo in the double-blind study to the effect of melperone seen in the double-blind study. Short-term analyses of efficacy were to compare 6 weeks of open-label data in placebo rollover (melperone-naïve) subjects versus 6 weeks of double-blind data in subjects who received melperone in the double-blind study. Covariates such as baseline UPDRS and baseline neuropsychiatric scales were to be used to adjust for different baseline conditions. Short term changes in efficacy measures in the open-label study were to be compared to changes in all subjects in the double-blind study who received melperone, using data from their double-blind baseline to double-blind Day 43.

The goal of the long-term analysis of efficacy was to examine longitudinal changes in response. Long-term efficacy analyses were to include all open-label subjects using changes from the subject's last assessment before receiving melperone (whether in the double-blind study or in the open-label study) to Months 6, 12, etc. in the open-label study. Long-term changes were to be compared to each subject's last observation before receiving melperone.

The study was terminated due to lack of efficacy in Lundbeck-sponsored study OV-1003 and efficacy analyses were not performed; values for neuropsychiatric scales are provided by subject in the listings.

Safety:

All subjects who took at least 1 dose of melperone in the open-label study were included in the analysis of safety.

For subjects who received melperone in the double-blind study, adverse events emergent in the double-blind and in the open-label studies were assessed. For subjects who received placebo in the double-blind study, adverse events emergent only in the open-label study were assessed. For any time-to-event analyses, time was measured from the first day of treatment with melperone, whether in a double-blind or the open-label study.

AEs were coded by system organ class (SOC) and preferred term using Medical Dictionary for Regulatory Activities version 10.1. (MedDRA v. 10.1). Overall incidence of adverse events was tabulated by SOC and preferred term. The incidence of AEs was summarized by severity and by relationship to study drug. AEs in various time intervals (e.g., after 6 months of treatment with melperone) also may have been assessed.

Demographic and baseline characteristics were summarized using data from the double-blind baseline period. Data were summarized for all subjects as well as by initial treatment (placebo or melperone, regardless of dose). Descriptive statistics included number and percentage for categorical variables (e.g., sex, race) and mean, standard deviation, median, minimum and maximum for continuous measures (e.g., age, weight).

Summary of Results

Summary statistical tables are provided in Appendix 1and by-subject listings are provided in Appendix 16.2.

Subject Disposition:

A total of 28 subjects enrolled in the study; all 28 subjects prematurely discontinued from the study. Reasons for discontinuation were subject requested study withdrawal (6 subjects, 21.4%), adverse events (5 subjects, 17.9%), treatment failure (5 subjects, 17.9%), Investigator requested study withdrawal, lost to follow-up, and death (1 subject each, 3.6%), and other (9 subjects, 32.1%; study discontinued [6 subjects], sponsor safety concerns due

to consistently low heart rate [1 subject], discontinued per sponsor due to QTC > 500 msec [1 subject], and patient forgot a few doses, then decided to not re-start [1 subject]).

Safety:

A total of 21 subjects (75.0%) experienced at least 1 AE. A total of 64 events were reported during the study; the most frequently reported events (i.e., reported in ≥ 5% of all subjects) were urinary tract infection (6 subjects, 21.4%), Parkinson's Disease (5 subjects, 17.9%), nasopharyngitis, asthenia, oedema peripheral, bradycardia, vision blurred, and constipation (2 subjects each, 7.1%). A tabular summary of AEs by subject is provided below.

Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Total (N=28) n (%)
Nervous system disorders	**11 (39.3)**
Parkinson's Disease	5 (17.9)
Dyskinesia	1 (3.6)
Headache	1 (3.6)
Hypersomnia	1 (3.6)
Motor Dysfunction	1 (3.6)
Multiple System Atrophy	1 (3.6)
Presyncope	1 (3.6)
Somnolence	1 (3.6)
Infections and infestations	**9 (32.1)**
Urinary Tract Infection	6 (21.4)
Nasopharyngitis	2 (7.1)
Lower Respiratory Tract Infection	1 (3.6)
Skin Infection	1 (3.6)
Upper Respiratory Tract Infection	1 (3.6)
General disorders and administration site conditions	**5 (17.9)**
Asthenia	2 (7.1)
Oedema Peripheral	2 (7.1)
Chest Pain	1 (3.6)
Fatigue	1 (3.6)
Gait Disturbance	1 (3.6)
Oedema	1 (3.6)
Cardiac Disorders	**4 (14.3)**
Bradycardia	2 (7.1)
Atrial Flutter	1 (3.6)
Coronary Artery Disease	1 (3.6)
Gastrointestinal disorders	**4 (14.3)**
Constipation	2 (7.1)
Gastrooesophageal Reflux Disease	1 (3.6)
Nausea	1 (3.6)
Oesophageal Stenosis	1 (3.6)
Eye disorders	**3 (10.7)**
Vision Blurred	2 (7.1)
Blepharitis	1 (3.6)
Vascular disorders	**3 (10.7)**
Hypertension	1 (3.6)
Orthostatic Hypotension	1 (3.6)
Poor Peripheral Circulation	1 (3.6)

Adverse Events by System Organ Class and Preferred Term (Safety Population), continued	
Musculoskeletal and connective tissue disorders	**2 (7.1)**
Arthralgia	1 (3.6)
Back Pain	1 (3.6)
Intervertebral Disc Protrusion	1 (3.6)
Osteoarthritis	1 (3.6)
Psychiataric disorders	**2 (7.1)**
Confusional State	1 (3.6)
Somnambulism	1 (3.6)
Reproductive system and breast disorders	**2 (7.1)**
Acquired Hydrocele	1 (3.6)
Breast Pain	1 (3.6)
Respiratory, thoracic, and mediastinal disorders	**2 (7.1)**
Dyspnoea Exertional	1 (3.6)
Pneumonia Aspiration	1 (3.6)
Ear and labyrinth disorders	**1 (3.6)**
Tinnitus	1 (3.6)
Endocrine disorders	**1 (3.6)**
Hyperprolactinaemia	1 (3.6)
Injury, poisoning, and procedural complications	**1 (3.6)**
Fall	1 (3.6)
Wound	1 (3.6)
Investigations	**1 (3.6)**
White blood cells urine positive	1 (3.6)
Metabolism and nutrition disorder	**1 (3.6)**
Decreased appetite	1 (3.6)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**1 (3.6)**
Multiple myeloma	1 (3.6)

Source: Statistical Table 14.3.1.1

The majority of AEs were mild (33/64 events, 51.6%) to moderate (24/64 events, 37.5%); a total of 7 events (7/64 events, 10.9%) were reported as severe. A total of 17 events (17/64 events, 26.6%) were considered to be possibly, probably, or definitely related to study drug; 47 events (47/64 events, 73.4%) were considered to be unlikely or not related to study drug. All of the AEs considered to be possibly, probably, or definitely related to study drug were mild to moderate in severity.

One death was reported during this study. Subject 005-159 experienced a severe AE of pneumonia aspiration considered unlikely related to study drug. The event was considered an SAE, study drug was discontinued, and the subject died due to the event ("resolved" was to be indicated on the CRF in the event of death of the subject; therefore, Listing 16.2.7.2 states that this event was resolved 23May2006 - 04Jun2006). A total of 9 subjects (9/28 subjects, 32.1%) experienced 11 SAEs as follows: atrial flutter, bradycardia, coronary artery disease, Parkinson's Disease, presyncope, oesophageal stenosis, chest pain, urinary tract infection, multiple myeloma, multiple system atrophy, and pneumonia aspiration (1 subject each, 3.6%). All of the 11 SAEs reported were considered to be unlikely or not related to melperone. A total of 6 subjects experienced AEs that led to premature discontinuation as follows: multiple system atrophy, Parkinson's disease, hyperprolactinemia, urinary tract infection, multiple myeloma, and pneumonia aspiration (1 subject each, 3.6%). The adverse event of pneumonia aspiration led to death. Four of the AEs leading to discontinuation were also considered to be SAEs (multiple myeloma in

Subject 013-323, urinary tract infection in Subject 019-153, multiple system atrophy in Subject 019-189, and the aspiration pneumonia in Subject 005-159). Of the 6 AEs that led to premature discontinuation, most were considered to be unlikely or not related to melperone; 1 AE of Parkinson's disease (Subject 007-121) was considered to be possibly related to study drug and 1 AE of hyperprolactinemia (Subject 009-142) was considered to be definitely related to study drug.

There were no clinically meaningful changes in mean values over time (from baseline to 6 months) in hematology, chemistry, urinalysis, lipid profile, and other laboratory variables (ie, prolactin and glycosylated hemoglobin). A total of 7 subjects experienced a potentially clinically significant abnormal laboratory value (Subjects 001-119, 002-167, 005-131, 009 142, 011-120, 013-323, and 021-127). Subject 001-119 had abnormal urinalysis results including the presence of blood, ketones, leukocyte esterase, protein, and elevated white blood cells per high power field values (WBC/HPF) and RBC/HPF on Day 1; none of the abnormal laboratory results were considered to be AEs. The subject had experienced an SAE of benign prostatic hyperplasia at the end of Study OV-1003; the SAE was moderate, was considered to be not related to study drug, was considered resolved following elective prostate surgery, and study medication was continued throughout hospitalization. All of the abnormal laboratory results related to prostate surgery for Subject 001-119 had returned to normal by Week 6.

Subjects 002-167, 011-120, and 021-127 had clinically significant laboratory values consistent with AEs of urinary tract infections; all 3 AEs were mild in severity, unlikely or not related to study drug, and resolved with treatment. All abnormal urinalysis results returned to normal for Subject 021-127. Subject 002-167 requested study withdrawal and no further laboratory results were available. Subject 011-120 experienced the AE of urinary tract infection and abnormal laboratory results (protein, ketones, blood, leukocyte esterase, WBC/HPF, RBC/HPF, WBC, neutrophils, and neutrophils [%]) at the 6-month visit; The AE was resolved by the last visit (Month 12); urinalysis values remained abnormal for protein, blood, leukocyte esterase, RBC/HPF and WBC/HPF at the last visit.

Subject 005-131 experienced an AE of white blood cell urine positive and clinically significant urinary WBC/HPF values (51 WBC/HPF) at the early termination visit following discontinuation due to lack of efficacy. The AE was moderate in severity and unlikely related to melperone. No treatment was provided for this event and no further laboratory results were available.

Subject 009-142 experienced an AE of hyperprolactinemia with clinically significant prolactin (conversion)-CL values (45.62 ng/mL); prolactin remained elevated at retest 30 days later (96.57 ng/mL) then returned to normal range (11.09 ng/mL) by the follow-up visit performed 57 days after onset of the AE of hyperpolactinemia. The AE was moderate in severity, definitely related to study drug, and resolved following discontinuation from study drug due to the event.

Subject 013-323 experienced an AE of multiple myeloma and had clinically significant serum calcium (EDTA) (13.1 mg/dL; normal range = 8.3 - 10.6 mg/dL); the event was severe and was considered an SAE, was not related to study drug, and resolved following treatment. Calcium (EDTA) levels returned to normal (8.6 mg/dL) by the final visit. The subject discontinued melperone due to the event and succumbed to the multiple myeloma 199 days later, prior to database lock.

There was no change in body weight over time (from baseline to Week 6).

CONCLUSIONS

The study was discontinued due to lack of efficacy in Lundbeck-sponsored Study OV-1003. Efficacy analyses were not performed for the current study. Melperone was generally safe and well-tolerated with long-term use in this study.

Final Date: 01 March 2012

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