Title of Trial: A Double-blind, Placebo-controlled, Multicenter, Multinational Phase III Study to Evaluate the Safety and Efficacy of Sarizotan HCl 1 mg b.i.d. in Patients with Parkinson's Disease Suffering from Treatment-associated Dyskinesia (PADDY-1).

Investigational Product: Sarizotan HCl

Trial No.: EMR 62225-018

Study Centers: This study was conducted in 88 centers in North America, Europe (France, Italy, United Kingdom), Israel and Australia/New Zealand.

Trial Duration: 24 Weeks

Development Phase: Phase 3

Publication (reference): None

Study Objectives:

Primary Objective: To demonstrate efficacy of 1 mg Sarizotan HCl b.i.d. after 12 weeks in the treatment of dyskinesia in PD and to demonstrate that it is not worsening the symptoms of PD.

Secondary Objective: To collect safety and tolerability data for 1 mg Sarizotan HCl b.i.d. in Parkinson patients.

Methodology: This was a multicenter, multinational, placebo-controlled, randomized, double-blind, parallel-group Phase III study, conducted to demonstrate efficacy for the anti-dyskinetic effect and non-worsening in PD (the latter as added in Amendment 1) of 1 mg Sarizotan HCl b.i.d. compared to placebo in out-patients with PD. It was planned to include a total of 600 subjects in order to obtain 500 subjects in the intention-to-treat (ITT) population.

After inclusion (Visit 2) there was a placebo run in period of 4 weeks. The double-blind treatment duration was to be 24 weeks, followed by a treatment-free follow-up period of 4 weeks. The 3 major visits (Baseline, Endpoint 1 at Week 12, Endpoint 2 at Week 24) followed an identical agenda in order to exclude influences of accompanying tasks and shifts of the time schedule on the assessment of the primary target variable. At the end of the 4-week follow-up period, subjects were offered the chance to enter a long-term, open-label, safety follow-up study. The instruments to assess tolerability, safety, and efficacy were to be applied at inclusion and/or baseline and thereafter at intervals of 6 weeks or multiples thereof. Diary cards were to be used to record ON and OFF states of the underlying PD and to assess the patient's dyskinesia. At a follow-up visit, a final assessment of safety and efficacy was to be performed.

Number of Subjects (Planned and Analyzed):

Number of subjects	Planned per	Analyzed		
	Regimen	Sarizotan	Placebo	Total
Per protocol	-	213	217	430
Intention-to-treat	500	253	253	506
Safety	-	252	252	504

Diagnosis and Main Criteria for Inclusion/Exclusion:

1. The subject gave his/her written informed consent to participate in the study.
2. The subject was an out-patient aged 30 years or above.
3. (For female subjects of child-bearing potential) The subject was using a reliable method of contraception and provided a negative pregnancy test at entry into the study.
4. The subject presented with a diagnosis of idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria.
5. The subject presented with Stage 2.5 or above on the Hoehn and Yahr staging system.
6. The subject's dyskinesia was present during more than 25% of the waking day (historical information in agreement with the assessment of the investigator according to item 32 of UPDRS).
7. The subject's dyskinesia was at least moderately disabling (historical information in agreement with the assessment of the investigator according to item 33 of UPDRS).
8. The subject had at least 4 ticks/day “ON time with dyskinesia” on each of the two days the diary was completed before the inclusion visit (at Visit 2).
9. The subject had participated successfully in a diary-card training session.
10. The subject had been on a stable dose of anti-Parkinsonian drugs except L-dopa for a period of at least 8 weeks up to the screening visit.
11. In the judgment of the investigator based on the subject’s history, previous treatments, and the investigator’s overall knowledge of PD, the subject was considered as being optimally treated at the present time (i.e. further adjustments of current medication would not have further improved the subject's symptoms of PD).
12. The subject had at least 4 ticks/day “ON time with dyskinesia” on each of the two days the diary was completed before Visit 3.
13. The subject showed adequate compliance with the instructions for filling in the diary.
14. The subject showed adequate compliance with the schedule for intake of study medication

Exclusion criteria comprised safety-related issues such as pregnancy/lactation, renal/hepatic impairment, medical history and recent medication, as well as participation in other studies.

Study Treatment: Sarizotan HCl.

Dose: 1 mg bid

Mode of administration: Oral

Duration of Treatment: 28 weeks: 4 weeks placebo run-in; 24 weeks double-blind treatment phase.

Reference Therapies:

Placebo: Dose: 0 mg b.i.d; Mode of administration: oral.

Criteria for Evaluation:

Primary efficacy target variable:

- Responder rate based on the Unified Parkinson's Disease Rating Scale (UPDRS) items 32 and 33, measured at baseline, after 12 weeks of treatment (Endpoint 1) and after 24 weeks (Endpoint 2). A subject was defined as a responder if the sum score of item 32 and 33 of the UPDRS improved at least 25% compared to baseline at Visit 3.
- The primary non-worsening-in-PD variables were defined as daily time OFF assessed by the subjects' diary as difference to baseline and as sum score of items 18 to 31 of the UPDRS (Part III) as difference to baseline, respectively.

Secondary efficacy target variables:

- Responder rates based on different definitions
- UPDRS (Parts I to VI)
- Variables derived from the subject's diary
- Modified Abnormal Involuntary Movement Scale, at rest and provoked
- Patient's and clinical global impression
- Daily dose of L-dopa

Pharmacokinetic variables:

- Plasma concentrations of Sarizotan and its metabolites.

Safety variables:

- Adverse events (AEs) – incidence and type
- Withdrawals due to AEs
- Laboratory values (chemistry, hematology, endocrine)
- Vital signs
- Electrocardiography

Statistical Methods:

The statistical objectives of the study were to reject the null hypothesis that 1 mg Sarizotan HCl has equal efficacy as Placebo after 12 weeks treatment and to demonstrate that the treatment of 1 mg Sarizotan HCl is non-inferior to Placebo egarding the primary non-worsening-in-PD variables. The analysis for non-worsening in PD was performed as a

metaanalysis to pool the observations from studies EMR 62 225-018 ("PADDY1") and EMR 62 225-019 ("PADDY2"). Relating to multiplicity, the co-primary target variables were tested without any adjustments since all coprimary variables needed to be significant.

The confirmatory analysis for the primary efficacy target variable was performed with the ITT population, using the Cochran-Mantel-Haenszel test, stratified by geographical regions. Estimates of the size of the treatment effects were presented with 95% confidence intervals.

The confirmatory analysis for the primary non-worsening-in-PD target variables were performed with the ITT population, using analysis of covariance (ANCOVA, main effect model: treatment, geographical region; covariables: baseline value of the target variable and Hoehn & Yahr stage at baseline).

All further continuous secondary variables were analysed using ANCOVA as described above. The incidence and type of AEs were summarized by treatment group. Laboratory values were evaluated using mean values, the number of subjects who had values outside normal values, and listing values considered clinically relevant by the investigator.

Results:

Efficacy Results:

The efficacy was assessed using several widely used assessments of dyskinesia in patients with PD. There was neither a clinically relevant nor a statistical significant difference seen between the treatment effect of Sarizotan to that of placebo of the primary efficacy variables analyses either after 12 weeks or 24 weeks of treatment. This was confirmed by the PP analysis and sensitivity analyses.

Safety Results:

Droupouts: During the course of the study, 76 (15.0%) subjects withdrew, the reasons for which are shown below:

Reason for discontinuation	**Number (%) of subjects**	
	Sarizotan (N=253)	**Placebo (N=253)**
Prephase Dropout	1 (0.4)	0 (0)
Adverse Events	16 (6.3)	19 (7.5)
Insufficient efficacy	1 (0.4)	0 (0)
Withdrawal of consent	10 (4.0)	6 (2.4)
Subject lost to follow-up	3 (1.2)	0 (0)
Protocol violation	1 (0.4)	2 (0.8)
Other	8 (3.2)	9 (3.6)
Total	40(15.8)	36(14.2)

Adverse Events:

The spectrum of AEs and SAEs observed during the study did not reveal any new information that would change the risk evaluation of Sarizotan treatment in this group of Parkinson patients. The reporting of TEAEs was similar in the 2 treatment groups for all types of TEAEs. At least 1 TEAE was reported by 67.9% of Sarizotan and 70.6% of placebo subjects and about 25% of subjects in either treatment group had events considered related to study medication. SAEs were reported by a small proportion of subjects (9.1% of Sarizotan and 9.9% of placebo subjects) and <1% of subjects had a SAE considered related to study medication.

The system organ classes most commonly affected during the study were Nervous system disorders, Musculoskeletal and connective tissue disorders, Injury, poisoning and procedural complications, Infections and infestations and Psychiatric disorders (all with >15% of subjects in either treatment group). However, except for Nervous system disorders, for which >15% of subjects reported a related event, related TEAEs were reported in ≤5% of subjects in these system organ classes.

Depression was reported as a TEAE in Sarizotan subjects with twice the frequency of that seen in placebo subjects, both overall (6.0% vs 2.8%) and for related events (1.2% vs 0.4%). A higher frequency of depression in Sarizotan compared to placebo subjects was also seen in study EMR 62225-019. However, there was no indication for this seen in animal behavioral models and the clinical significance is unknown.

Other:

The endocrine panel data showed that the subjects had normal endocrine values at the start of the study. No relevant effects of Sarizotan treatment were seen on cortisol levels during the course of the study. Aldosterone levels, however, decreased in subjects treated with Sarizotan. By Visit 6, after 22 weeks of treatment with Sarizotan, the decrease in the Sarizotan group was statistically significant (p=0.0060) compared to the placebo group. As would be expected with a reduction in aldosterone, there was a corresponding increase in renin levels during the study in Sarizotan subjects. This decrease in basal aldosterone levels and corresponding increase in renin was seen previously in the SPIRID study. These changes are probably due to the dual inhibition of the 2 enzymes CYP11B1 and CYP11B2 that represent the effect of Sarizotan on hormones at the dose used.

The data suggest a possible affect of Sarizotan on potassium levels. Although the increase in potassium at Visit 6 was small (0.12 mmol/L), the difference compared to placebo wasstatistically significant (p=0.0002). However, only 4 Sarizotan subjects actually had an increase in potassium that was above the normal range. In addition, the mean increase seen could be due to the inclusion of patients with a previous risk for potassium increases due to additional pathologies (e.g. type 2 diabetes) and/or concomitant medications (e.g. ACE inhibitors, AT1 antagonists, nonsteroidal anti-inflammatory drugs). These possibilities will be explored in more detail in the pooled analysis of subjects from this study and study EMR 62225-019, and will be reported in the study report for study EMR 62225-019.

The slight decrease in mean systolic blood pressure in Sarizotan subjects (-4.4 mmHg; 95% CI: -6.92; -1.94) reported at Visit 6 shows that Sarizotan does not increase systolic blood

pressure. The decrease seen in Sarizotan subjects is compatible with the decrease in aldosterone seen in these subjects.

Death: No deaths were reported during the treatment phase of the study. There were 3 deaths reported post-treatment, 1 Sarizotan subject and 2 placebo subjects. In no case was the death considered to be related to the study medication.

Conclusion: In conclusion, the data collected in this study demonstrate that Sarizotan is not superior to placebo in reducing treatment-associated dyskinesias. Evaluation of AEs and SAEs that were reported during the study did not identify any unexpected events that would indicate concern. Monitoring of changes in an endocrine panel indicate that Sarizotan does not have any central effect on the pituitary-adrenal axis or on the production of cortisol.