CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20658

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	**20-658**
SPONSOR:	**SmithKline Beecham**
DRUG:	**Ropinirole(SK & F 101468-A) Requip Tablets**
PHARMACOLOGIC CATEGORY:	**Dopamine D_2 Agonist**
INDICATION:	**Symptomatic treatment of Parkinson's disease**
DOSAGE FORM:	**Tablet 0.25, 0.5, 1.0, 2.0, 5.0 mg**
DATE OF DOCUMENT:	**12-29-95**
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1.0 Background:

An investigational new drug (IND) application for ropinirole was submitted in June 1988 to explore its efficacy and safety in the treatment of Parkinson's disease (IND). Domestic clinical trials in human volunteers began in July of that year; however, FDA placed a "hold" on clinical trials in patients because of concerns regarding chemistry and manufacturing. This restriction was lifted in March 1991 and studies were initiated in U.S. patients. Meanwhile, European studies in volunteers and patients began in 1988 and proceeded uneventfully. The worldwide ropinirole clinical trials program includes studies conducted in 16 countries. Proposed pivotal phase III U.S. placebo-controlled protocols (044; 054) and a request for guidance were submitted to the Division on 05 August 1992. End of Phase II meeting with the Division was held in June 1993, and in March 1995 a pre-NDA meeting was held with the Division. The NDA was submitted in December 1995.

Ropinirole was initially investigated by the Cardiovascular Research Group of SmithKline and French at Swedeland (Upper Merion) Pennsylvania, USA. The compound was identified as a dopamine agonist with cardiovascular and central nervous system activity. Its development, however, was targeted for the symptomatic treatment of Parkinson's disease.

The first marketing applications for ropinirole were to be submitted in the U.S.

2.0 Proposed Labeling

"Ropinirole is indicated in the symptomatic treatment of PD. It can be used alone or as an adjunct to L-dopa therapy.

"Ropinirole provides symptom control and delays the need to initiate L-dopa by six to twelve months in PD patients who have not previously required dopaminergic therapy.

"When used as adjunctive treatment to L-dopa/DCI in the management of PD, ropinirole provides enhanced symptomatic control, permits a mean reduction in L-dopa dose (~20%) while maintaining symptomatic control, and reduces the ' on-off ' and 'end of dose ' fluctuations associated with chronic L-dopa therapy.

"Ropinirole should be given in divided doses tid with meals. Patients are individually titrated based on response and tolerability. Therapy with ropinirole should be initiated with a dose of 0.25 mg tid. This dose may be increased by 0.25 mg tid weekly to a dose of 1.0 mg tid. Thereafter, weekly increments of 0.5 mg to 1.0 mg tid may be given.

"When ropinirole is used as an adjunct therapy to L-dopa (DCI), the dose of L-dopa may be cautiously decreased as ropinirole is increased.

"Doses greater than 24 mg/day have not been studied in clinical trials."

3.0 The Clinical Trial Program

The clinical trial program has been designed to provide data from adequate and well controlled trials to establish the efficacy of ropinirole as symptomatic treatment of Parkinson's disease. The trials are outlined in the Table of Studies (attached). Hence, the efficacy of ropinirole has been examined as early primary therapy for PD in patients not treated with l-dopa (two studies, 32 and 54), and as adjunct therapy in combination with l-dopa for the treatment of more advanced PD (6 studies, 30, 34, 36, 38, 40, 44). There are two active controlled studies 53 and 56. A total of 2106 patients have been enrolled in therapeutic studies, 1364 have been treated with ropinirole, 298 with placebo and 444 with active comparators (bromocriptine or l-dopa).

3.1 Methods

All studies that are presented to demonstrate efficacy were double-blind, placebo controlled, randomized studies conducted according to GCP. The active controlled studies were conducted to a similar standard. Some of the studies incorporated a 2:1 randomization to recruit more patients into the ropinirole group. In the Phase III studies, randomization was stratified according to concurrent selegiline administration. Patients in the selegiline stratum had to be taking the drug at least 4 weeks before the start of the study and continue throughout the six-month study period with the dose unchanged. This was considered necessary in light of the possible neuroprotective and symptomatic effects of selegiline and its extensive use in PD patients.

Studies 053, 054 and 056 were stratified for patients currently taking selegiline although only Study 054 had sufficient patients in each selegiline stratum to give sufficient power to detect a statistically significant difference between ropinirole and placebo.

While more than one dosing regimen in this program was used (bid in phase II and t.i.d. in phase III), a t.i.d. regimen has been established as the preferred regimen and guidelines are given on initial dosage, titration, dose range and daily regimens.

3.2 Population

The patient populations studied in the early and adjunct therapy studies are comparable to those encountered in clinical practice.

The early therapy studies (032, 053, 054, 056) were confined to patients with symptoms of idiopathic PD based on medical history and physical examination, that were of sufficient severity to require dopaminergic therapy (Hoehn & Yahr Stages I-III). None of the patients had received l-dopa or dopamine agonists for more than 6 weeks at any time in the history of their illness (or 6 months in the case of Study 032) prior to study entry and none had received such treatment for PD in the 2 weeks prior to entering the trials. In the studies with an active control (053 and 056), amantadine and anticholinergic therapy could continue, provided the dose remained unchanged.

Entry into the adjunct therapy studies (030, 034, 036, 038, 040, 044) was confined to patients with idiopathic PD (Hoehn and Yahr Stages II-IV) who were not controlled by l-dopa as evidenced by end-of-dose akinesia or simple 'on'/'off' fluctuations. All of the patients had received l-dopa for 3 to 10 years (studies 030, 034) or for sufficiently long to demonstrate lack of control with l-dopa therapy and all had been maintained on a stable dose for a minimum of 2-4 weeks prior to entry. Patients with advanced disease who had severe disabling peak-dose or biphasic dyskinesias and/or unpredictable or widely swinging fluctuations while receiving stable doses of l-dopa, were excluded.

3.3 Efficacy Assessments

3.4 Early Therapy

The primary efficacy measure for ropinirole as early therapy was percentage improvement in the motor score from the Unified Parkinson's Disease Rating Scale (attached). The Unified

Parkinson's Disease Rating Scale (UPDRS) is composed of four parts. The first part measures the severity of symptoms and signs of Parkinson's disease and includes a mentation section and activities of daily living section, as well as the motor section; the second part assesses the complications of dopaminergic therapy of PD; the third part contains the modified Hoehn & Yahr staging used to measure the progression of disease and the fourth part contains the modified Schwab and England Activities of Daily Living (ADL) scale used to measure the patient's global disability.

The UPDRS is a universally accepted rating scale for assessing PD. It is derived from a common and uniform method for the evaluation of PD. It has good inter-rater reliability and its internal consistency is good for all factors except tremor, motivation/initiative and depression, which appear to be independent factors. It has become the most widely used PD rating scale for comparing patient populations and for judging the effect of therapeutic interventions in clinical practice and in clinical trials. A 20% improvement in total UPDRS motor score following apomorphine challenge has been adopted as a standard diagnostic criterion for PD. In the ropinirole clinical program, responders were defined as patients who had a $\geq$ 30% reduction in total UPDRS motor score from baseline. The total motor exam score was calculated as the sum of the 14 individual motor examination components (numbers 18-31) and their subitems (right plus left side of body) of the UPDRS and could take values ranging from 0 to 108. In the original analysis, motor score was calculated using data from either the patient's left or right side, whichever side was worse at baseline. This allowed the totals to range from 0 to 72. The current method of calculating total motor score is to use both the left and right side scores, which allows the totals to range from 0 to 108.

Missing data was handled as follows: for those items which are midline and independent of the side (left/right) of the patient (i.e. items 18,19,20 {face, lips, and chin}, 22 (neck) and 27-31) the mean of all the scores was calculated and substituted for each missing item score (if only 1 or 2). For those items measured on the patient's side (i.e. items 20-26, excluding 20 (face, lips, chin) and 22 (neck), the mean of the scores for the items of the left side only was calculated and substituted for each missing item score; similarly, the mean of the right side scores was substituted for missing items (as long as there were no more than 2 scores missing). If more than two items were missing, that evaluation was omitted.

Secondary outcome measures used to support the efficacy of ropinirole in the early therapy of PD were the requirement for l-dopa rescue and changes in the Clinical Global Impression (CGI) or Clinician's Global Evaluation (CGE) scales (attached).

The CGI was evaluated in studies 053, 054, and 056. This instrument comprises two items: a severity of illness scale which rates the magnitude of disability in relation to other parkinsonian patients, from 'normal' (=1) to 'among the most extremely ill' (=7); and a global improvement scale which scores the patient's condition relative to baseline, from 'very much improved' (=1) to 'very much worse' (=7).

In study 032 a clinician's global evaluation (CGE) was used in place of the CGI. This used a

five point scale to score changes in the patient's condition relative to baseline from 'marked improvement' (=1) to 'markedly worse' (=5). Again, the proportion of patients with scores of 1 or 2 was compared between the placebo and ropinirole groups.

In the early therapy studies, improvement in motor function, assessed by the motor examination of the UPDRS, was chosen as the primary efficacy measure. The early therapy population was defined as patients with minimal or no prior treatment with dopaminergic agents, but who presented with motor symptoms of sufficient severity to warrant the initiation of dopaminergic therapy. Therefore, control or alleviation of these symptoms is the primary target of therapy for these patients.

3.5 Adjunct therapy

The adjunct therapy population was defined as patients treated with l-dopa and experiencing at least simple motor fluctuations. The aim of dopamine agonist therapy in this population is to extend the duration of symptom control and reduce the exposure to l-dopa; these endpoints were assessed in the clinical trials as reduction in awake time spent "off" and reduction in total daily dose of l-dopa, respectively. Adjunct therapy studies were designed to target either awake time spent "off" and/or reduction in l-dopa dose as the primary efficacy endpoint. The primary efficacy measures in the adjunct therapy trials were either improvement in symptomatic control or reduction in l-dopa dose. Symptomatic control was assessed in terms of the percentage of awake time spent 'off' obtained from diary card records of symptom fluctuations.

In study 30 a responder analysis was undertaken, where a responder was defined as a patient with a reduction of 30% or more in proportion of awake time spent "off". The 30% reduction would equate to an increase of approximately 2.5 hours of useful time per day assuming that 40% or more of awake time was spent "off". In study 034, and initially in study 044, responders were defined in terms of reduction in l-dopa dose. Following guidance received from the FDA in August 1992 and to ensure that patients reducing l-dopa dose derived clinical benefit, this endpoint was amended to extend the criteria of response in study 044 to include reduction in time "off". Thus, responders in study 044 were defined as those who had $\geq$20% reduction in awake time 'off' (representing an additional 1.5 hours of productive awake time) and $\geq$20% reduction in dose of l-dopa.

4.0 Monotherapy Studies

4.1 Study 032: Anti-Parkinson efficacy of ropinirole v. placebo as monotherapy in Parkinson's Disease. Study Dates: June 1990 to October 1991.

Objective: To evaluate the anti-Parkinson efficacy of ropinirole v. placebo as monotherapy in de novo Parkinsonian patients.

Study Design

This was a randomized, multicenter, international, double-blind , placebo-controlled study of 12 weeks treatment duration. After a screening phase to determine patient eligibility, patients were randomly assigned to receive treatment for 12 weeks with either ropinirole or placebo, using a 2:1 randomization in favor of ropinirole.

The study was divided into three phases: screening, treatment and follow-up. At screening, patient eligibility criteria were assessed and baseline evaluations undertaken. Assessments of efficacy and safety were undertaken after 1,2,3,4,6,8,10, and 12 weeks of treatment.

Dosage and Administration
Ropinirole could be taken at doses in the range 1.0 mg to 10.0 mg daily in two divided doses. All patients started at the dose of 0.5 mg b.i.d. followed by incremental increases of .5 bid weekly or no greater than 1.0 mg b.i.d. to a maximum dose of 5.0 mg b.i.d. from the start of week 10 (Visit 9). A modification to the dosage regimen was allowed in the event of unacceptable adverse experiences. The dose of study medication was adjusted to control dopaminergic effects. The dose of study drug could be kept constant, or reduced if appropriate, until the next study visit. If appropriate, further dose increases at 0.5 mg unit dose increments were made at subsequent visits.

Patients were permitted to continue their usual anti-Parkinson treatment with anticholinergics, amantadine or selegiline. Patients who were previously treated with either l-dopa, or dopamine agonists, for up to six months, were withdrawn from such treatment for a minimum period of two weeks before screening. Patients were not allowed to receive dopamine antagonists such as domperidone, metoclopramide or sulpiride. If such medication was required, the patient was withdrawn from the study.

At the end of the treatment phase, patients were considered for entry into an extension phase of the study, performed under a separate protocol. Those who did not enter this phase were followed up 7 to 10 days after the last dose of study medication.

Prestudy screening, Enrollment, and Baseline Phase
Patients were entered into the study from nine hospital centers in six countries, mostly in the U.K. Patients who fulfilled the following inclusion criteria were entered into the study: male or female patients aged 30 to 80 years diagnosed with idiopathic Parkinson's disease with Hoehn and Yahr stage I-IV based on presence of bradykinesis and at least one other feature of Parkinson's disease- tremor, rigidity, or postural instability. Patients who were candidates for dopaminergic therapy and patients who had not previously received dopamine therapy were eligible. Patients who had previously received l-dopa or dopamine agonists as monotherapy for up to six months were also eligible, provided that there had been a wash-out period of at least two weeks before screening. Patients previously treated with non-dopaminergic antiparkinson drugs (e.g. anticholinergics, amantadine, selegiline) which no longer provided satisfactory control could enter the trial, provided that the dose had remained constant for at least one month before screening.

Within one to seven days after successful completion of the screening visit, eligible patients were randomly assigned in a 2:1 ratio to treatment with either ropinirole or placebo, in addition to any permitted background medication. The first dose of study medication at the start of the double-blind phase (Visit 2) was administered under medical supervision at the hospital, and vital signs were measured before and after the drug was given.

Treatment Phase
Patients returned to the hospital for each specified visit, at which the following assessments were made:

-assessment of Parkinson's disease symptoms and signs (clinician's global evaluation, Unified Parkinson's Disease Rating Scale (UPDRS) and the finger tap test
-vital signs (supine and standing blood pressure and pulse), measured pre-dose and one and two hours post-dose
-laboratory testing, after weeks 4, 8 and 12 (Visits 6,8, and 10)
-an ECG, during Visit 10

Post Treatment Phase
One to two weeks after the last administration of study drug, patients returned to the hospital for a follow-up evluation (Visit 11). Patients continuing into the extension study were not required to attend. The following tests were performed:

-medical history and physical examination
-vital signs data
-laboratory tests
-assessment of status of PD
-another 12-lead ECG was performed if any abnormalities were detected at Visit 10

Efficacy Assessments
The primary outcome was the motor score of the Unified Parkinson's Disease Rating Scale (UPDRS). A responder was defined as a patient with at least a 30% reduction in the UPDRS motor scale. During Visits 2 to 10 inclusive, the evaluation comprised the total score from the complete UPDRS before study drug administration and a partial UPDRS using the motor examination criteria (items 18 to 31) performed two hours post dosing. At screening and at followup one complete UPDRS assessment was performed.
Secondary measures of efficacy were the Clinician's Global Evaluation (CGE), scores for the mental and activities of daily living (ADL) of the UPDRS and the finger tap test.

Patient Disposition
63 patients were recruited into the study from nine centers in six countries, mostly (34, 54%) the UK and randomized 2:1 (41/22). 36 patients (87.8%) from the ropinirole group completed the study; 27 of these entered the extension study. In the placebo group 19 patients (86.4%) completed the study and 7 of these entered the extension study.

There was no significant difference between the two treatment groups in the number of patients who withdrew from the study. The reasons for withdrawal are as follows:

Number (%) of randomized patients who completed the study or were withdrawn by the reason for study withdrawal

Reason for Study Conclusion	Ropinirole (n=41)	Placebo (n=22)
Completed study	36 (87.9%)	19 (86.3%)
Adverse Experience	3 (7.3%)	1 (5.4%)
Insufficient therapeutic effect	0 (0%)	2 (9.1%)
Other	2 (4.9%)*	0 (0%)

*Patient 0075 requested withdrawal and patient 0118 was withdrawn due to elective surgery

The following table presents demographic details:

Demographic Parameter	Ropinirole (n=41)	Placebo (n=22)
Males	18 (43.9%)	14 (63.6%)
Females	23 (56.1%)	8 (36.4)
Mean age+SD (years)	59.2 + 9.4	56.5 +10.3

The mean duration of Parkinson's Disease was 28.3 months (SD 23.9, range: 4 to 109 months) for ropinirole patients, compared with a mean duration of 25.8 months (SD 17.6, range 5 to 77 months) for placebo patients. Baseline Hoehn and Yahr classification follows:

Hoehn & Yahr	Ropinirole (n=41)	Placebo (n=22)
I	7 (17.1%)	5 (22.7%)
I.5	7 (17.1%)	2 (9.1%)
II	20 (48.8%)	7 (31.8%)
II.5	3 (7.3%)	2 (9.1%)
III	3 (7.3%)	5 (22.7%)
IV	1 (2.4%)	1 (4.5%)

In the ropinirole group 34 patients (82.9%) presented with PD Hoehn & Yahr status II or less, compared with 14 patients (63.6%) in the placebo group.

Concomitant medications taken most frequently (in > 10% of patients) during the study follow:

Medication	Ropinirole (n=41)	Placebo (n=22)
Selegiline	8 (19.5%)	7 (31.8%)
Amantadine	6 (14.6%)	8 (36.4%)

The following table presents the number of patients at each dose level at endpoint (intent-to-treat population:

Test Dose (mg b.i.d.)	Ropinirole (n=41)	Placebo (n=22)
1.0-2.5 mg	11 (26.8%)	1 (4.5%)
3.0-4.5 mg	17 (41.5%)	6 (27.3%)
5.0-6.0 mg	13 (31.7%)	15 (68.2%)

Efficacy Results

Primary Efficacy Parameter-UPDRS Total Motor Score: % Change from Baseline

A patient was classified as a responder if a reduction of 30% or more was obtained in total motor score (UPDRS items 18 to 31) from baseline. Twenty-nine patients (70.7%) in the ropinirole group had achieved a response in motor score reduction at endpoint compared with 9 (40.9%) in the placebo group (intent-to-treat population). This difference was significantly in favor of ropinirole (p=0.021, chi-square test; C.I. (5.0%, 54.6%). The numbers of patients classed as responders at the time of each visit are summarized in Table 15 (attached).

Forty six patients (30 ropinirole and 16 placebo) were included in an efficacy evaluable analysis at visit 10. At visit 10 (post-dose), 23 (76.7%) of the 30 evaluable patients on ropinirole were classed as responders compared with 8 (50.0%) of the 16 evaluable patients in the placebo group. The difference between treatment groups was not statistically significant (p=0.066, chi square test)(C.I.[-2.1%,55.5%]).

The sponsor performed an additional analysis using logistic modeling. The chosen model contained the following terms: treatment and selegiline. The treatment by selegiline interaction could not be investigated because all the ropinirole patients treated with selegiline were classed as responders. The odds ratio after fitting this model is

Log Odds	Odds Ratio	95% C.I. for Odds Ratio
1.57	4.83	(1.44,16.20)

Since the 95% confidence interval around the odds ratio does not include one, there was a statistically significant effect at the 5% level, a result which agrees with the original analysis. There was also a significant treatment by center interaction in the efficacy-evaluable population which was present, although not statistically significant for the intent-to-treat population.

Due to the significant treatment by selegiline interaction which was not seen in the original analysis, the results are presented separately for each selegiline stratum.

	Ropinirole		Placebo	
	Ratio	SE	Ratio	SE
Selegiline	0.158	0.1133	0.792	0.0841
Non-selegiline	0.692	0.0448	0.881	0.0612

Treatment effects and 95% confidence intervals were calculated within each selegiline stratum, For the selegiline group the treatment difference was -0.634 (95% C.I.(-0.915,-0.353)) and for the non-selegiline group the treatment difference was 0.189 (95%C.I.(-0.329,-0.049)). The improvement was considerably larger for patients treated with both ropinirole and selegiline (84%, compared with 31% in the ropinirole/non-selegiline group, 21% in the placebo/selegiline group and 12% in the placebo/non-selegiline group).

By Country Analysis

Sponsor's Table 24 that follows shows the number of patients (ITT population) who responded to treatment at endpoint by country as well as the percentage change from baseline in total motor score by country.

Variable (endpoint)	Ropinirole group		Placebo Group	
	UK	Other	UK	Other
	N=23	N=18	N=11	N=11
Responders	17(74%)	12(67%)	7(64%)	2(18%)
% Change from baseline	-44.68%	-41.69%	-34.385	-7.60%

For the patient response analysis, there was a statistically significant treatment by country interaction. There was a non-statistically significant difference in the number of responders in the UK between the two treatment groups (p=1.000, Fisher's Exact test), but a significant difference between the two treatments for the non-UK patients. The responder analysis showed a significant treatment by country interaction due to an extremely high response rate on placebo in the UK: the response rate in the ropinirole group for UK ratients was almost the same as that in the placebo group.

Secondary Efficacy Parameters

Clinician's Global Evaluation

At endpoint, there was a statistically significant difference between the treatment groups in the proportion of patients in each category of the CGE classification (p=0.008, Mann-Whitney test). Twenty-nine of the 41 patients (70.7%) receiving ropinirole showed an improvement in their Parkinson's disease symptoms at endpoint, compared with 9 of the 22 patients (40.9%) receiving placebo. There was a statistically significant difference between the two treatment groups (p=0.021, Chi-square test). The percentage of patients who had improved (i.e. marked or mild/moderate improvement) at each visit is shown in Table 28 (attached). The analysis of success rates as evaluated by the clinician's global evaluation is a mirror of the responder analysis for the motor score of the UPDRS suggesting that there is a high degree of correlation between these two assessments.

A regression model fitted consisted of treatment and age. The odds ratio after fitting this model was:

Log Odds	Odds Ratio	95% C.I. for Odds Ratio
1.58	4.84	(1.45, 19.19)

As the 95% C.I. only includes values >1, there is a statistically significant effect in favor of ropinirole, which agrees with the original analysis

Activities of Daily Living (ADL) Component of UPDRS
The mean total ADL score in the ropinirole group at Visit 2 was 7.1 compared with 7.6 in the placebo group. At endpoint the mean percentage change from baseline in the total ADL score was -37.5% in the ropinirole group compared with -30.8% in the placebo group. There were no statistically significant difference between the groups (p=0.564, F-test; C.I. (-31.7%, 18.2%)).

Modified Hoehn & Yahr Staging
At Visit 2 the majority of patients 33 (80.5%) in the ropinirole group and 14 (63.6%) patients in the placebo group were classed as Stage II or below. At endpoint, 37 (90.2%) ropinirole patients and 17 (77.3%) patients in the placebo group were classed at Stage II or below.

Modified Schwab & England ADL Scores
There was no statistically significant difference between the two groups in the mean ADL score from baseline to endpoint as determined by the patient, the patient's family and the clinician,

Summary
This study evaluated early parkinsonian patients up to 12 weeks and employed a b.i.d. dosing regimen to a maximum daily dose of 10 mg. Ropinirole treatment was significantly superior to placebo in mean percentage reduction in UPDRS motor score. The results provide evidence at 3 months of the anti-parkinsonian activity of ropinirole. There was, however, selegiline interaction (the improvement was considerably larger for patients treated with both selegiline and ropinirole) as well as center interaction (there was an extremely high response rate on placebo in the UK; the response rate in the ropinirole group for UK patients was almost the same as that on placebo).

4.2 Study 054; A Double-Blind, Placebo Controlled, Parallel Group Study of Oral Doses of Ropinirole for Six Months in the Treatment of Early Parkinsonian Patients Not Receiving Dopaminergic Therapy. Start 27 August 1992-Ended 30 September 1994
This multicenter Study was conducted in the U.S. at 25 sites.

Study Design
This was a randomized, placebo-controlled, double-blind parallel group study for six months' duration in adult patients with early Parkinson's disease not currently treated with dopaminergic therapy.

Study Population
Early parkinsonian adult (over 30 years old) patients (Hoehn & Yahr Stage I-III) who were candidates for and warranted dopaminergic therapy, who had not previously received l-dopa or dopamine agonists for more than 6 weeks in total were eligible to participate. Patients could not have received any Parkinson's therapy (other than selegiline) four weeks prior to the screening

visit. Selegiline was permitted provided that the patient remained on a stable dose for at least four weeks prior to visit 1. The duration of prior selegiline therapy was not restricted.

Treatment and Administration

Patients who completed screening procedures were entered into a seven day placebo run-in period. Patients received placebo t.i.d. and were assessed for safety, vital signs, UPDRS and the CGI. Following the successful completion of the run-in period, patients were stratified according to concomitant use of selegiline and were randomly assigned at a ratio of 1:1 to receive either ropinirole or placebo. Patients were titrated to an optimal dose of study medication from a starting dose of 0.25 mg t.i.d. (Level 1) to a maximum dose of 8 mg t.i.d. (Level 13). Dose increases were separated by a minimum of 1 week. All patients had to be titrated to at least 1.5 mg t.i.d. (Level 5). Patients could then be maintained on this dose level or higher once an optimal therapeutic response was achieved (Sponsor's Table 3, attached)..

Sinemet was permitted to be added to the double-blind medication as "rescue" medication. Patients who did not experience sufficient symptomatic benefit despite titration to the highest tolerated dose of study medication could be rescued with l-dopa. UPDRS motor exam should be performed prior to the administration of rescue medication. The dosing schedule for the rescue medication was in accordance with the investigator's standard practice. The patient was permitted to continue on open label l-dopa and double-blind medication for the remainder of the trial.

Study visits were scheduled at weekly intervals for the first month, every other week for the next two months, and at monthly intervals for the remaining three months. At each study visit, VS, adverse events, and CGI were assessed. The UPDRS was performed at the week 4, 12, and 24 visits.

Evaluation Criteria

The mean percentage reduction from baseline in the UPDRS motor score was the protocol defined primary analysis. Secondary efficacy variables were the number of responders (>30% reduction from baseline in UPDRS motor score), the Clinical Global Impression, the number of patients requiring l-dopa rescue, time to l-dopa rescue, number of patients with insufficient therapeutic response and time to insufficient therapeutic response.

Patient Disposition

A total of 268 patients were screened, of which 241 patients were randomized 1-to-1 to study medication: 116 (48.1%) in the ropinirole group and 125 (51.9%) in the placebo group. A total of 58 of 116 patients (50.0%) in the ropinirole group were stratified to the selegiline group. Sixty-one (61) of 125 patients (48.8%) in the placebo group were stratified to the selegiline group.

The number of patients still present in the study at each week is displayed in Table 7 (attached). At least 80% of randomized patients were still present in the study at week 12 of the treatment phase; 81.9% of patients in the ropinirole group and 88% of patients in the placebo group.

Similar results were noted for the selegiline and non-selegiline strata in both treatment groups: non-selegiline strata 79% of ropinirole patients and 85.9% of placebo patients; selegiline strata 84.5% of ropinirole patients and 90% of placebo patients. Beginning at week 12, there was a larger percentage of patients remaining in the placebo group compared to the ropinirole group. At week 24, only 68% of patients in the ropinirole group remained compared to 84% in the placebo group.

The number of patients by treatment group and by reason for withdrawal are presented in Table 8 (attached). 57 of 241 patients in the intent to treat population were withdrawn prior to completing the six month study; 37 in the ropinirole group and 20 in the placebo group. This difference in withdrawal rates was statistically significant (Fisher's exact test, p=0.004). Forty (40) patients were withdrawn because of adverse experiences, including disease progression. A statistically significant greater percentage of ropinirole treated patients were withdrawn due to adverse experiences compared to placebo treated patients (23% v. 10%, Fishers exact test p=0.009). An imbalance in the number of patients withdrawing due to adverse experiences was observed between the selegiline strata (14 selegiline patients and 26 non-selegiline patients), and study treatment: (27 patients in the ropinirole group-16 non-selegiline v. 11 selegiline; and 13 patients in the placebo groups-10 non-selegiline v. 3 selegiline). There was a notable increase in the number of patients withdrawn in the ropinirole group in the interval between week 12 and week 16 of the treatment phase; 8 withdrawn due to adverse experiences and 2 withdrawn for other reasons. The pattern of withdrawal from the placebo group was not notable at any time interval. A total of 14 patients were identified as not reaching Dose Level 5; 8 in the ropinirole group (6.9%) and 6 in the placebo group (4.8%).

A total of 119 patients were receiving selegiline at the time of entry into the study and were assigned to the selegiline strata: 58 (50%) in the ropinirole group and 61 (48.8%) in the placebo group. There were slight differences between the non-selegiline and selegiline groups with respect to sex, age, and race. There was a lower percentage of females in the selegiline stratum particularly in the placebo treatment group. Non-selegiline patients were slightly older than the selegiline patients (mean age 65.4 v. 60.1 years, respectively). Ten of the 12 non-white patients were in the non-selegiline stratum. (See Sponsor's Table page 14, attached).

All patients enrolled in the study were designated Hoehn & Yahr Stages I-III at the screening assessment. The distribution of patients in each stage was comparable in the two treatment groups. The mean duration of Parkinson's disease was very similar for each treatment group; 24.6 ± 20.5 months in the ropinirole group and 22.8 ± 19.3 months in the placebo group. A greater number of patients in the non-selegiline strata were Hoehn & Yahr stage II.5 and stage III at screening when compared to the selegiline group. Patients in the selegiline stratum presented with a longer duration of disease (28.9 months) compared to the non-selegiline stratum (18.5 months).(Table 14, attached).

Prior Medications

233 of the 241 patients (97.7%) entering the study were receiving medication prior to the screening visit. CNS agents were the most frequently used. The most frequently reported agents

were Parkinson's disease medications: selegiline (61.2% in the ropinirole group and 65.6% in the placebo group), levodopa (20.7% in the ropinirole group and 29.6% in the placebo group); and carbidopa (20.7% in the ropinirole group and 28.0% in the placebo group).

Treatment Exposure

Table 16 (attached) summarizes the total daily dose of study medication by week and treatment group. The mean dose of study medication at endpoint for the intention-to-treat population was 15.7 ± 8.3 mg in the ropinirole group and 19.6 ± 7.1 mg in the placebo group. The mean dose of study medication from week 10 to the end of the study was lower in the ropinirole group when compared to the placebo group. Similar differences were observed between the selegiline and non-selegiline strata in the two treatment groups. The maximum dose of study medication was 24 mg in both treatment groups.

Efficacy Results

The primary analysis of the efficacy of ropinirole was conducted on the LOCF endpoint dataset of the intent-to-treat population. For patients who received rescue therapy, the LOCF consisted of the last assessment conducted prior to rescue. Both the analysis of percentage change from baseline in the motor score and the total motor score at endpoint adjusted for baseline score were conducted.

Mean Percentage Change in UPDRS Motor Score

The mean baseline UPDRS motor scores for the intent-to-treat population were comparable between the two treatment groups; 17.9 + 8.8 in the ropinirole group and 17.7 + 8.1 in the placebo group. The mean percentage change from baseline in the UPDRS motor score is presented in Table 17 (attached). There was a larger mean percentage change in the UPDRS motor score in the ropinirole treatment group compared to placebo at week 4, 12, and 24. The estimated treatment difference between ropinirole and placebo was statistically significant (-22.99, 95% CI:-33.85, -12.13)).

There was a significant treatment by selegiline strata interaction. In the selegiline strata, the mean percentage change at endpoint in the ropinirole group was -28.2 compared to +11.5 in the placebo group. In the non-selegiline strata, the mean percentage change at endpoint was -14.7 in the ropinirole group and -4.1 in the placebo group. Based on these results, the placebo group concomitantly treated with selegiline experienced a worsening of motor impairment during the study. In contrast, the placebo group not concomitantly treated with selegiline experienced a slight improvement in motor function. Reviewer statisician Dr. Kun Jin identified six patients (3% of the subjects) whose data accounted for the interaction (attachment 000, 001). This reviewer examined all the data for these subjects- baseline demographics, case report forms, etc.- and found nothing in these variables to account for their contribution to the outcome. All were male, half received ropinirole and the other half placebo, age ranged from 38 to 80, disease duration ranged from 3 to 26 years. Therefore, rather than term this an interaction, the six patients should be termed outliers.

The results of the placebo/selegiline group prompted further investigation of the data. An

analysis of the total motor score at endpoint adjusted for baseline score was conducted.

Total UPDRS Motor at Endpoint Adjusted for Baseline Score
The firm modeled the data which provided the following regression coefficients:

	Estimate	SE(Estimate)
Ropinirole	0.756	0.0309
Placebo	1.026	0.0295

In a regression plot of total motor score at endpoint versus total motor score at baseline (ITT), the regression line for the placebo group was almost superimposed on the no-effect line indicating little treatment effect of placebo on motor score. The regression line for the ropinirole group was below the no effect line indicating a reduction in endpoint motor score compared to baseline. This represents an average improvement of 24% in the ropinirole group. The difference between ropinirole and placebo was statistically significant ($p<0.001$).

In addition, regression coefficients were obtained for each treatment group and selegiline stratum constrained such that the difference between treatments was constant across all strata:

	Estimate	SE(Estimate)
Ropinirole-Selegiline	**0.762**	**0.0387**
Ropinirole-Non-Selegiline	**0.749**	**0.0359**
Placebo-Selegiline	**1.032**	**0.0361**
Placebo-Non-Selegiline	**1.019**	**0.0363**

These results were presented graphically for the two selegiline strata separately. In both strata, the regression lines for the placebo group were almost superimposable on the no-effect line. In both strata, the regression lines for the ropinirole group were below the no-effect line. An analysis of the regression coefficients demonstrated that the coefficients for the placebo groups were not significantly different than 1.0. The regression coefficient for ropinirole treatment was significantly lower than a slope of 1 and were also significantly lower than the slopes of the placebo groups. This analysis also indicated that there was no significant difference in the treatment group regression lines in the separate selegiline strata. Overall, ropinirole provided a 24%-25% improvement in motor score.

The model was also fitted to the 70% endpoint and the week 24 OC. All estimates are similar to those obtained in the ITT endpoint data. The magnitude of the ropinirole response in the week 24 OC dataset was larger with an average improvement of 34% compared to 24% in the ITT endpoint dataset. The results in the efficacy evaluable population were also similar to the ITT population.

Secondary Efficacy Parameters
Patient Response (> 30% reduction in UPDRS motor score)
Table 19 (below) presents the number and percentage of patients who achieved at least a 30%

reduction from baseline in the total motor score of the UPDRS at endpoint in the intent-to-treat population. There was a significantly greater percentage of patients in the ropinirole treatment group who met criteria for response compared to the placebo group.

Number and Percent of Patients with at least a 30% reduction in UPDRS Motor Score

	Ropinirole	Placebo	Odds Ratio	(95%CI)
All Strata	47% (50/107)	20% (23/118)	4.45	(2.26,8.78)
Selegiline	56% (30/54)	14% (8/58)	12.13	(4.14,30.5)
Non-Selegiline	38% (20/53)	25% (15/60)	1.87	(0.75,4:40)

There was a significant treatment by selegiline interaction (p=0.008). Analysis of the separate strata resulted in a statistically significant treatment effect in favor of ropinirole in the selegiline stratum but not in the non-selegiline stratum. A similar response rate and treatment by selegiline interaction was seen in the 70% endpoint in the intent-to-treat population.

The percentage of patients who met criteria for response at week 24 was larger than at endpoint. This was due to the preferential loss of patients who were non-responders, suggesting that these patients were either withdrawn or rescued prior to the week 24 assessment. Overall, similar response rates to the intent-to-treat population were seen in the efficacy evaluable population.

The differential treatment effect in the two selegiline strata for response rate was similar to that obtained in the analysis of the mean percentage change in motor score. In each selegiline stratum there was a greater percentage of patients meeting criteria for response in the ropinirole treatment group compared to placebo group. The magnitude of the difference between ropinirole treatment and placebo treatment was larger in the selegiline stratum.

Dose at first response

Sponsor's Table 20 (attached) presents the number and percent of patients who were responders and the total daily dose at which they first met criteria for response (response defined as 30% reduction on Total Motor Score). In both treatment groups, response criteria were first met most frequently at a total daily dose of less than 4.0 mg or at a total daily dose greater than 20 mg. The majority of responders ended the trial at a total daily dose greater than 20 mg (66% ropinirole, 74% placebo) indicating that responders continued to titrate upward on study medication even after a substantial improvement in motor score was achieved. Similar results were seen in the separate selegiline strata.

Patient Improvement (Score of 1 or 2 on CGI Improvement Item)

Thirty-three percent (38/115) of ropinirole patients and 12% (15/123) of placebo patients achieved a CGI improvement item score of 1 or 2 at endpoint. There was a significant treatment effect favoring ropinirole over placebo (odds ratio: 4.06, 95% CI: 2.00,8.22). In the selegiline stratum, 37.9% (22/58) ropinirole treated patients and 11.5% (7/61) placebo treated patients achieved improvement on the CGI and in the non-selegiline stratum, 28% (16/57) of ropinirole

patients and 13% (8/62) of placebo patients were improved on the CGI. There was no significant interaction between selegiline strata and treatment. Therefore, the treatment effect was similar in both selegiline strata.

In the analysis of the 70% endpoint dataset, there was a significant interaction between treatment and selegiline strata. The odds ratios and 95% CI across selegiline strata were similar to that obtained in the endpoint dataset and demonstrated an overall significnt treatment effect favoring ropinirole over placebo. The selegiline interaction in the 70% endpoint dataset was due to a small difference in the distribution of improvers, so that there was a significantly greater percentage of patients improved in the selegiline stratum than in the non-selegiline stratum.

Number of Patients Requiring l-dopa Rescue

In the ITT population, 29% (36/125) of placebo patients required rescue with l-dopa during the study as compared with 11% (13/116) of ropinirole treated patients. The odds ratio was 0.3 with a 95% C.I. of 0.14 and 0.61 indicating a statistically significant treatment difference in favor of ropinirole. Similar proportions of patients were rescued in the separate selegiline strata.

Number of Patients with Insufficient Therapeutic Response

There was also a statistically significant treatment difference in favor of ropinirole treatment in the number of patients with an insufficient therapeutic response. In the ITT population, 12% (14/116) ropinirole patients compared with 30% (37/125) of placebo patients met the criteria for insufficient response (odds ratio:0.31, 95% C.I.: 0.15, 0.63). Similar proportions of patients had an insufficient therapeutic response in the separate selegiline strata.

Summary

The results of this study provide evidence that ropinirole treatment is effective in reducing the level of motor disability in naive parkinsonian patients in the absence of other anti-parkinsonian therapy. Motor function was significantly improved in the ropinirole group compared to the placebo group as assessed by the reduction in UPDRS motor score at endpoint. However, concomitant selegiline treatment had a substantial interaction on the the magnitude of the treatment difference between ropinirole and placebo in the protocol defined mean percentage change analysis of motor score. In both the selegiline and non-selegiline strata, there was a mean percentage reduction in motor score in the ropinirole group. However, in the placebo group there was a mean percentage increase in motor score in the selegiline strata and a mean percentage reduction in the non-selegiline strata. Therefore, as a group, the patients in the selegiline strata who received placebo appeared to experience a worsening of their motor function. This worsening of motor function was not evident in the placebo treated patients who did not receive concomitant selegiline. This apparent difference in the behavior of the selegiline strata of the placebo group was unexpected since selegiline has been shown to provide some modest symptomatic benefit in Parkinson's disease.

However, the sponsor claims regression on total motor is better than studying the mean percentage change in motor score. When analyzed as a regression analysis, examining total motor score at endpoint, adjusted for differences in the baseline score, the ropinirole group had a

24%-25% improvement in motor score over placebo. Placebo treatment had little effect on motor score. The treatment difference between ropinirole and placebo was similar in the two selegiline strata and thus, the treatment by selegiline interaction seen in the protocol defined analysis seems to be an artifact of the analysis of percentage change in motor score. The results of this study demonstrate that the anti-parkinsonian activity of ropinirole can be extended to 6 months.

4.3 Study 053 A 6 Month Report of a Double-blind, Bromocriptine Controlled, Multicenter Study of Ropinirole at a Flexible Oral Dose of 0.25-8 mg three times daily for three years in the Treatment of early Parkinsonian Patients not treated with L-dopa. Start Date 24 November 1992. 37 centers in Belgium, Finland, France, Germany, Hungary, Israel, Italy, the Netherlands, Norway, Slovenia, South Africa, Switzerland and the UK.

Objectives
Whereas the primary objective of the study was to compare the safety profile of ropinirole against bromocriptine, the secondary objective was to compare the anti-Parkinson efficacy of ropinirole as early therapy in Parkinsonian patients not treated with l-dopa, comparative to bromocriptine, and to establish the time period of delay before initiating l-dopa therapy achieved for ropinirole compared with bromocriptine.

Study Design
This was a multicenter, multicountry, randomized double-blind study. At baseline, patients were stratified for concomitant selegiline use. Eligible patients entered a 7 day placebo run-in period before proceeding to active treatment. During active treatment, patients were assessed weekly for the first month, every two weeks for the next two months and monthly for the next three months.

Study Population
Eligible patients were recruited who had a diagnosis of idiopathic Parkinson's disease and who had not previously received l-dopa or a dopamine agonist. Patients previously treated for less than 6 weeks with moderate or low doses of l-dopa or a dopamine agonist could be enrolled if such treatment was discontinued for at least 2 weeks before screening.

Treatment and Administration
Ropinirole (active and placebo) was supplied as white tablets and bromocriptine (active and placebo) was supplied as capsules. After a one-week placebo run-in patients took one tablet and one capsule three times a day (double dummy design). The total daily dose for ropinirole ranged from 0.75-24.0 mg and the total daily dose for bromocriptine ranged from 1.25 -39.9. Patients were titrated according to their individual response. Dose level 5 was defined as the minimum expected therapeutic dose and the dose could be adjusted throughout the study. The dosing guideline provided to the investigator is shown in Table 2 (attached).

Evaluation Criteria
The UPDRS motor examination was the primary outcome, secondary included Clinical Global

Impression (CGI), patients receiving l-dopa rescue and time to rescue, patients with insufficient therapeutic response (receipt of l-dopa rescue and/or withdrawal due to lack of efficacy) and time to insufficient therapeutic response.

Statistical Methods

Dichotomous response variables were analysed using Fisher's exact test or, if there were sufficient data, logistic regression. The ratio of absolute motor score to baseline motor score was analysed at endpoint using weighted linear regression. Percentage change from baseline in total motor score was analysed using analysis of covariance.

Patients were allocated to one of the two treatments in the ratio of 1:1. Randomization was stratified according to whether or not there was concomitant use of selegiline.

Patient Disposition and Demographics

A total of 354 patients entered the study at 37 centers in Belgium, Finland, France, Germany, Hungary, Israel, Italy, the Netherlands, Norway, Slovenia, South Africa, Switzerland and the UK. Nineteen (19) patients were withdrawn during the placebo run-in phase and were not randomized to double-blind medication. Of the 335 who were randomized, 168 received ropinirole and 167 received bromocriptine. 144 ropinirole patients completed six months and 143 bromocriptine patients completed six months.

The distribution of patients by selegiline stratum is shown in Table 6 that follows:

Study stage	Non-selegiline			Selegiline		
	ropinirole	bromocrip	total	ropinirole	bromocrip	total
Entered			**225**			**110**
Randomized	**115**	**110**	**225**	**53**	**57**	**110**
Completed 6 month	**100**	**92**	**192**	**44**	**51**	**95**
ITT population	**115**	**110**	**225**	**53**	**57**	**110**

A total of 144 patients (85.7%) in the ropinirole group and 143 patients (85.6%) in the bromocriptine group completed the first 6 months of the study. The reasons for withdrawal are shown in Table 9 following:

Reason for Withdrawal	Ropinirole (N=168)	Bromocriptine (N=167)
Adverse experience	8 (4.8%)	16(9.6%)
Lack of efficacy	4 (2.4%)	2(1.2%)
Protocol Violation	6 (3.6%)	1 (0.6%)
Lost to follow-up	3 (1.8%)	2 (1.2%)
Other	3 (1.8%)	3 (1.8%)

In the selegiline stratum of patients, the proportions withdrawing due to advese experiences were similar in the two treatment groups: 4 patients (7.5%) in the ropinirole group and 5 patients (8.8%) in the bromocriptine group. In the non-selegiline stratum, however, the proportion in the bromocriptine group was higher than that in the ropinirole group, although absolute numbers were small: 4 patients (3.5%) in the ropinirole group and 11 patients in the bromocriptine group (10.0%).

Only 24 patients were ineligible for the therapeutic dose intent-to-treat population as they did not reach dose level 5 of study medication either for reason of withdrawal or slower than suggested titration.

The baseline characteristics of the patients' Parkinson's disease follow in Sponsor's table 13.

Baseline characteristic	Ropinirole(n=168)	Bromocriptine (n=167)
Disease duration (months)		
Mean (s.d.)	**22.8(21.1)**	**26.8(25.5)**
Range	0-160	0-162
Hoehn & Yahr		
I n(%)	20 (11.9%)	23 (13.8%)
I.5 n(%)	18 (10.7%)	23 (10.8%)
II n(%)	66 (39.3%)	72 (43.1%)
II.5 n(%)	45 (26.8%)	39 (23.4%)
III n(%)	19 (11.3%)	15 (9.0%)

Eighty patients (47.6%) in the ropinirole group and 87 patients (52.1%) in the bromocriptine group received concomitant anti-Parkinson medication during the trial. The most commonly received concomitant medication was selegiline (53 {31.5%}) in the ropinirole group and (56{33.5%}) in the bromocriptine group. Amantadine was taken by 23(13.7%) and 29 (17.4%) in the respective groups. Other antiParkinson medication taken by between 5 and 10% of patients in either group was trihexyphenidyl.

Medication Exposure

Compliance with study medication was defined as receiving at least 80% of the prescribed medication. Seven patients, all in the ropinirole group, were excluded for reasons of non-compliance.

The initial total daily dose of ropinirole was 0.75 mg and of bromocriptine, 1.25 mg. It was intended for the dose of study medication to be increased at weekly intervals, but the investigator titrated to and maintained an optimal dose for each patient according to that individual's clinical response.

At endpoint, the mean total daily dose of study medication was 8.3 mg(s.d.5.0) in the ropinirole group, representing a mean dose of ropinirole between dose levels 7 and 8 (7.5 and 9.0). In the

bromocriptine group at endpoint, the mean total daily dose of bromocriptine was 16.8(s.d.8.4), also representing a mean dose between dose levels 7 and 8 (15.0 and 17.5 mg).

In the group of patients not receiving selegiline, the mean total daily dose at endpoint was slightly higher: 9.0 mg (s.d.5.2) in the ropinirole group and 17.2 (s.d.8.8) in the bromocriptine group. The mean total daily dose in the selegiline stratum was correspondingly lower: 7.0 mg (s.d.4.4) in the ropinirole group and 16.0 mg (s.d..7.60) in the bromocriptine group. Only three patients (1.8%) in the ropinirole group and 5 patients (3.0%) in the bromocriptine group reached level 13, the maximum total daily dose (24.0mg for the ropinirole group and 39.9mg for the bromocriptine group. Of these patients, three in the ropinirole group and 4 in the bromocriptine group were in the lower age range (<65).

Primary Efficacy
UPDRS Motor Score

Mean UPDRS motor score at baseline and endpoint are summarized in sponsor's Table 5.1.3.2. following:

	Mean UPDRS Motor Score	
	Ropinirole (n=168)	**Bromocriptine (n=167)**
Baseline		
Mean	23.3	22.9
(Range)	(2-61)	(1-52)
Endpoint		
Mean	15.6	17.2
(Range)	(0-69)	(2-52)

There was a statistically significnt treatment-by-selegiline interaction in this study, investigation of which meant that the two subgroups cannot be combined. Results presented following are percentage improvement estimates derived from the regression analysis.

Among patients not receiving selegiline the reduction was approximately 14% higher in the ropinirole group (34%) than in the bromocriptine group (20%). The difference in the non selegiline stratum was statistically significantly in favor of ropinirole. In the selegiline subgroup the reduction in motor score was 34% with ropinirole and 37% in the bromocriptine group, giving a 3% reduction in favor of bromocriptine. Similar findings were obtained from the 24-week observed case analysis, the efficacy evaluable populations and from the 70% analysis.

These results suggest that selegiline has an added effect when administered in combination with bromocriptine. It does not effect the percentage improvement in the ropinirole group.

Responder Analysis
Overall 58% of patients treated with ropinirole (93/161) and 43% in the bromocriptine group (68/157) achieved at least a 30% reduction in UPDRS motor score and were classified as

responders. Because of the treatment by selegiline interaction in the responder analysis, responder data is also presented separately for each of the selegiline subgroups.

This study was powered for the responder analysis to be used to assess whether ropinirole could be considered equivalent to bromocriptine. In this case the underlying assumption was that if there were 70% responders on bromocriptine, then the rate on ropirinole must be 55% or more (i.e., the difference was less than 15 percentage points). The interval around the Odds Ratio for this assumption was (0.52, 1.92). For ropinirole to be considered equivalent to or better than bromocriptine, the confidence interval for the Odds Ratio must exceed completely the lower bound 0.52. The results that when administered with selegiline, there is evidence to suggest that ropinirole and bromocriptine are equivalent. Without selegiline, there is strong evidence that ropinirole is better than bromocriptine, as the confidence interval is entirely in the area in favor of ropinirole and lies mostly above the upper limit 0.92, for the interval for equivalence.

A significant treatment-by-country interaction was also found. This reflected that centers with small numbers of subjects were combined to form each country and was not considered to be clinically relevant.

CGI

The percentage of patients showing an improvement on the CGI are summarized in sponsor's table 5.1.3.3 following. The 95% CI for the Odds Ratios show that ropinirole was more effective than bromocriptine among patients not taking selegiline but there was no statistical evidence of a treatment difference in the selegiline subgroup.

	Ropinirole		**Bromocriptine**
Selegiline	**53%**		**58%**
Odds Ratio		0.72	
90%CI		(0.32,1.59)	
Non-Selegiline	**46%**		**30%**
Odds Ratio		2.26	
90% CI		(1.24,4.13)	

Sponsor's Figures 5.1.3.3 a and b (attached) show the number of patients rated much improved or very much improved on the CGI at each visit, by selegiline stratum. The results show that in the non-selegiline subgroup the response separates at week 12 when there are more responders in the ropinirole group than in the bromocriptine group. In the selegiline subgroup, the data separate at week 16 with slightly more bromocriptine patients with improvement on the CGI than patients on ropinirole.

l-dopa rescue

Twelve patients receiving ropinirole (7%) and 19 patients in the bromocriptine group (11%) required l-dopa rescue therapy. Six patients, all in the bromocriptine group, were receiving selegiline. The between-treatment difference was not statistically significant (p=0.193 Fisher's exact test).

Three additional patients in the ropinirole group and two additional patients in the bromocriptine group had an insufficient therapeutic response.

Summary

This study provided evidence that ropinirole was superior to bromocriptine in the absence of selegiline, although there was no difference between the treatments for patients also receiving selegiline. A statistically significant treatment by selegiline interaction prevented the combination of data from both selegiline strata.

4.4 Study 056 A Six Month Report of a Double-blind, L-dopa plus Benserazide Controlled, Multicentre Study of Ropinirole at a Flexible Oral Dose of 0.25-8mg Three Times Daily for Five Years in the Treatment of Early Parkinsonian Patients Not Treated with L-dopa.

Start July 20 1992 to October 20 1994. 30 centers in Belgium, Canada, France, Israel, Italy, the Netherlands and the UK.

The results of a prospectively planned 6 month interim analysis of the 5 year study 056 are presented to show the relative efficacy of ropinirole as early symptomatic therapy in Parkinsonian patients, both with and without selegiline, comparative to l-dopa.

Study Design

This was a multicenter, multicountry, randomized double-blind study to compare ropinirole and l-dopa (randomized 2:1) as early therapy in Parkinsonian patients not treated with l-dopa. At baseline, patients were stratified for concomitant selegiline use. It was planned to recruit 240 patients with a diagnosis of idiopathic Parkinson's disease (Hoehn & Yahr stages I-III) and who had not previously received l-dopa or a dopamine agonist. Patients previously treated for less than 6 weeks with moderate or low doses of an l-dopa preparation or a dopamine agonist were eligible provided they discontinued such treatment for a minimum of two weeks before screening. Eligible patients entered a 7 day placebo run-in period before proceeding to active treatment. During active treatment, patients were assessed weekly for the first month, every two weeks for the next two months and monthly for the next three months.

Drug Administration

During placebo run-in, patients took one placebo ropinirole tablet three times a day, and one placebo l-dopa capsule a day, in the morning. During active treatment, patients took one tablet and one or two capsules three times a day. The active dose form depended on the randomization. The initial dose of ropinirole was 0.25 mg tid and 50 mg l-dopa od (taken in the morning). The dose of study medication could be increased at weekly intervals, but the investigator was to titrate to and maintain an optimal dose for each patient according to that individual's clinical response. Dose level 5 (4.5mg ropinirole and 250mg l-dopa) was defined as the minimum expected therapeutic dose and level 13 (8.0mg tid ropinirole and 1200 mg l-dopa) was the maximum dose. The dose could be adjusted throughout the study.

Rescue L-dopa

Patients who lost therapeutic efficacy during treatment were initially to be titrated to a higher dose level of study medication. If the highest tolerated dose level was reached without therapeutic effect, open l-dopa could be added to the double-blind study medication as rescue therapy. The dose of l-dopa was to be increased by no more than 50mg l-dopa a week, until an optimal response was reached. These patients continued in the study; the dose of study medication remained blinded and the dose of rescue l-dopa was recorded on the Case Report Form. There was to be a maximum dose of open label l-dopa of 1200 mg per day, giving a maximum total dose of all anti-Parkinsonian medication of either ropinirole 24mg/day plus l-dopa 1200mg/day, or l-dopa 2400 mg/day.

Statistical Evaluation

Sample size determination was based on demonstrating equivalent or better efficacy with ropinirole than with l-dopa. To assess whether ropinirole could be classed as being clinically eqivalent to or better than l-dopa,(i.e. the l-dopa response rate was not more than 15% higher than the ropinirole response rate), 90% confidence intervals were produced. These intervals are based on given an underlying l-dopa response rate of 85%, the minimum ropinirole response rate that would be classed as being equivalent to or better than l-dopa is 70%. On this basis, 240 patients were to be enrolled in a 2:1 ratio, 160 to receive ropinirole and 80 to receive l-dopa in up to 24 centers. Randomization was stratified according to concomitant selegiline use. Because of uneven recruitment at some centers of patients with/without concomitant use of selegiline, formal stratification of randomization was dropped during the course of the study.

Efficacy Variables

Primary Variable

The primary efficacy variable was derived by expressing the difference between the baseline UPDRS motor score and endpoint UPDRS motor score as a percentage of the baseline value.

Secondary Variables

The following were secondary variables:

-percentage of patients responding to treatment, defined as at least a 30% reduction from baseline in the total motor score of the UPDRS
-CGI Global improvement
-percentage of patients requiring l-dopa rescue
-percentage of patients with an insufficient therapeutic response
-dose at first reponse

Formal hypothesis testing was performed only on the selegiline/non-selegiline subgroup. However, the primary conclusions about the overall effectiveness of ropinirole were based on the combined analysis of the two selegiline strata.

Patient Disposition

A total of 282 patients entered the study at 30 centers in Belgium, Canada, France, Israel, Italy, the Netherlands, and the UK. Fourteen patients were withdrawn during the placebo run-in phase and were not randomized to double-blind medication. Of the 268 who were randomized in a 2:1

fashion, 179 received ropinirole and 89 received l-dopa as portrayed in Table 5 following:

Study stage/population	Ropinirole	l-dopa	Total
Entered			282
Randomized	179	89	268
Completed 6 months	160	77	237
ITT Population	.179	89	268
Therapeutic dose ITT population	147	72	219

49 patients (32 ropinirole, 17 l-dopa) were excluded from the therapeutic dose intent-to-treat population as their maximum dose of study medication did not reach dose level 5, corresponding to ropinirole 4.5 mg daily or l-dopa 250 mg daily.

The distribution of patients by selegiline stratum follow in sponsor's Table 6:

Study stage/ population	Non-Selegiline Ropinirole	l-dopa	total	Selegiline Ropinirole	l-dopa	total
Entered			152			122
Randomized	98	50	148	81	39	120
Completed 6 months	85	45	130	75	32	107
ITT Population	98	50	148	81	39	120

Reasons for withdrawal are shown in sponsor's table 9:

Reason for withdrawal	Ropinirole (n-179)	l-dopa (n=89)
Adverse experience	14(7.8%)	12(13.5%)
Lack of efficacy	1 (0.6%)	0
Protocol violation	3 (1.7%)	0
Other	1 (0.6%)	0

There was no significant difference between the treatment groups in the proportion of patients withdrawing from the study (Fisher's Exact Test p=.054). The number of patients withdrawing during the first 6 months was relatively small. In the non-selegiline stratum of patients, the proportions withdrawing due to adverse experiences were similar in the two treatment groups: 11 patients (11.2%) in the ropinirole group and 5 patients (10.0%) in the l-dopa group. In the selegiline stratum, the proportion withdrawing in the l-dopa group was higher than that in the

ropinirole group, although absolute numbers were small: 3 patients (3.7%) in the ropinirole group and 7 patients in the l-dopa group (17.9%). There was no clear pattern of withdrawals due to adverse experiences by week, although 86% of these withdrawals in the ropinirole group occurred during the first 8 weeks of the study, compared with 33% in the l-dopa group.

Demographic characteristics of the ITT population follow:

Demographic Characteristic	**Ropinirole**	**l-dopa**
Age (years)	63(8.9)	63(9.1)
range		
Sex		
male n(%)	113 (63%)	51 (57.3%)
female n(%)	66 (36.9%)	38 (42.7%)
Disease duration (Months)		
mean (sd)	30 (34.3)	29 (27.2)
range		
Hoehn % Yahr		
I n(%)	23 (12.9%)	20 (22.5%)
I.5 n(%)	27 (15.1%)	8 (9.0%)
II n (%)	66 (36.9%)	33 (37.1%)
II.5 n(%)	46 (25.7%)	19 (21.4)
III n (%)	17 (9.5%)	9 (10.1%)

Prior/Concomitant Medication
Previous medication received by > 10% of patients in either group (ITT population) follows

Medication	**Ropinirole**	**l-dopa**
Selegiline	94(52.5%)	43 (48.3%)
l-dopa	26 (14.5%)	7 (7.9%)
Amantadine	18 (10.1)	9 (10.1%)

Concomitant antiParkinsonian medication received in either group (ITT population) includes selegiline 81(45.3%) in the ropinirole group and 39 (43.8%) in the l-dopa group, amantadine (7.3% of patients in the ropinirole group and 4.5% of patients in the l-dopa group).

Dose level 5 was reached at week 6 for both ropinirole (4.5 mg) and l-dopa (250 mg). At endpoint, the mean total daily dose of study medication was 9.7 mg (s.d.6.0) in the ropinirole group, representing a mean dose of ropinirole between dose levels 8 and 9 (9.0 and 12.0). In the l-dopa group at endpoint, the mean total daily dose of l-dopa was 463 mg (s.d. 266.0)

representing a mean dose between dose levels 7 and 8 (400 and 500mg).

Efficacy Evaluation

Primary Efficacy Parameters- UPDRS Motor Score

At baseline, the mean total motor score in the ropinirole group was 21.5(s.d.10.5), compared with 21.7 (s.d.11.3) in the l-dopa group. At endpoint, the mean score had been reduced in both treatment groups, to 15.7 (s.d.9.0) in the ropinirole group and to 13.3 (s.d.8.6) in the l-dopa group. This represented a mean percentage change from baseline at endpoint of 23% in the ropinirole group and 31% in the l-dopa group. The mean percentage change from baseline in UPDRS motor score at endpoint for the selegiline subgroup follows:

Medication	**Ropinirole**	**l-dopa**
Selegiline	81(31%)	39 (43.8%)
Non selegiline	**98(32%)**	**50 (44%)**

There was no difference in response rates in either of the selegiline strata.

UPDRS Responder Analysis

In total 48% of patients treated with ropinirole and 58% treated with l-dopa were classified as responders in that they achieved a > 30% reduction in UPDRS motor score. This difference is not statistically significant.

Many centers had zero responders. Centers were nominally grouped by country to effect an analysis. This showed the presence of a significant treatment by-country interaction.

Summary

At the six month endpoint, an average improvement in UPDRS total motor score of 44% was observed for patients receiving l-dopa compared with an average improvement in score of 32% for patients receiving ropinirole. The difference between the groups was statistically significant. Comparison of the number of patients defined as responders in each treatment group revealed that the odds of a ropinirole patient being classed as a responder relative to an l-dopa patient was 0.64. This was not statistically significant. The finding that l-dopa was of superior efficacy to ropinirole is expected as l-dopa is recognized as the most potent anti-Parkinson agent.

This was a highly powered study, so it was important to discover whether ropinirole could be classed as being clinically equivalent to, or better than l-dopa, which was defined as improvement and responder rates for l-dopa not more than 15% higher than those for ropinirole. This was established by the 90% confidence intervals around these average differences between the treatment groups for these two variables. In neither case could ropinirole be classified as equivalent, although the two treatments were close to equivalent.

Comparison of the number of patients defined as "improvers" (i.e. scoring either 'very much

improved' or 'much improved' on the CGI at endpoint) revealed that the odds of a patient in the ropinirole group being classed as an 'improver'relative to a patient in the l-dopa group being so classed was 0.50. For this secondary efficacy variable a significant treatment by Hoehn & Yahr disease stage interaction was found. After adjusting for country and selegiline stratum, a significant treatment effect in favor of l-dopa was found for patients classified as disease stage II.5/III, although equal efficacy was found for both treatments for the other disease stage groupings (I/I.5 and II).

Seven ropinirole patients (4%) and one l-dopa patient (1%) required l-dopa rescue during the first 6 months. For this variable there was no significant difference between treatments ($p=0.44$, intent-to-treat population). The small number of patients requiring rescue suggests that, although motor improvement was less marked with ropinirole, a majority of these patients had been sufficiently well controlled on ropinirole alone for 6 months, since they were only included in the study if they were considered to require dopaminergic therapy. To conclude, l-dopa showed superiority over ropinirole in terms of efficacy during six months treatment.

Conclusions in Early Therapy

Studies 32 and 54 provide evidence that ropinirole was superior to placebo at reducing UPDRS motor scores at three and six months of treatment in early Parkinson's disease. Improved motor function was supported by the responder analysis. The patients' overall condition assessed by CGI/CGE scores improved significantly more with ropinirole than with placebo.

The requirement for l-dopa rescue was significantly lower in the ropinirole group than in the placebo group for study 54. In study 56 no significant difference was found for l-dopa rescue between ropinirole and l-dopa. The percentage of patients treated with ropinirole requiring rescue was low in all studies, indicating that patients experience sufficient benefit to be maintained on ropinirole alone for six months.

Study 56 shows that ropinirole is not as effective as l-dopa in improving motor symptoms. Equivalence of ropinirole and l-dopa was not proven in this study. The CGI improvements with ropinirole were not statistically significantly different from l-dopa in patients with disease stage Hoehn & Yahr Stage I and II, but there was a significant difference in favor of l-dopa in the more severe stages. Overall, these results suggest ropinirole to be less effective than l-dopa, especially in more severe patients.

In study 53 there was a statistically significant difference in favor of ropinirole compared with bromocriptine in the non-selegiline stratum for improvement in the UPDRS motor score, UPDRS responder analysis and CGI improvement scores. This study suggests that ropinirole was better than bromocriptine when used as early therapy for Parkinson's disease in the absence of selegiline.

Interpretation of the data from the early therapy studies was complicated by the presence of treatment-by-selegiline interactions. In study 53 concurrent administration of selegiline

appeared to have an additive effect when administered in combination with bromocriptine, but was without additional effect in the ropinirole group. The two drugs had similar efficacy when given with selegiline. In contrast, ropinirole was more effective than bromocriptine when given without selegiline. In study 32, patients treated with selegiline and ropinirole had a better response than those treated with ropinirole alone. The sponsor suggests it is possible that selegiline may increase the effects of ropinirole at sub-optimal doses as 10 mg was the maximum daily dose used in this study compared with 24 mg in the Phase III program. Study 54 does not follow this trend. More placebo patients not on selegiline responded compared with those on selegiline but for the ropinirole group the reverse was true. The firm suggests that the small symptomatic effect of selegiline has an additive effect in patients who achieve a suboptimal response with bromocriptine or a suboptimal dose of ropinirole.

5.0 Adjunct Studies

5.1 Study 044: A Double-Blind, Placebo Controlled, Parallel Group Study of Oral Doses of Ropinirole for Six Months' Treatment as Adjunct Therapy in Parkinsonian Patients not optimally Controlled on l-dopa.

The study began on 24 September 1992 and ended on 30 September 1994. This multicenter study was conducted in the US at 16 sites.

Study Design

This was a multicenter, randomized, placebo-controlled, double-blind, parallel study of six months' treatment with ropinirole as an adjunct to l-dopa in Parkinsonian patients not optimally controlled on l-dopa. Patients who completed all screening procedures at Visit 1 and who satisfied all inclusion and exclusion criteria were entered into a seven day placebo run-in period. Following the successful completion of the run-in period (at least 80% compliant with placebo medication), patients were stratified according to concomitant use of selegiline and randomized at a ratio of 2:1 to receive ropinirole or placebo. The maximum duration of past selegiline exposure was not restricted, but patients were required to be on a stable dose regimen for four weeks prior to Visit 1 and to remain on this regimen throughout the six month study. Reductions in the selegiline dose were permitted but increases were prohibited.

The following assessments were conducted at every visit after baseline during the trial: vital signs, review of diary cards, AIMS, CGI, concomitant medications, adverse events, l-dopa dosing, study medication compliance. ECG were performed at weeks 12 and 24 only. Laboratory testing and UPDRS assessments were performed at weeks 4, 12, 24 and followup.

Drug Administration

The starting dose (Level 1) was 0.25 mg t.i.d. Each dose increase during upward titration was to be separated by at least a one week interval. Upward titration could proceed at a slower rate based on tolerability. The maximum dose of study medication was 8 mg t.i.d. (Level 13). All patients had to be titrated to at least 2.5 mg t.i.d (Level 7).

Patients were required to be on a stable dose of l-dopa for at least 4 weeks prior to screening. The l-dopa formulations permitted were Sinemet, Sinemet CR, or a combination of the two. This

dose was to be maintained until titration to dose level 7 (2.5 mg, t.i.d.) when a reduction in l-dopa dose was required. This reduction was accomplished by lowering the Sinemet or Sinemet CR by ½ or 1 tablet (Sinemet CR being lowered before Sinemet). The l-dopa dose was reduced by an additional ½ or 1 tablet with each subsequent upward titration of study medication. If symptom control was lost, upward titration of the study medication was continued in the absence of reduction in l-dopa dose. Patients experiencing no improvement following two upward titrations of study medication warranted reinstatement of l-dopa.

In the event of dopaminergic adverse experiences, the following sequence of events was recommended: first, the l-dopa unit dose was lowered while maintaining the ropinirole dose; second, the frequency of the l-dopa dose was reduced while maintaining the ropinirole dose; and third, the ropinirole dose was reduced. If an unacceptable loss of efficacy resulted from the above actions, the l-dopa dose was returned to baseline level and, if necessary, was increased above the baseline level to maintain adequate control.

Prior and Concomitant Medication

Previous dopamine agonist use was allowed provided that therapy was terminated at least four weeks prior to the start of the study. Prior treatment with ropinirole was not allowed. Previous use of selegiline, amantadine and anticholinergics was permitted if the dose was stable for at least four weeks prior to study start. Patients could continue on these agents during the study. The doses of these agents could be reduced during the trial, but increases were not permitted.

Efficacy Assessments

Primary Efficacy Parameter

The protocol states l-dopa reduction as the primary efficacy parameter. This endpoint was discussed with the Division at the end of phase 2 meeting in June 1993 and with other expert neurologists and it was suggested that a reduction in l-dopa on its own was not an optimum endpoint. Thus a decision was taken to assess the primary efficacy parameter in terms of a responder analysis taking into account a reduction in the amount of time spent "off". This proposal for the analysis of efficacy data appeared in a June 29, 1994 submission serial number S098. The primary efficacy variable was the proportion of patients with at least a 20% reduction in l-dopa dose in conjunction with at least a 20% reduction in awake time spent "off". Percent reductions were calculated from baseline levels. L-dopa reduction was based exclusively on those reductions which were mandated by the protocol only, i.e., those not due to adverse events. Patients meeting both of these criteria were defined as responders.

Diary cards completed by the patients were used to assess the duration of "on" and "off" periods. Two 24 hour diary cards were completed by the patient prior to each visit. (The protocol states "The patient will complete two daily diary cards per week preceding each study visit. The patient is asked to complete the diary cards on the same two days of each relevant week."). Each 30 minute period was marked as either "on", "off", or asleep. Prior to study entry, the investigator discussed with the patient the definition of "on/off" periods. The general definition of "off" includes a lack of mobility (bradykinesia) with or without additional features such as tremor or rigidity. Patients individually defined what constituted an "off" period in discussions

with the investigator. The total number of hours spent both "off" and "on" were summed for the period between study visits and the proportion of awake time spent "off" was calculated:

$$\frac{\text{Total daily awake hours "off"}}{\text{Total daily awake hours "off"+ total daily awake hours "on"}} \times 100$$

Secondary Efficacy Variables

Secondary efficacy parameters included: the number of patients with at least a 20% reduction in l-dopa dose, the number of patients with at least a 20% reduction in percent awake time spent "off", the number of patients with CGI improvement, the number of patients reinstated back up to or above their baseline l-dopa dose, the mean percentage reduction in l-dopa dose, and the mean change in percent awake time spent "off". Reductions in the l-dopa dose were calculated only after excluding reductions due to adverse events. Patients were dichotomized as having an improvement if their Global Improvement score was Very Much Improved (1), Much Improved (2) or Minimally Improved (3) and were classed as having no improvement if their score was No Change (4), Minimally Worse (5), Much Worse (6) or Very Much Worse (7).

Patient Disposition

Of 160 patients screened, 149 were randomized to receive either ropinirole (95) or placebo (54). Reasons for screening failures include: patient inability to comply with protocol requirements (3), significant lab value abnormalities (2), lack of informed consent (2), unstable l-dopa dose for 4 weeks prior to study start (1), no diagnosis of Parkinson's disease stage II-IV (1), primary care giver incapacitated (1), information unavailable (1).

Table 7 (attached) displays the number of patients remaining in the study at each week. By week 24, 79% of ropinirole treated patients remained in the study compared to 65% in the placebo group. The number of patients who completed the study and the number and reason for withdrawals are presented in Sponsor's Table 8 which follows

	Ropinirole (n=95)		Placebo (n=54)	
	n	%	n	%
Completed Study	74	77.9	35	64.8
Withdrawal Reason				
Adverse Event	15	15.8	9	16.7%
Insufficient Effect	4	4.2	8	14.8
Lost to Follow-up	2	2.1	0	0
Other	0	0	2	3.7
Total Withdrawn	21	22.1	19	35.2

The demographic characteristics of the intent-to-treat population follow:

Demographics	Ropinirole (n=95)		Placebo (n=54)	
Sex	n	%	n	%
Male	60	63.2	37	68.5
Female	35	36.8	17	31.5
Age (years)	63		63	
Selegiline Strata				
Selegiline	48	50.5	30	55.6
Non-Selegiline	47	49.5	24	44.4
Disease duration(years)				
Mean (SD)	8.6	(4.7)	9.4	(6.3)
L-Dopa duration (years)				
Mean (SD)	7.3	(4.3)	7.5	(5.6)
Total daily l-dopa dose (mg).				
Mean (SD)	758.5	(421.6)	842.6	(516.9)
Range				
Hoehn & Yahr @ screen	n	%	n	%
I.5	0	0	1	1.9
II	10	10.5	11	20.4
II.5	29	30.5	9	16.7
III	38	40.0	23	42.6
IV	18	19.0	10	18.5

Sponsor's Table 13 (attached) displays the baseline measures of Parkinson's disease symptoms for patients in the intent-to-treat population. The mean percentage of awake time spent "off" was 39.3% for patients receiving ropinirole and 43.4% for patients receiving placebo. There were no notable differences in baseline percentages between selegiline and non-selegiline patients.

Prior and Concomitant Anti-Parkinson Therapy

The most common anti-Parkinson agents received by patients prior to entry into the study were amantadine (18.8%) and trihexyphenidyl (14.8%). Selegiline was received by 56.4% of the population and l-dopa was received by all patients in the trial.

The most common anti-Parkinson medications received by patients during the trial were amantadine (14.1%) and trihexyphenidyl (12.8%). Selegiline was a concomitant medication in 53.7% of patients. All patients were concomitantly treated with l-dopa preparations.

Efficacy Results

Primary Efficacy Measure

Sponsor's Table 17 (following) displays the number and percentage of patients who were classed as responders in the ITT population. A patient was defined as a responder if they had at least a 20% reduction from baseline to endpoint in l-dopa dose and at least a 20% reduction from

baseline to endpoint in percentage awake time spent "off".

	Ropinirole		Placebo	
Week	**# Responders**	**%**	**# Responders**	**%**
6	0/90	0	1/43	2.3
8	10/79	12.7	2/44	4.6
10	27/81	33.3	6/43	14.0
12	31/80	38.8	4/40	10.0
16	28/77	36.4	5/40	12.5
20	28/72	38.9	5/33	15.2
24	24/75	32.0	6/34	17.7
Endpoint	26/94	27.7	6/54	11.1

More patients in the ropinirole group were classed as responders compared to the placebo group at every week and at endpoint (27.7% ropinirole vs. 11.1% placebo). The treatment effect observed at endpoint was statistically significant with an odds ratio of 4.4 and a 95% CI of 1.533, 12.658. The sponsor chose a covariate analysis; when it fit final model by treatment plus group plus selegiline plus Hoehn and Yahr Stage (<II, >II.5), it was significant. The ITT endpoint analysis was supported by analyses of the 70% endpoint dataset and by endpoint analysis of the forced l-dopa reduction ITT and efficacy evaluable populations. Analysis of the week 24 OC dataset showed that the treatment effect was not statistically significant (p=0.062), yet the odds ratio was still consistent with that in the ITT endpoint analysis. This difference was due to a higher withdrawal rate of non-responders compared to responders prior to week 24.

Secondary Efficacy Results

Formal hypothesis testing was performed on the LOCF ITT population for the secondary efficacy parameters described below.

Secondary Endpoints	**Ropinirole(n=95)**		**Placebo(n=54)**		**Odds Ratio**
	n	**%**	**n**	**%**	**(95%CI)**
>20% reduction in l-dopa dose	46/94	48.9	9/54	16.7	6.059 (2.492,14.730)
>20% reduction % awake time "off"	52/88	59.1	23/52	44.2	1.817 (0.891,3.702)
CGI Improvement	55/94	58.5	17/53	32.1	2.981 (1.462,6.080)
Reinstatement with l-dopa,up to or above baseline level	25/94	26.6	23/54	42.6	0.229 (0.097,0.545)

Overall, there were more ropinirole patients (48.9%) who achieved at least a **20% reduction in l-dopa dose** compared to placebo (16.7%). The treatment difference observed for all patients

was statistically significant with an odds ratio of 6.059 (95%CI 2.492,14.730). The percentage of patients with at least a 20% reduction in l-dopa dose was slightly higher for patients receiving selegiline (52.1% ropinirole, 20.0%placebo) compared to non-selegiline patients (45.7% ropinirole, 12.5% placebo).

The treatment effect observed in the ITT population for the number of patients with at least a **20% reduction in the percent awake time spent "off"** at endpoint was not statistically significant. The odds ratio was 1.817 with a 95%CI of (0.891, 3.702). Similarly, the 70% endpoint dataset and the forced l-dopa reduction ITT analysis showed no statistically significant treatment effect. The efficacy evaluable analysis indicated a statistically significant treatment effect using the same model as in the ITT endpoint analysis. The week 24 OC showed no significant treatment effect when using the same model as the ITT endpoint analysis, but showed a statistically significant selegiline by center grouping interaction at the 10% level (p=0.059). The difference is due to the number of patients withdrawing before week 24. The percentage of ropinirole patients classed as a responder is similar at week 24 and at endpoint for both strata, but for the placebo group the number of responders in the non-selegiline strata decreases between week 24 and endpoint, and the number of responders in the selegiline strata increases.

Sponsor's Table 24 following displays the number of patients that experienced improvement as assessed by the **CGI Global Improvement** item for the ITT endpoint. Treatment by selegiline and treatment by center grouping interactions were found to be highly statistically significant for all analyses.

ITT Endpoint	**Ropinirole**		**Placebo**	
	N	**%**	**N**	**%**
Selegiline	22/48	45.8	13/30	43.3
Non-Selegiline	33/46	71.7	4/23	17.4
All Patients	55/94	58.5	17/53	32.1

The treatment by selegiline interaction appears to be due to the larger treatment difference in the non-selegiline stratum compared with the selegiline stratum. The treatment by group interaction appears to be due to the larger treatment difference in one center grouping compared to the other two center groupings.

The following estimates of the treatment odds for each of the selegiline strata were determined:

	Log Odds	Odds Ratio	95% CI for odds ratio
Selegiline	0.128	1.136	0.451, 2.862
Non-selegiline	2.473	11.859	3.371,41.716

These results indicated a statistically significant treatment difference in the non-selegiline stratum with a significantly larger percentage of patients in the ropinirole group improving compared with the placebo group. The treatment difference in the selegiline stratum was not

statistically significant.

The number of patients in each of the individual categories of the CGI improvement score indicated that more ropinirole patients were "much improved" compared to placebo patients and, conversely, more placebo patients were "minimally worse" compared to ropinirole patients.

Table 25- The number of patients in each category of the CGI score at endpoint

	Ropinirole		Placebo	
	N	%	N	%
Very Much Improved	2	2.1	0	0
Much Improved	23	24.5	6	11.3
Minimally Improved	30	31.9	11	20.8
No Change	27	28.7	21	39.6
Minimally Worse	8	8.5	11	20.8
Much Worse	4	4.3	4	7.6
Very Much Worse	0	0	0	0

Categories were ranked 1 (very much improved) to 7 (very much worse). The median difference between treatment groups was -1 (95%CI of -1 to 0), indicating a difference of one category, with patients in the ropinirole group showing more improvement.

Table 26 (following) displays the number of patients who were reinstated back up to or above their baseline l-dopa dose for all patients and across selegiline strata. There were fewer patients reinstated in the ropinirole group compared to the placebo group. The treatment effect observed for all patients was statistically significant ($p<0.0001$). The odds ratio was 0.229 with a 95% CI of 0.097, 0.545.

Table 26-The number of patients reinstated back up to or above their baseline l-dopa dose

	Ropinirole		Placebo	
	N	%	N	%
Selegiline	12/48	25.0	14/30	46.7
Non-Selegiline	10/47	21.3	9/24	37.5
All patients	22/95	23.2	23/54	42.6

Summary

This study provides some evidence that ropinirole is effective as an adjunct therapy to l-dopa, permitting a reduction in the concomitant dose of l-dopa and an improvement in "on/off" motor flucuations. The primary efficacy assessment was defined as at least a 20% reduction in total daily l-dopa dose and at least a 20% reduction in the percentage of awake time spent "off". A statistically significantly greater percentage of patients in the ropinirole treatment group met this combined criterion for response compared to the placebo group (27.7% vs 11.1%, respectively).

This measure was particularly strict since the study was designed to maximize the reduction in l-dopa dose over the six month study while maintaining an equivalent level of symptom control. However, it appears that all of the effect in the response variable came from reduction in l-dopa dose, as percent time "off" was not significant.
In addition to the combined measure of l-dopa sparing and improvement in motor fluctuations, the effect of ropinirole on other measures of l-dopa sparing was found to be significantly positive in favor of ropinirole over placebo. A statistically significantly greater percentage of ropinirole treated patients compared to placebo treated patients were able to sustain at least a 20% reduction in l-dopa (48.9% vs 16.7% respectively). The mean percentage reduction in l-dopa dose at endpoint was also significantly greater in the ropinirole treatment group compared to the placebo group (-19.4% vs -2.8%, respectively). Significantly fewer patients in the ropinirole groups required reinstatement of their l-dopa dose back to or above baseline dose (26.6% ropinirole, 42.6% placebo). In addition, ropinirole patients were reinstated at a later time than placebo patients.
Measures of improvement in "on-off" fluctuations were also examined independently of reductions in l-dopa dose. Both ropinirole and placebo treatment groups reported a lower mean percent time spent "off" at endpoint than at entry into the study. When analyzed as the mean percentage change in percent awake time spent "off", each treatment group appeared to have experienced an overall increase in percent time spent "off". The inclusion of patients with low baseline values for time spent "off" provided for extremely large increases at endpoint. Examination of change from baseline in time spent "off" provided a more sensitive assessment of the treatment effect on this variable. The mean change from baseline in percent awake time spent "off" was significantly greater in the ropinirole group compared to placebo group (-11.7 vs -5.1, respectively). However, analysis of the percentage of patients with at least a 20% reduction in the percent awake time spent "off", did not support a significant treatment differential in the ropinirole group at endpoint (59.1% ropinirole vs 44.2% placebo).

The positive impact of ropinirole treatment on the overall improvement in the patients' status was demonstrated by the analysis of the global improvement item of the CGI. More ropinirole treated patients were rated as improved on the CGI as compared to placebo treated patients, and this difference was statistically significant in patients not concomitantly treated with selegiline in all measures of l-dopa sparing.

To summarize, this study demonstrated that one can substitute l-dopa with ropinirole without making patients worse, although they also are not significantly better. The compound outcome makes little sense here, as the two factors l-dopa reduction and percent time off are independent.

5.2 Study 030-Anti Parkinson Efficacy of Ropinirole vs Placebo as Adjunct Therapy in Parkinsonian Patients not Optimally Controlled on L-Dopa. Study start date April 1990, end date September 1991. The study was conducted in two centers: Center 1 UK, Center 2 France

Study Design
This was a two-center, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of ropinirole during a 12-week period as an adjunct treatment for

symptoms of Parkinson's disease not optimally controlled by l-dopa. The patients will have received between three and ten years of l-dopa therapy and be not optimally controlled as evidenced by reduced efficacy to l-dopa with end of dose akinesia, and exhibiting mild to moderate on/off fluctuations.

On the first visit, patients were screened for eligibility criteria. Suitable patients were then assessed during a seven-day baseline period to establish baseline disease status, l-dopa dose maintenance criteria, and the duration of waking time in the "on" and "off" states with diary cards. If no off-periods were documented during the baseline period, or if the patient was unable to complete the diary cards satisfactorily, the patient was withdrawn at this stage. The stable dose of l-dopa was continued throughout the duration of the study. At the end of the baseline period, patients were randomized to 12 weeks treatment with either ropinirole or placebo as adjunct to treatment with l-dopa, the first dose of active treatment being given at the end of the baseline period under medical supervision. The dosage level was increased in increments of 0.5 mg bid ropinirole at each further visit, at the discretion of the investigator, to a maximum dose level of 4.0 mg bid from the end of Visit 9. Patients returned to the hospital at the end of 1, 2, 3, 4, 5, 8, 10 and 12 weeks of treatment when efficacy parameters, VS, and adverse events were recorded.

If significant adverse events were observed, The dose of study medication was held constant or, if necessary, reduced, until the next study visit. Thereafter, if appropriate, further increase in study drug dose could be attempted at 0.5 mg bid increments during subsequent study visits. The dose of l-dopa was at no stage to be altered from the dose specified during the optimal baseline period. In addition to their usual anti-Parkinson therapy of l-dopa, patients were permitted to continue treatment with anticholinergics, amantadine or selegiline. Patients previously treated with dopamine agonists, such as bromocriptine, were to omit such treatment for a minimum period of two weeks prior to screening.

Efficacy Assessments

Primary Efficacy Measure

The primary efficacy measures were the duration of "off" periods and the proportion of awake time spent in an "off" state, as recorded by the patient in a daily diary. A responder was defined as a patient with a 30% reduction in awake time spent "off"

Secondary Efficacy Measures

Secondary measures of efficacy included the Clinician's Global Evaluation (CGE), the motor component of the Unified Parkinson's Disease Rating Scale (UPDRS), and the finger tap test.

The protocol was modified by three amendments dated April 20, 1990, May 31, 1990, and October 11, 1990. The final study protocol was dated 11 October 1990.

Patient Disposition and Demographic Data

A total of 46 patients entered the study: 23 received ropinirole and 23 received placebo. Each centre recruited 23 patients. There were equal numbers of male and female patients in each

treatment group (14 males, 9 females). The mean age of patients was 61.5 years for ropinirole and 63 years for placebo. Most patients in each group were Hoehn & Yahr stage III (ropinirole 12, placebo 13) or IV (ropinirole 4, placebo 5).

A total of 11 patients were withdrawn prematurely: 2 in the ropinirole group and 9 in the placebo group. Four patients withdrew due to adverse events in the placebo group compared with two in the ropinirole group.

Primary Efficacy Measures

In the original responder analysis, a statistically significant interaction was found between center and treatment (P=0.059). For the intent-to-treat population, there were no significant differences between ropinirole and placebo in relation to the number of responders, as classified by at least a 30% reduction in the duration of "off" periods, either for center 1 (UK), ropinirole -placebo = -3.8% (95% C.I. {-44.3%, 36.8%}) or overall, ropinirole -placebo =26.1%, (95%C.I. {-1.8%, 54%}). For Center 2 (France), however, the number of responders was significantly higher in the ropinirole group, ropinirole-placebo =56.8%(95% C.I.{23.4%, 90.3%}).

For the efficacy-evaluable population, the number of responders was significantly greater overall in the ropinirole group (p=0.009):15 patients (75%) were responders compared with 4 patients (29%) in the placebo group. In center 2, the number of responders was significantly higher in the ropinirole group (ropinirole-placebo =77.5%, 95%C.I. {48%, 100%}) but, as in the intent-to treat population, no significant treatment difference was found at center 1 (ropinirole-placebo = 10.0%, 95%C.I. {-40.2%, 60.2%}).

In the analysis of the mean percentage change from baseline of the proportion of awake time spent "off", no statistically significant treatment effect was found for the intent-to-treat population . (The mean percentage change from baseline was -44.3 for the ropinirole group and -24.0 for the placebo group (95%C.I.{44.8%, 3.0%}). There was, however, a significant difference in favor of ropinirole (p=0.039) in the efficacy evaluable population.

As the mean percentage change of the proportion of awake time spent "off" was affected by a few patients with low values at baseline, an additional analysis of the change in the proportion of awake time spent "off" was performed. This demonstrated a significant treatment effect in favor of ropinirole from visit 9 (p=0.041) which continued at Visit 10 (p=0.042) but just failed to reach significance at endpoint (p-0.053).

There were five patients in the ropinirole group who were taking concomitant selegiline, and two of these patients responded to therapy. Two of the seven placebo group patients who were taking selegiline responded to treatment. There was no statistically significant treatment by selegiline interaction.

Additional Analyses

An additional analysis of the proportion of responders (defined as patients who had at least a 30% reduction from the baseline period in the amount of awake time spent in the off state, at

endpoint) was performed for the intent-to-treat population using logistic modeling to further investigate the center interaction. The chosen model consisted of only the following terms: treatment, sex. The odds ratio after fitting this model was:

Log Odds	Odds Ratio	95%C.I. for Odds Ratio
1.21	3.37	(0.92, 11.31)

The odds ratio represents the odds of a ropinirole patient being classed as a responder, relative to the odds of a placebo patient being classed as a responder. The sponsor suggests that although the 95% confidence interval around the odds ratio includes one, the lower limit is very close to one, suggesting that although there is no statistically significant effect at the 5% level, a larger sample size could have resulted in a significant effect in favor of ropinirole. Other confounding factors that could not be easily investigated due to the small number of patients in this study included sex and l-dopa dose.

Duration of "Off" periods: Proportion of Awake time spent "Off"

For the ITT population, in the ropinirole treatment group, the mean proportion of awake time spent "off" during the baseline period was 47.3% compared with 43.6% in the placebo group. The mean percentage changes from baseline to endpoint by treatment center are summarised in Sponsor's Table 14 following:

Table 14 Mean percentage change from baseline to endpoint in the proportion of awake time spent "off" for the ITT Population

	Ropinirole	Placebo	p-value
Center 1	-44.7 (n=11)	-37.1 (n=12)	
Center 2	-43.8 (n=12)	-9.7 (n=11)	
Pooled data	-44.3 (n=23)	-24.0 (n=23)	NS

There was no statistically significant treatment by center interaction, and an analysis of data pooled from both centers was considered valid. There was no statistically significant difference between treatment groups in the percentage change from baseline period to endpoint in the proportion of awake time spent "off".

Secondary Efficacy Measures

Clinician's Global Evaluation: there was a signficant difference in favor of ropinirole for the intent-to-treat population at endpoint in the percentage of patients improving, 78% for ropinirole vs 35% for placebo (p=0.004).

UPDRS motor scale: there was a significant difference in favor of ropinirole for the intent-to-treat population at endpoint in the mean change in motor score from baseline for data combined over centers (-50.5% for ropinirole vs -15.4% for placebo (p=0.008)), but this should be interpreted with caution in view of the center by treatment interaction.

Table 18 Percentage change from baseline in motor score (regardless of baseline status) in the ITT population

	Ropinirole	Placebo	p-value
Center 1	-29.8% (n=11)	-29.8% (n=11)	NS
Center 2	-69.5% (n=12)	-13.4% (n-10)	0.015
Pooled data	-50.5% (n=23)	-15.4% (n=21)	0.008

There was no statistically significant difference between treatment groups at center 1. At center 2 (p=0.015), and for the pooled data (p=0.008) , however, the difference in percentage change in motor score from baseline was significantly greater in the ropinirole treatment group.

Finger Tap Test: there was a significant difference in favor of ropinirole for the intent-to-teat population but again there was a center interaction.

Summary

This study assessed the efficacy of ropinirole in terms of a responder's analysis. A patient was classed as a responder to treatment if he had at least a 30% improvement over baseline in the proportion of time spent in the "off" state. The other primary analysis was the mean percentage change in the proportion of awake time spent"off". Three secondary efficacy parameters were also analyzed.

In the original responder analysis, a statistically significant interaction was found between center and treatment.In the ITT analysis of the percentage of patients who responded to treatment, there was a statistically significant interaction between center and treatment. At center 2, there was a statistically higher number of responders in the ropinirole group than in the placebo group, but at center 1 and in the analysis using data pooled from both centers, no statistically significant differences were found.

No statistically significant treatment by center interaction was found in the analysis of the proportion of awake time spent in an "off" state. The ropinirole group had a greater mean reduction in awake time spent"off" than the placebo group in both centers. However, the difference between that two treatment groups was much larger in center 002. This was true in both the intent-to-treat and efficacy-evaluable analyses, although only the efficacy-evaluable analysis showed a statistically significant difference between treatment groups.

For the ITT population, there were no significant differences between ropinirole and placebo in relation to the number of responders, as classified by at least a 30% reduction in the duration of "off" periods, either for center 1, ropinirole-placebo=-3.8%, (95%C.I.{-44.3%,36.8%}) or overall, ropinirole-placebo =26.1%,(95%C.I.{-1.8%, 54.0%}). For center 2, however, the number of responders was significantly higher in the ropinirole group, ropinirole-placebo =56.8%, (95%C.I.{23.4%, 90.3%}).

The results of the analyses of the secondary efficacy parameters were generally similar to those of the primary analyses, with center 2 showing a larger difference between the treatment groups than center 001.

5.3 034: **Anti-Parkinson efficacy (l-dopa sparing effect) of ropinirole vs placebo as adjunct therapy in Parkinsonian patients not optimally controlled on l-dopa.** The study

took place between September 1990 and September 1991. This was a multicenter study conducted at 6 centers in the UK and 2 in Israel.

Study Design

This was a double-blind, placebo-controlled three month study of ropinirole (dose range 0.5 mg to 5 mg bid) used as adjunct treatment for symptoms of Parkinson's disease not optimally controlled by l-dopa. The design is similar to that of Study 30 discussed above. On the first visit, patients were screened for eligibility criteria. Suitable patients were then assessed during a seven-day baseline period with diary cards to establish baseline Parkinson's disease status (duration of waking time "on" or "off") and l-dopa dose, which then remained constant during the baseline period. At the end of the baseline period, patients were randomized in a 2:1 ratio to 12 weeks treatment with either ropinirole or placebo as adjunct to treatment with l-dopa. The first dose of active treatment (0.5mg ropinirole or placebo) was given at the end of the baseline period under medical supervision. The dosage level was titrated at each further visit, at the discretion of the investigator, to a maximum dose level of 5.0mg bid.

Patients returned to the hospital at the end of 1, 2, 3, 4, 6, 8, 10 and 12 weeks of treatment when efficacy parameters, vital signs and adverse event data were recorded. Patients were permitted to continue treatment in a blinded medication extension study for a further nine months.

Dosage and Administration

Eligible patients included those receiving treatment with l-dopa for between three and ten years (tid dosing) who were demonstrating lack of control with end of dose akinesia and simple "on/off" fluctuations. Patients must have been receiving l-dopa at a stable dose for at least two weeks prior to screening. The dose then being administered was held constant during the baseline period and the first six weeks of active treatment, but was reduced from the end of week 6 (Visit 7) by which point a dose of 3.0 mg bid ropinirole would have been reached. (A dose of 3.0 mg (bid) ropinirole is considered to be an effective dose.). It was suggested to the investigators that the l-dopa dose could be reduced by 10% to 20% of the baseline dose without loss of control over Parkinson's symptoms. This reduction was achieved either by a reduction in the frequency of administration or by reducing the unit dose of l-dopa. If, following l-dopa dose reduction, unacceptable dopaminergic effects persisted or reappeared at subsequent visits, the dose of study mediction was kept constant or reduced to an acceptable level.

In addition to their usual anti-Parkinson therapy of l-dopa, patients were permitted to continue treatment with anticholinergics, amantadine, or selegiline. Dopamine agonists were prohibited for at least two weeks prior to screening.

Treatment Phase

Study medication was administered twice daily, in addition to the optimal l-dopa dose, which was given at the usual time. This stable dose of l-dopa was continued until the end of week 6 Visit 7), when the dose was reduced by 10% to 20% if possible, while maintaining control over Parkinson's symptoms. Patients returned to the hospital for each specified visit, at which the following assessments were made: investigator review of diary cards, clinician' global evaluation, UPDRS scale, VS, lab tests (Visits 6, 8, and 10) and ECG (Visit 10).

There were two written amendments to the protocol. The first (dated 31 May 1990) permitted all patients (as opposed to only those patients who responded to study medication) to enter the nine month extension study after satisfactory completion of 12 weeks study medication. The second (dated 29 October 1990) increased the statistical power of the study from 80% to 90%, increasing the required sample size.

Efficacy Assessments

Primary Efficacy Measure

The primary efficacy parameter was the percentage reduction in total daily dose of l-dopa. This was analyzed in two ways, the number of responders and the magnitude of the reduction in l-dopa dose in each treatment group. A patient was classed as a responder if a reduction of 20% or more from baseline was made in total daily dose of l-dopa, while maintaining control over Parkinson's symptoms (CGE scores of 1, 2, or 3). For magnitude of response, the results are expressed as percentage change from baseline in total daily dose of l-dopa.

Secondary Efficacy Measures

Secondary efficacy parameters were assessment of symptoms using the CGE, UPDRS motor component, duration of "on/off" periods and finger tap test. Throughout the study, patients completed a daily diary card documenting the number and duration of "on" and "off" periods. An estimate of the average awake period per day spent "on" or "off" in terms of frequency and duration in hours was obtained following discussion between the clinician, patient, and caregiver. The percentage of time spent in the "off" state in the diary period prior to each study visit was compiled from the investigator's summary of the completed days of the patient's diary card and was computed as follows:

$$\frac{\text{Total daily awake hours "off"}}{\text{Total daily hours "off" + total daily hours "on"}} \times 100$$

The total motor exam score was calculated as the sum of the 14 individual motor examination components (numbers 18-31) of the UPDRS and could take values ranging from 0 to 72.

Patient Disposition

A total of 68 patients were enrolled into the study and all were randomized to treatment, 46 with ropinirole and 22 with placebo. Eighteen (82%) patients in the placebo group completed the study; 13 of these patients then entered into the extension phase study. In the ropinirole group, 31 patients (68%) completed the study; 28 continued in the extension study. Four placebo patients and 15 ropinirole patients discontinued prematurely from the study; the reasons are tabulated as follows:

Withdrawal reason	Ropinirole n=46	Placebo n=22
Adverse event	8 (17.4)	3 (13.6)
Insufficient therapeutic effect	4 (8.7)	1 (4.5)
Protocol violation/other	2 (4.3)	0
Lost to followup	1 (2.2)	0
Total withdrawn	15 (32.6)	4 (18.2)

Completed the study	31 (67.4)	18 (81.8)

Demographics

68 patients were recruited from eight centers. Thirty-six (52.9%) were recruited in the UK while the remaining 32 (47.1%) were recruited in Israel. In the ropinirole group there were 29 males and 17 females compared with 12 males and 10 females in the placebo group. Mean age was 63 for both groups.

Hoehn & Yahr state	Ropinirole n=46	Placebo n=22
Stage II	9 (19.6)	4 (18.2)
Stage II.5	7 (15.2)	3 (13.6)
Stage III	24 (52.2)	14 (63.6)
Stage IV	6 (13.0)	1 (4.5)

The majority of patients in each group were classified within Stages III and IV of the disease. The mean duration of the disease (84 months ropinirole and 85 months placebo) and duration of l-dopa treatment (65 months and 69 months, respectively) were similar in both groups. The mean optimal total daily dose of l-dopa was higher in the ropinirole group (676mg) than the placebo group (520mg).

At endpoint, the dose level received by patients in each treatment group is displayed in Sponsor's Table 13:

Test Dose (mg bid)	Ropinirole n=46	Placebo n=22
0.5	6 (13.0)	0
1.0-2.5	10 (21.7)	3 (13.6)
3.0-4.5	10 (21.7)	6 (27.3)
5.0-6.0	20 (43.5)	13 (59.1)

Efficacy Results

Primary Efficacy Measure

Of the 41 patients remaining in the ITT population for the responder's analysis, at endpoint, 20 (48.8%) patients in the ropinirole group responded to treatment compared with 8 (36.4%) patients in the placebo group. The difference between treatment groups was not statistically significant (C.I.: -12.8%, 37.7%). In addition, two patients (034.047 and 034.088) in the ropinirole group achieved a reduction in their total daily dose of l-dopa from baseline of at least 20%, however, the CGE did not support the criteria for response that control over Parkinson's symptoms was maintained, and these patients were therefore classed as non-responders.

For the magnitude of response, at the end of the baseline period, the mean total daily dose of l-dopa in the ropinirole group was 667.7 mg (N=41) compared with a mean daily dose of 520.5 mg (n=22) in the placebo group. At endpoint, the mean percentage change in total daily dose from baseline was -22.3% in the ropinirole treatment group and -19.1% for patients in the placebo group. The difference between treatment groups was not statistically significant (C.I.:-16.4%, 9.8%).

In both treatment groups, a large number of patients (13 in the ropinirole group and 9 in the placebo group) had no reduction in l-dopa dose at all at endpoint, while in the placebo group a small number (5 patients) had large reductions in l-dopa dose.

Use of Selegiline

In the ITT population, 36 (57%) of the 63 patients included in the analysis were taking concomitant selegiline at the start of the study. Twenty-one of these patients were in the ropinirole group and the other 15 were treated with placebo. Thirteen (62%) ropinirole group patients and four (27%) placebo patients receiving selegiline responded to treatment. Of the remaining 27 non-selegiline users, 7/20 (35%) ropinirole patients and 4/7 (57%) placebo patients responded to treatment. There was a statistically significant treatment by selegiline interaction ($p=0.041$). Analyzing the two strata separately, there was no statistically significant difference in response rates between the two groups for non-selegiline users, but there was a significantly higher response rate in the ropinirole group for patients who were selegiline users ($p=0.037$).

Maintenance of Control over symptoms

In the ITT population, control over Parkinson's symptoms was maintained by 37 (90.2%) ropinirole treated patients compared with 19 (86.4%) placebo treated patients.

Secondary Measures

There was no significant difference between treatment groups in the proportion of patients in each category of the CGE classification at endpoint. Regarding the change in motor score of the UPDRS, (ITT) comparing the two treatment groups non-parametrically showed no statistically significant difference in the percentage change in total motor score at endpoint. At endpoint, the mean proportion of time spent in the "off" state was reduced by 22.6% in the ropinirole group compared with a mean reduction of 2.5% in the placebo group. The difference was not statistically significant. Twenty (47.6%) of the 42 evaluable ropinirole group patients had reduced the percentage of time spent in the "off" state by at least 30% compared with 6(27.3%) of the 22 evaluable placebo patients. The difference was not statistically significant.

Summary

The principal objective of this study was to evaluate the efficacy of ropinirole by reducing the optimum daily dose of l-dopa, while maintaining control over Parkinson's disease symptoms. Control over symptoms was evaluated in terms of an improvement in CGE or no change, relative to the end of baseline visit. A confirmatory statistical analysis was performed only on the primary efficacy variable (>20% reduction in l-dopa dose while maintaining control over Parkinson's symptoms). At the end of 12 weeks treatment, 69% of patients treated with ropinirole had achieved at least a 20% reduction from baseline in total daily dose of l-dopa, while maintaining control over Parkinson's symptoms, compared with a response rate of 29% in the placebo group. In the ITT population, the difference between treatment groups in patient response was not statistically significant, although there was a trend of responders among ropinirole-treated patients than placebo group patients.

The magnitude of response (reduction in mean daily dose of l-dopa) from baseline to Visit 10

(Week 12) was also greater in the ropinirole treatment group (674.75mg to 469.7mg) than in the placebo group (487.50 mg to 379.9 mg). The mean percentage reduction in total daily dose of l-dopa from baseline to Visit 10 was 28.7% in the ropinirole group compared with 18.8% in the placebo group. This difference between treatment groups was not statistically significant.

For the ITT population evaluated to endpoint, the difference between treatment groups in mean percentage change in total daily dose from baseline (-22.3% in the ropinirole group and -19% in the placebo group) was less marked and not statistically significant. The sponsor suggests that the difference between the two analyses may be explained by the fact that the ITT population included patients who withdrew early from the study and therefore did not reach their optimal dose of study medication. In addition, the design of the study suggested that investigators should not attempt to reduce the l-dopa optimal dose until Visit 7; patients who withdrew prior to Visit 7 may not have been given an opportunity to reduce the dose of l-dopa, even if this would have been feasible.

For eleven patients, investigators did not reduce the l-dopa dose when a reduction was indicated by the clinician's global assessment, presumably attempting to improve the patient's condition by maintaining the optimal l-dopa dose, in the absence of any signs of intolerance.

There were no statistically significant differences in the percentage change from baseline in total motor scores between the two treatment groups. In both the efficacy-evaluable and ITT analyses, a greater improvement (percentage reduction in motor score from baseline) was observed among placebo group patients than patients treated with ropinrole. However, in both treatment groups there was considerable fluctuations in the mean scores at each assessment and the various combinations of "on/off" states may have added to the variability.

Analysis of diary card data showed a trend in the ropinirole group in the percentage amount of time spent in the "off" state, but the difference between treatment groups was not statistically significant.

The percentage of patients withdrawing from the study was higher in the ropinirole group, although the difference was not statistically significant. The proportion of patients withdrawing due to adverse events was similar in both treatment groups. However, a higher proportion of patients in the ropinirole group withdrew because of insufficient therapeutic effect (4{8.7%}) in the ropinirole group and 1 (4.5%) in the placebo group.

To summarize, this study does not provide a source of evidence of the efficacy of ropinirole as adjunct therapy in the treatment of Parkinson's disease.

5.4 036 Anti-Parkinson efficacy of ropinrole vs placebo as adjunct therapy in Parkinsonian Patients not optimally controlled on l-dopa. The study began 27 July 1990 and the last patient entered the study 6 June 1991.

Study Design

This was a multinational, multicenter, randomised, double-blind, placebo-controlled assessment

of 12 week's treatment with ropinirole given in the dose range 0.5 to 5 mg twice daily in patients with Parkinson's disease not optimally controlled on l-dopa. Five centers were to recruit a total of 45 patients with idiopathic Parkinson's disease (Hoehn & Yahr, Stages II-IV) but although six centers were involved, only 29 patients entered the study. Inclusion criteria included patients age 30 to 80 years demonstrating lack of control to l-dopa therapy such as end of dose akinesia, simple on/off fluctuations. Patients should have been taking l-dopa therapy for between three and ten years and receiving stable and optimal doses for at least two weeks prior to screening. Patients previously treated with a dopamine agonist were to stop such treatment for a minimum of at least two weeks prior to screening with adjustment to a stable l-dopa dose as necessary.

The previous stable background dose of l-dopa was kept constant to maintain control of Parkinson's disease symptoms throughout the study. However, in the event of unacceptable dopaminergic side effects the dose of l-dopa could be reduced. It was recommended that the reduction be in the region of 10 to 20% of the baseline l-dopa dose. The reduction could be performed either by reducing the frequency of administration or by reducing the unit dose of l-dopa. The dose of study medication could be increased at this visit and all subsequent visits by no more than 0.5 mg unit dose. Patients continued to receive their usual anti-Parkinson therapy, i.e. l-dopa, with or without anticholinergics , amantadine, selegiline.

Eligible patients entered a seven day placebo run-in period during which the dose of l-dopa was kept constant and the patients completed a daily diary card documenting l-dopa consumption and the number and duration of awake time "on" and "off". The definition of "on/off" periods was discussed with the patient by the investigator and an "off" period was individually defined for that patient. This generally included a lack of mobility (bradykinesia) with or without additional features such as tremor or rigidity.

Dosage and Administration

The first dose of study medication was administered during Visit 2. Eligible patients were randomized to receive either ropinirole or placebo twice daily in addition to their usual dose of l-dopa. The dose of study medication was to be increased in 0.5 mg increments up to Visit 7 (3.0 mg) and then in 1 mg increments thereafter to visit 10 (5.0 mg bid). At each visit the first dose of study medication was administrated under medical supervision in hospital with two-hour monitoring post-dose. The patient attended a further eight study visits at weekly intervals for the first month and two weekly intervals therafter.

Efficacy Assessments

Primary Efficacy Assessment

The principal evaluation of efficacy was by assessment of Parkinson's symptoms using daily diary cards for the awake periods spent "on" and "off". During the baseline period (between Visits 1 and 2) diary cards were completed daily. Between Study Visits 2 to 9 inclusive the patient completed the diary card during the two days preceding a study visit. Between Study Visits 9 and 10 and the follow-up evaluation, the patient completed the diary card for the seven days preceding the study visit.

A patient was classed as a "responder" to treatment if he had at least a 20% improvement over

baseline in the percentage of time spent in the "off" state. Baseline was defined as the diary period between screening and Visit 2. The percentage of time spent in the "off" state was calculated as follows:

$$\frac{\text{Total daily awake hours "off"}}{\text{Total daily hours "off" + total daily hours "on"}} \times 100\%$$

An improvement was a reduction in this percentage from the baseline period. In addition, a responder analysis was performed using 30% improvement as the cut-off point, so that results from this study could be combined with results from other studies which used a 30% responder analysis.

Secondary Efficacy Assessments

Secondary outcome measures included Clinician Global Evaluation, motor section of UPDRS, modified Hoehn & Yahr staging, Finger tap test, Abnormal Involuntary Movement Scale (AIMS).

Patient Demographics

Twenty-nine patients were recruited into the study from six centers, ranging from one to 7 patients per center. Of these 29 patients, 20 patients (69.0%) were randomized to receive ropinirole and nine patients (31%) received placebo. Of the 20 patients who took ropinirole, 15 patients (75%) were male and five (25%) were female. Of the nine who took placebo, four patients (44.4%) were male and five patients (55.6%) were female. At screening, there were two patients (6.9%) in Hoehn & Yahr Stage II, six (20.7%) in Stage II.5, 16 patients (55.2%) in Stage III and five patients (17.2%) in Stage IV. The proportion of ropinirole patients in each Hoehn & Yahr staging was approximately equal to that of the placebo patients.

The median duration of disease for patients on ropinirole was 8.5 years ranging from 2.1 to 30.9 years. The median duration of disease for placebo patients was 6.8 years ranging from 3.8 to 8.9 years. The median duration of l-dopa therapy for patients on ropinirole was 6.5 years ranging from 0.1 to 17.9 years. The median duration of l-dopa therapy for patients on placebo was 5.9 years ranging from 1.4 to 8.9 years. The mean optimal total daily dose of l-dopa for ropinirole patients was 645 mg ranging from 200 to 1250 mg. The mean optimal total daily dose of l-dopa for placebo patients was 672.2 mg ranging from 200 to 1250 mg.

Patient Disposition

Seventeen of the 20 patients treated with ropinirole (85%) completed the study. Three patients (15%) withdrew because of an adverse event. All nine placebo patients completed the study.

Nine patients in the ropinirole group (45%) altered their total daily dose of l-dopa during the study. Of these, eight patients reduced and one patient increased the total daily dose. Of the nine patients on placebo, four patients (44.4%) altered their total daily dose during the study (three patients reduced and one patient increased the total daily dose).

Efficacy Evaluation

The proportion of patients responding to therapy at endpoint as defined by a 20% improvement by treatment group in the ITT population was 11/19 (58%) evaluable patients who took ropinirole and 4/9 (44%) patients on placebo. Comparing these response rates revealed no significant difference between treatments (p=0.689 Fisher's exact test). An approximate 95% confidence interval for the difference (ropinirole-placebo) in response rates was (-25.9%,52.8%). Sponsor's Table 6.1.2a gives number (%) of patients responding (20% improvement) to therapy at endpoint by treatment group and dose in the same population. The highest proportion of respponders was seen at the higher endpoint doses of ropinirole. No similar pattern was observed in the placebo group. With response defined as 30% improvement at endpoint by treatment group in the ITT population, 11 in the ropinirole group (58%) responded to therapy compared to two patients who took placebo (22%).

The mean proportion of awake time spent in the "off" state during the baseline period was 40.4% (N=19, SD=25.0%) in patients on ropinirole compared to 48.5% (N=9, SD=15.3%) in patients on placebo. The mean percentage change from baseline period to endpoint in the proportion of awake time spent "off" was -39.1% (N=19,SD=34.6%) for evaluable patients on ropinirole compared to -21.3% (N=9, SD=31.4%) on placebo. The 95% CI for the difference (ropinirole-placebo) in means is (-45.8,10.2). There was no statistically significant difference (p=0.204, F test) between treatment groups in the percentage change from baseline period to endpoint in the proportion of awake time spent "0ff".

Regarding the secondary outcomes, there was no statistically significant treatment difference for UPDRS motor score, finger taps, Hoehn & Yahr, AIMS. There was a significant difference between treatment groups in favor of ropinirole for the CGE.

Summary

58% ropinirole subjects vs 44% placebo patients had at least a 20% reduction in the proportion of time spent in the "off" state at endpoint. The result was not statistically significant, perhaps due to the small number of patients. This is suggested by the response rate based on 30% improvement from baseline where the response to ropinirole is almost the same but the number of placebo responders is halved. The analysis of the magnitude of patient response gave similar results. In the ITT population, the ropinirole group had a greater mean percentage reduction in awake time spent "off" than placebo, but the difference was not statistically significant. The results of the secondary measures of efficacy show similar patterns: no statistical significance but some trends to indicate the efficacy of ropinirole. The data from this study are insufficient to be able to recommend a dosage regimen for use in patients with Parkinson's disease. Overall, this study failed to demonstrate significant differences between ropinirole and placebo.

5.4 Protocol 038 Antiparkinson efficacy of ropinirole vs placebo as adjunct therapy in Parkinsonian patients experiencing late stage complex on/off fluctuations. The first patient entered in June 1990, the last patient completed the study in September 1991.

Study Design

This was a randomized, multinational, multicenter, double-blind, placebo-controlled assessment

of 12 weeks treatment with ropinirole given in the dose range 0.5 to 4 mg twice daily in patients with Parkinson's disease experiencing late stage complex on/off fluctuations. Six centers were to recruit a total of 66 patients with idiopathic Parkinson's disease (Hoehn & Yahr Stage III-IV) but only 36 patients entered the study from five centers before study close.

Patients were to be experiencing late stage unpredictable (complex) on/off fluctuations and dyskinesias, unusally significant disabling peak dose or biphasic in nature. Other than the greater severity of the symptoms of the population, the study design was identical to that of Study 036 preceding. Eligible patients entered a seven-day run-in period during which they completed a daily diary card documenting l-dopa consumption and the number and duration of "on/off" periods.

Dosage and Administration

The first dose of study medication was administered during Visit 2. Eligible patients were randomized to either ropinirole or placebo twice daily and titrated by .5mg bid to 4 mg bid. The previous, stable background dose of l-dopa was kept constant to maintain control of Parkinson's disease symptoms throughout the study. It was to be taken at the usual time. However, in the event of unacceptable dopaminergic side effects relative to baseline (e.g. dyskinesias, dystonias) the dose of l-dopa could be reduced. It was recommended that reduction occur in the region of 10 to 20% of the baseline l-dopa dose, either by reducing the frequency of administration or by reducing the unit dose. If the above modifications resulted in unaccepable loss of efficacy warranting return of l-dopa dose to baseline level, the patient was to be withdrawn from the study if unacceptable dopaminergic side effects persisted.

Patients continued to receive their usual anti-Parkinson therapy (i.e. l-dopa, with or without anticholinergics, amantadine, selegiline). Patients previously treated with dopamine agonists discontinued this treatment for at least 2 week prior to screening.

Efficacy Assessments

Primary Efficacy Measure

The principal evaluation of efficacy was by assessment of Parkinson's disease using daily diary cards for the awake periods spent both "off" and "on". (During the baseline period (i.e. between Visits 1 and 2) diary cards were completed daily. Between study visits 2 to 9 inclusive the patient completed the diary card during the two days preceding a study visit. Between study Visits 9 and 10 and between Visit 10 and follow-up evaluation, the patient completed the diary card for the seven days preceding the study visit). The percentage of time spent in the "off" state was calculated as follows:

$$\frac{\text{Total daily awake hours "off"}}{\text{Total daily hours "off" + total hours "on"}} \times 100\%$$

An improvement was a reduction in this percentage from the baseline period. In addition, a responder analysis was performed using 30% improvement as the cut-off point, so that results from this study could be combined with the results from other studies using a 30% responder analysis.

There was also an investigator assessment of the number and duration of periods spent in the "off" state during the eight-hour hospital assessment at Visit 7 and 10 compared with the end of baseline assessment. The percentage of time spent in the "off" state was computed as follows:

$$\frac{\text{Total daily awake hours "off"}}{\text{Total daily hours "off"} + \text{total daily hours "on"} + \text{total awake hours "on with dyskinesias"}} \times 100\%$$

A responder analysis was performed on this parameter where a patient was classed as a responder to treatment if he had at least a 20% improvement in the amount of time spent "off" during hospital visits compared to baseline. The number of periods that a patient spent "off" was compared between treatment groups.

Secondary Efficacy Measures

Investigator assessment of the "on" and "off" periods during an eight-hour hospital admission occured at Visits 2, 7, and 10. The patient status was checked by the investigator at 30 minute intervals to determine any change in patient status. During study visit 2 (end of baseline period) motor assessments (items 18-31) of the UPDRS were performed when a change in patient status (either "on" to "off" or vice versa) was observed during an eight-hour period pre-dosing. Other secondary measures included CGE, finger tap test, AIMS.

Study Power

The sample size was estimated on the basis that 33 evaluable patients were sufficient to show a 40% difference in response rate between treatment groups, with an expected 10% placebo response rate, at the 5% level of significance and a power of 0.8. The primary analysis considered is an endpoint analysis of of the ITT population.

Patient Demographics and Disposition

Thirty-six patients were recruited into the study from five centers in different countries, 24 (67%) to ropinirole and 12 (33%) to placebo. Of the 24 patients who took ropinirole, 15 patients (63%) were male and nine (37%) were female. Of the 12 patients who took placebo, seven patients (38%) were male and five (42%) were female. The mean age of patients in the ropinirole group was 61.8 years ranging from 42 to 70 years. The mean age of patients in the placebo group was 57.9 years ranging from 42 to 70 years. The mean duration of Parkinson's disease for patient on ropinirole was 145.8 months ranging from 70 to 377 months. The mean duration of disease of placebo patients was 179.5 months ranging from 69 to 328 months. The mean duration of l-dopa therapy for patients on ropinirole was 120.6 months ranging from 11 to 317 months. The mean duration of l-dopa therapy for patients on placebo was 144.5 months ranging from 57 to 245 months. At the screening visit the mean optimal total daily dose of l-dopa for patients on ropinirole was 834mg ranging from 300 to 1900 mg. The mean optimal total daily dose of l-dopa for patients on placebo was 742 mg ranging from 200 to 1700mg. At screening in the ropinirole group, there were 14 patients (58%) in Hoehn & Yahr Stage IV and ten (42%) in Stage III. For the placebo group, four (33%) had Stage IV and eight (67%) had Stage III disease.

Seventeen of the 24 patients treated with ropinirole (71%) completed the study. Three patients (12.5%) withdrew because of an adverse event. Nine patients (75%) on placebo completed the study; one patient withdrew due to an adverse event. Other patients in each group were withdrawn due to protocol violations or insufficient therapeutic effect. There was no statistically significant difference between treatment groups in the number of patients who completed the study.

Efficacy Results

Primary Measure

Of the 23 evaluable patients who took ropinirole, 11 patients (48%) responded to therapy. Of the 12 patients on placebo, five patients (42%) responded to therapy. Comparing these response rates revealed no significant difference between treatments (p=0.728, chi-square test).

Sponsor's Figure 6.1.1a (attached) plots the percentage of patients responding to therapy during each diary period and endpoint in the ITT population, A trend was seen in a diary period related manner (therefore a dose-related manner) for patients receiving ropinirole until period 9-10 when a fall in the number of responders appeared to occur at endpoint. The sponsor attributed this to dropouts being carried forward with low efficacy scores. The proportion of responders during period 9-10 was 61% for ropinirole and 44% for placebo.

Sponsor's Figure 6.1.2a (attached) plots the mean proportion of awake time spent "off" during each diary period and at endpoint. In general more time was spent "off" by patients in the ropinirole group but the sponsor suggests this probably reflects the more advanced stage of the disease (screening Hoehn & Yahr score) in these patients.

The mean percentage change from baseline period to endpoint in the proportion of awake time spent "off" was -17.1% (N=23,SD=33.9%) for patients on ropinirole compared to -20.6% (N=12, SD+52.3%) on placebo. This slight difference was not significant (p=0.811, F test).

There was no statistically significant treatment by selegiline interaction. There was no effect of center on the number of patients responding.

Regarding response defined as 30% improvement at endpoint by treatment group in the ITT population, 7/23 patients in the ropinirole group (30%) responded to therapy compared with 3/12 patients who took placebo (25%). This slight difference between treatments was not significant (p=1.00, Fisher's exact test; 95% confidence interval -25.5%, 36.3%).

For the investigator's assessment of the proportion of time spent "off", no significant differences between groups were observed. Fourteen (70%) out of the 20 evaluable patients who took ropinirole responded to treatment (i.e. had at least a 20% reduction in the proportion of awake time spent "off" from baseline) compared with seven (70%) patients who took placebo (no significant difference, p=1.000, chi-square test). At endpoint the mean percentage change in the proportion of awake time spent "off" from baseline was -44.0% (N=20, SD =48.83%) in patients who received ropinirole compared to -29.3% (N=10, SD-73.70%) in patients who received placebo. This difference was not significant, p=0.519, F test. For the eight-hour in hospital

post-dose monitoring period, no significant results in favor of ropinirole were apparent.

Secondary Measures
Regarding the CGE, at Endpoint 19 of the 23 evaluable patients in the ropinirole group (83%) had improved. Of the 12 patients who took placebo, eight patient (67%) had improved. The difference is not significant (p=0.402, Fishers exact test).

There was no significant difference between the two treatment groups for the "off" and "on" state, finger taps, modified Hoehn & Yahr, AIMS.

Summary
The primary objective of this study was to evaluate the reduction in the amount of awake time spent "off" as assessed by patient diary cards in patients exhibiting late stage complex "on/off" fluctuations. A patient was classed as a responder to treatment if he had at least a 20% reduction in the amount of awake time spent "off" compared to baseline. In both the ITT and efficacy evaluable analysis the proportions of patients who responded to treatment at endpoint and Visit 10 respectively was higher in the ropinirole group although the differences between the two treatment groups were small and not statistically significant in either analyses. The mean percentage change from baseline in the proportion of time spent "off" was reduced slightly more in the placebo group, showing again that there was no difference between the two treatment groups.

The percentage of patients who responded to treatment according to the investigator's assessment of the amount of time spent "off" was similar in both treatment groups in both the ITT and efficacy evaluable analyses although the mean percentage reduction from baseline in the proportion of awake time spent"off" was greater in the ropinirole group.

Overall, this study failed to demonstrate a significant difference between ropinirole and placebo. The sponsor suggests this is likely to be due to the small number of patients studied and the large placebo effect observed.

5.4 040 Ropinirole 0.5 mg bid, 1.0 mg bid, or 2.0 mg bid vs placebo as adjunct to l-dopa in the treatment of Parkinson's disease. The study was initiated 15 September 1991 and ended 30 October 1992 and was conducted at 15 centers in the U.S.

Objectives
The objective of the study was to evaluate the minimum effective dose of ropinirole as adjunct to l-dopa in patients with Parkinson's disease not optimally controlled on l-dopa preparations.

Study Design
This was a multicenter, double-blind, placebo-controlled parallel group, randomized trial. Doses of ropionirole investigated were 0.5 mg bid, 1.0 mg bid, and 2.0 mg bid. Eligible patients were those with idiopathic Parkinson's disease (Hoehn & Yahr Stages II-IV). Patients must have received between 3 and 10 years of l-dopa therapy and be poorly controlled as evidenced by

residual Parkinsonian symptoms. Patients were recruited at 15 centers. Total duration of trial was 9 weeks: one week placebo run-in, three week titration phase, four week treatment phase, and one week follow-up.

Visits were scheduled at weekly intervals. Daily patient diary cards were used for recording awake time spent "on" and awake time spent "off". The UPDRS motor exam and the CGE was performed at each visit.

Patients with at least a 20% improvement from baseline in duration of awake time spent "off" were identified as responders. The target enrollment for this trial was 120 patients. This number was calculated to obtain at least 88 patients who completed the trial. The sample size was estimated on the basis that 22 evaluable patients per group would be sufficient to demonstrate a 40% difference in response rates, with an expected placebo response rate of 10%, at the 5% level of significance and a power of 0.9.

Patients who satisfied all criteria for eligibility entered a 7 day placebo run-in period. Patients received one tablet twice a day. During this period, the dose of l-dopa was kept constant. Patients were instructed to complete a daily diary card for each day. The amount of l-dopa and the duration of awake time spent "on" and "off" were recorded on the diary cards.

Dosage and Administration

Patients were continued on their anti-Parkinson's medication for the duration of the trial. The dose of l-dopa was kept constant for 4 weeks prior to the screening visit and for the duration of the study. Patients were permitted to continue other medications, i.e. anticholinergics, amantadine, selegiline for the duration of the trial. Dopamine agonists must have been discontinued a minimum of 2 weeks prior to the screening visit.

Patients were titrated upward on study medication for 3 weeks according to the schedule outlined in Table 3 (attached). At week 4, patients were maintained on their randomized dose level for 4 weeks. Reductions or increases in study medication was not permitted.

Efficacy Assessment

The severity of motor symptoms was assessed at each visit both prior to administration and 2 hours post-dosing by the motor examination section of the UPDRS. At the baseline visit, week 4, week 5 and week 8, the complete UPDRS was assessed. The therapeutic response to study medication was evaluated at each visit by the CGE. The severity of dyskinesias was assessed by the AIMS.

The duration of "on" and "off" periods was assessed by patient diary cards. One diary card was completed by the patient for each 24 hour period. Each 30 minute period was marked as "ON", "OFF", or asleep. The definition of "on/off" periods was discussed by the investigator with each patient prior to entry into the study. "Off" periods were individually defined for each patient. The definition of "off" period generally included lack of mobility (bradykinesia) with or without additional features such as tremor or rigidity.

Primary Efficacy Variable
The total number of hours spent "off", "on", and awake were summed for the one week period between study visits. The proportion of awake time spent "on" and spent "off" were determined for each one week period. The primary efficacy variable was the duration of time spent "off". The duration of "off" periods were presented as the percentage of total awake time. The percentage change from baseline was determined at each study visit and at endpoint.

Secondary Efficacy Variable
The secondary efficacy variables included the responders and the improvement in UPDRS motor score and improvement in CGE. Response was defined as at least a 20% reduction from baseline in the percentage of awake time spent "off". Improvement in UPDRS score was determined as the percentage change from baseline. Improvement in CGE was defined as a CGE score of 1 or 2 indicating at least mild improvement in Parkinson's symptoms.

Statistical Methodology
The data analyzed to test hypotheses in this study were of two types, proportion of patients achieving a dichotomous response and percentage change from baseline scores. Tests of hypothesis concerning interaction terms were declared significant if the p-values were less than 0.10. However, since 75% of the treatment by investigator cells had less than three patients, only treatment effect was included in the model and no test was done for interaction. Tests of hypothesis concerning the significance of overall treatment effects and of linearity were declared significant if the p-values were less than 0.05. Pairwise comparisons were made only when the overall treatment effect was significant and were declared significant if the p-values were less than 0.05.

Patient Demographics and Disposition
125 patients were randomized into the following treatment groups: 31 to placebo, 32 to the 1.0 mg group, 32 patients into the 2.0 mg group and 30 patients into the 4.0 mg group. All patients entering the trial were Stage 2 through Stage 4 on the modified Hoehn & Yahr Staging. The majority of patients in each group were Stage 3. The duration of disease ranged from 3 months to 297 months. The placebo had the highest mean duration of Parkinson's disease of 118 months, compared to 99 months (1 mg), 95 months (2 mg), and 89 months (4 mg). The duration of l-dopa therapy ranged from 22 months to 201 months. The placebo group had the longest mean duration of l-dopa therapy of 91.4 months. In the other groups, the mean duration was 76-78 months. The baseline total daily dose of l-dopa ranged from 200 mg to 2500 mg. All groups had a wide range of l-dopa dose with mean doses between 590 mg and 690 mg.

Prior to entry into the trial, 16% of the study population was treated with a dopamine agonist: 9.4% of the 1.0 mg group, 15.6% of the 2 mg group, 16.7 of the 4.0 mg group and 22.6% of the placebo group. During the trial roughly 37% of the study population was concomitantly receiving anticholinergic therapy (40.6%, 1 mg group; 40.6%, 2 mg group; 40%, 4 mg group and 25.8%, placebo). Concomitant selegiline use occurred in 60% of the study population (62.5%, 56.3%, 63.3%, and 61.3%, respectively.

The four treatment groups were similar in all baseline measures of Parkinson's disease symptoms (Sponsor's Table 8, attached). The mean percentage of awake time spent "off" was approximately 39% for all treatment groups. The mean UPDRS motor score ranged from 15.7 to 19.2 indicating mild to moderate impairment in motor function.

Approximately 90% of patients (112/125) completed the trial. Ten (8%) patients discontinued the trial prematurely due to an adverse event. The remaining 2% withdrew due to protocol violation or insufficient therapeutic effect. The 4.0 mg group had the highest percentage of paatients who completed the trial (96.7%); the lowest percentage was in the 1.0 mg group (81.3%). The 1.0 mg group also had the highest percentage of patients who prematurely discontinued due to an adverse event (12.5%). The 4.0 mg group had the lowest percentage of patients who discontinued due to an adverse experience (3.3%).

Results

Proportion of Awake Time Spent "Off"

The primary efficacy parameter was the reduction in the proportion of awake time spent "off" (Table 12, attached). In general, there was a high degree of variability in the percentage change from baseline in the proportion of awake time spent "off", particularly in the 1.0 mg ropinirole group. In the 2.0 mg and 4.0 mg ropinirole groups, there was a mean reduction in the percentage of awake time spent "off" at endpoint. At the endpoint in the placebo and 1.0 mg groups, there was a mean increase in the percentage of awake time spent "off". None of the ropinirole treatment groups were significantly different from the placebo group.

The reduction in the proportion of awake time spent "off' was also assessed as the number of patients who responded to treatment, response defined as a 20% reduction from baseline in the percentage of awake time spent "off". The placebo group response rate was 33.3% at endpoint. The 1 mg and 2 mg ropinirole groups had similar response rates to the placebo group, 28.6% and 36.7% respectively. At endpoint, 50% of patients in the 4 mg group met criteria for response. None of the ropinirole dose groups had a significantly higher response rate compared to placebo.

Secondary Efficacy Parameters

At endpoint, there was no significant difference in the percentage change in total motor score in any of the ropinirole dose groups compared to the placebo group (Table 14, attached). Likewise, at endpoint, for the CGE (Clinician Global Evaluation), none of the ropinirole dose groups were significantly different from the placebo group (Table 16, attached). Finally, there was no significant differences from placebo in the mean AIMS score.

Summary

The objective of this trial was to investigate a minimum effective dose of ropinirole as an adjunct to l-dopa therapy in Parkinson's disease. Previous open-label studies provided evidence suggesting that anti-Parkinson effects began at 2 mg ropinirole bid (4 mg total daily dose). Three doses of ropinirole were investigated vs placebo: 0.5 mg bid, 1.0 mg bid and 2.0 mg bid. Patients were maintained, following upward titration, on the randomized dose level for 4 weeks. The dose of l-dopa was kept constant and efficacy was assessed as the reduction in the

proportion of awake time spent "off".

None of the ropinirole dose groups were significantly different from placebo in the improvement in the duration of "off" periods. The 4.0 mg ropinirole group demonstrated the largest improvement in the duration of "off" periods but the difference from the placebo group was not statistically significant.

The ropinirole dose groups also failed to distinguish from placebo in the percentage of patients who responded to treatment, response defined as at least a 20% improvement from baseline in the percentage of awake time spent "off". At endpoint, 33% of the placebo group met criteria for response compared to 29% in the 1 mg group, 37% in the 2 mg group and 50% in the 4 mg group. This high placebo response rate was unexpected. There was little difference in response rates from week 1 to week 4 after titrating to study dose level, indicating that maintaining a dose for periods greater than 1 week did not contribute to effectiveness.

The other efficacy measures including UPDRS motor score and CGE were consistent with the findings on improvement in percentage of awake time spent "off". None of the ropinirole dose groups were significantly greater than placebo. Based on these results, while subsets of patients demonstrated improvement at the 2 mg bid dose, it appears that doses higher than 2 mg bid (4 mg total daily dose) would be needed to demonstrate a statistically significant anti-Parkinson effect.

6.0 Population Pharmacokinetics

Population pharmacokinetics analysis was undertaken using plasma sampling collected from patients in studies 54 and 44. The plasma concentration of patients classified as responders was compared with those classified as non-responders. The responder criteria used were patients with a 30% reduction in UPDRS motor score in study 54 and 20% reduction in l-dopa dose and a 20% reduction in awake time 'off' in study 44. Results in patients who received ropinirole for early therapy of PD (54) show that there was considerable overlap in the range of plasma concentrations between responders and non-responders. The predicted plasma concentrations of ropinirole (mean $\pm$ SD) were 20.7 $\pm$ 10.4 ng/mL in responders and 14.9 $\pm$ 11.2ng/mL in non-responders. In adjunct therapy (44) the predicted plasma levels were almost two-fold higher in responders (27.6 $\pm$ 10.4 ng/mL) than in non-responders (15.4 $\pm$ 8.4 ng/mL).

The majority of responders in early therapy studies received doses $\geq$5mg tid, whereas the majority in adjunct therapy PD took doses of $\geq$6mg tid. In early and adjunct populations, concentrations at steady state for responders overlapped considerably those seen in nonresponders. One can conclude that there was no relationship between ropirinole plasma levels and response outcome, so that, in common with other dopaminergic agonists, the dosage of ropinirole has to be individually titrated based on tolerance and efficacy.

7.0 Summary and Conclusions

The proposed labeling makes the claim that ropinirole is indicated in the symptomatic treatment

of Parkinson's disease, either as monotherapy or as adjunct to l-dopa.

For monotherapy, response was identified as improvement in motor function as assessed by the UPDRS motor scale as well as delaying the need to initiate l-dopa by six to twelve months. There were four monotherapy studies performed in early PD patients as yet untreated with l-dopa- 32, 54, 53, and 56. Study 32 and 54 were similar in design, both placebo-controlled titration studies. However, in study 32, the maximum dose was 10mg (dosed bid) and the duration of the trial was 3 months, compared with study 54 where the top dose was 24mg (dosed tid) and the duration 6 months. There were two other active controlled studies performed in a similar population, 53 with bromocriptine as the comparator and 56 with l-dopa as the control. These were both 6 months duration with a maximum dose of 24 mg. Whereas both studies 32 and 54 had statistically significant outcomes in favor of ropinirole, the results were confounded by significant interactions with selegiline. It is not surprising that the two active-control studies did not show a difference between treatments. As to the claim that ropinirole delays the need to initiate l-dopa by six to twelve months, the evidence from the trials support only the six month claim, as that was the duration of the trials (study 32 was only three months).

There were six adjunctive studies from which to support a claim that ropinirole permits reduction in l-dopa (20%) while maintaining symptomatic control, reducing awake time "off" and end of dose fluctuations associated with chronic l-dopa therapy. Five of the studies (30, 34, 36, 38, and 44) were similar in design and duration (3 months). Study 44 was 6 months duration and top dose 24 mg. The other smaller studies had lower top doses of 4 or 5 mg bid. (These were the earlier studies conducted in 1990 and 1991). Except for Study 44, none of these were statistically significant in favor of ropirinole, and several had interactions with center (study 30) or selegiline (study 34). Study 40 identified a minimum effective dose of 4.0 mg. Study 44 demonstrated that ropinirole can substitute for l-dopa reduction without clinical worsening, although patients were not significantly better.

To conclude, evidence from the clinical program supports the claim of ropinirole in the symptomatic treatment of Parkinson's disease measured by the motor scale of the UPDRS as monotherapy and delays the need to initiate L-dopa by six months in Parkinson's disease patients who have not previously required dopaminergic therapy. When used as adjunctive treatment with L-dopa, there was some evidence that ropinirole permits a mean reduction in L-dopa dose of roughly 20%, but without concomitant reduction in "on-off" fluctuations.

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NDA 20-658
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NDA 20-658 TABLE OF STUDIES

DATE Mono	ID	C - C O E U N N T R E Y R	D E S I G N	D U R A T I O N	#PT RX/ PBO	DOSE	1° E P F A F R I M C E A T C E Y R	R E S U L T
6/90 - 10/91	32	UK 4 ex US 5	/PBO	3	41/22	T	30%↓ motor score UPDRS	70.7%/ 40.9 p=.021
8/92 - 9/94	54	US 25	/PBO	6	116/ 125	T	% Change UPDRS	-21.5/ +3.57 -22.9
Adjunct								
3/90 - 8/91	30	UK 1/ France 1	/PBO	3	23/23	T	30% time off	65/39 NS
8/90 - 9/91	34	UK 6 Israel 2	/PBO	3	46/22	T	20% ↓ l-dopa	48.8%/ 36%▲ 12.8
8/90 - 8/91	36	6 ex US	/PBO	3	20/9	T	20% awake time off	58/44 ▲ 14
7/90 - 10/91	38	5 ex US	/PBO	3	24/12	T	20% awake time off	48%/ 42%
9/91 - 10/92	40	15 US	/PBO	2	31-30-29-31	fixed 1-2-4-PBO	20% awake time off	p= 0.392
8/92 - 9/94	44	US 16	/PBO	6	95/54	T	20% ↓ l-dopa + 20%↓ "off"	28%/ 11% ▲ 17

SK&F	PROTOCOL NUMBER 101468/C7105	PATIENT IDENTIFICATION	PATIENT NUMBER

VISIT 3

UNIFIED PARKINSONS DISEASE RATING SCALE - POST-DOSE

Date ⌊ ⌋ ⌊ ⌋ ⌊ ⌋ (day month year) Time ⌊ ⌋ ⌊ ⌋ — 24 hr. clock

Number of hours since last L-Dopa dose ⌊ ⌋

Is the patient "On" or "Off"? ☐ "On" ☐ "Off"

Motor Examination

		0	1	2	3	4
18.	Speech	☐	☐	☐	☐	☐
19.	Facial Expression	☐	☐	☐	☐	☐
20.	Tremor at Rest					
	Face, Lips, Chin	☐	☐	☐	☐	☐

		Right					Left				
		0	1	2	3	4	0	1	2	3	4
	Hands	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	Feet	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
21.	Action Tremor	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
22.	Rigidity - Neck	☐	☐	☐	☐	☐					
	UE	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	LE	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
23.	Finger Taps	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
24.	Hand Movement	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
25.	Hand (Pronation-Supination)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
26.	Leg Agility	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

		0	1	2	3	4
27.	Arise From Chair	☐	☐	☐	☐	☐
28.	Posture	☐	☐	☐	☐	☐
29.	Gait	☐	☐	☐	☐	☐
30.	Postural Stability	☐	☐	☐	☐	☐
31.	Body Bradykinesia	☐	☐	☐	☐	☐

▶ Subtotal 18-31 ⌊ ⌋

Project	Protocol	Center	Document Number	Visit		Pa
101468	055 (Ext. 054)	0	00078	3		1:

CLINICIAN GLOBAL IMPRESSION

Severity of Illness

Considering your total clinical experience with this particular population, how ill is the patient at this time?

- 0 ☐ Not assessed
- 1 ☐ Normal, not at all ill
- 2 ☐ Borderline ill
- 3 ☐ Mildly ill
- 4 ☐ Moderately ill
- 5 ☐ Markedly ill
- 6 ☐ Severely ill
- 7 ☐ Among the most extremely ill patients

Global Improvement

Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment.

Compared to his/her condition at Baseline Visit of Study 054, how much has the patient changed?

- 0 ☐ Not assessed
- 1 ☐ Very much improved
- 2 ☐ Much improved
- 3 ☐ Minimally improved
- 4 ☐ No change
- 5 ☐ Minimally worse
- 6 ☐ Much worse
- 7 ☐ Very much worse

RESCUE L-DOPA MEDICATION

Does the patient require RESCUE L-Dopa medication at this visit?

☐ Yes ☐ No

Perform Motor Examination (go to page 54) prior to administration of First Rescue Medication. Update Rescue Medication record, page 55.

SB SmithKline Beecham Pharmaceuticals	PROTOCOL NUMBER	PATIENT INITIALS	DOCUMENT NUMBER
	SK&F 101468/C7106		

TREATMENT - VISIT 4

SM-02
2
00
04
02

STUDY MEDICATION COMPLIANCE

Date ___ day ___ month ___ year

		Securitainer 1	Securitainer 2
Number of Tablets Dispensed at Last Visit	A	16	16
Number of Tablets Returned	B		
Number of Tablets Taken (A - B)	C		
Number of Study Days Since Visit 3	D		
Minimum Number of Tablets to be Taken for Compliance (2 x D x 0.8)	E		
Is C ≥ E?		☐ Yes ☐ No ◙	☐ Yes ☐ No ◙

◙ If patient is non-compliant at this and previous visit, withdraw patient from study, schedule follow-up visit, and complete Study Conclusion, page 84.

CLINICIAN GLOBAL EVALUATION

Evaluate the therapeutic response relative to the Screening - Visit 1.

Markedly Worse (5)	Mild/Moderately Worse (4)	No Change (3)	Mild/Moderate Improvement (2)	Marked Improvement (1)
☐	☐	☐	☐	☐

Was any concomitant medication taken? ☐ Yes ☐ No

→ Record in Concomitant Medication section

Were any adverse experiences observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the last visit"? ☐ Yes ☐ No

→ Record in Adverse Experience section

Has the stable L-Dopa (DCI) dose changed? ☐ Yes ☐ No

→ Withdraw patient from the study.
Record dose change in Concomitant Medication section.

Table 15 Number of patients responding to treatment (intention-to-treat population)

Visit	Treatment Group				p-value at endpoint
	Ropinirole		Placebo		
	n (%)	N	n (%)	N	
Baseline	2 (4.9%)	41	3 (13.6%)	22	
Visit 3	9 (22.0%)	41	4 (18.2%)	22	
Visit 4	11 (27.5%)	40	8 (36.4%)	22	
Visit 5	13 (32.5%)	40	7 (33.3%)	21	
Visit 6	21 (52.5%)	40	9 (40.9%)	22	
wk 8 Visit 7 4 bid	18 (51.4%)	35	10 (45.5%)	22	
wk 9 Visit 8 4.5	25 (69.4%)	36	9 (42.9%)	21	
wk 10 Visit 9 5 bid	26 (76.5%)	34	8 (44.4%)	18	
Visit 10	24 (72.7%)	33	8 (47.1%)	17	
Endpoint	29 (70.7%)	41	9 (40.9%)	22	p=0.021

Key: n (%) = number and percentage of patient responding; N = total number of patients evaluated.

Efficacy-evaluable Population

Forty six patients (30 in the ropinirole treatment group and 16 receiving placebo) were included in the efficacy evaluable analysis at visit 10. Eleven (26.8%) ropinirole-treated patients and six (27.3%) placebo group patients were excluded from the analysis of the primary efficacy parameter at visit 10 (post dose).

At visit 10 (post-dose), 23 (76.7%) of the 30 evaluable patients on ropinirole were classed as responders compared with 8 (50.0%) of the 16 evaluable patients in the placebo group. The difference between treatment groups was not statistically significant (p = 0.066, chi-square test) (C.I. (-2.1%, 55.5%)).

(40.9%) receiving placebo, according to the definition of improvement given in Section 3.12.3. There was a statistically significant difference between the two treatment groups (p=0.021, Chi-square test).

The percentage of patients who had improved (i.e. had a marked or mild/moderate improvement) at each visit is shown in Table 28.

Table 28 Clinician's Global Evaluation: patients with improvement (intention-to-treat population)

Visit Number	Treatment Group					
	Ropinirole			Placebo		
	Marked	Mild/Mod	n	Marked	Mild/Mod	n
Visit 3	0	10 (24%)	41	0	1 (5%)	22
Visit 4	0	20 (50%)	40	0	6 (27%)	22
Visit 5	1 (3%)	23 (58%)	40	0	6 (27%)	22
Visit 6	5 (13%)	22 (55%)	40	1 (5%)	6 (27%)	22
Visit 7	7 (19%)	16 (44%)	36	2 (9%)	5 (23%)	22
Visit 8	11 (30%)	14 (38%)	37	2 (9%)	6 (27%)	22
Visit 9	11 (30%)	16 (43%)	37	2 (11%)	6 (32%)	19
Visit 10	13 (35%)	14 (38%)	37	2 (11%)	7 (37%)	19
Endpoint	13 (32%)	16 (39%)	41	2 (9%)	7 (32%)	22

The analysis of success rates as evaluated by the clinician's global evaluation is a mirror of the responder analysis for the motor score of the UPDRS suggesting that, as expected, there is a high degree of correlation between these two assessments.

Additional analysis :

The final model fitted consisted of treatment and age. The odds ratio after fitting this model was :

Log Odds	Odds Ratio	95% C.I for Odds Ratio
1.58	4.84	(1.45, 16.19)

The odds ratio represents the odds of a ropinirole patient being classed as a responder relative to the odds of a placebo patient being classed as responder. As the 95% C.I. only includes values >1, this indicates a statistically significant effect in favour of ropinirole, a result which agrees with the original analysis.

Efficacy-evaluable Population

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Table 3 Study Medication Dosing Schedule

Dose Level	Unit Dose (mg)	Total Daily Dose (mg)
1	0.25	0.75
2	0.5	1.5
3	0.75	2.25
4	1.0	3.0
5*	1.5	4.5
6	2.0	6.0
7	2.5	7.5
8	3.0	9.0
9	4.0	12.0
10	5.0	15.0
11	6.0	18.0
12	7.0	21.0
13	8.0	24.0

* Patients could be maintained on dose levels 5-13 once an optimal therapeutic response was achieved. All patients had to be titrated to Dose level 5.

Patients were started at dose Level 1 (0.25 mg t.i.d) and titrated upward by weekly intervals until an optimal therapeutic response was achieved. The maximum dose of study medication was 8 mg t.i.d. (Level 13). All patients had to be titrated to at least dose Level 5 (1.5 mg t.i.d.). Patients could then be maintained on this dose level or higher for the remainder of the study.

3.6.3 Methods of Blinding

The randomization code was prepared by the SmithKline Beecham Biometrics Department and is provided in Appendix A. The codes were designed to assign patients to the ropinirole or placebo treatment groups in a 1 : 1 ratio. Patients were stratified according to the concomitant use of selegiline. Patients had to remain on a stable dose of selegiline at least four weeks prior to visit 1 and throughout the study. Patients were assigned an 11 digit study medication code following the successful

Table 7 Number and Percent of Patients Present per Week - Intention to Treat Population

Time interval (week)	Ropinirole (n=116)		Placebo (n=125)	
	N	%	N	%
1	112	96.6%	122	97.7%
2	110	94.8%	122	97.6%
3	110	94.8%	120	96.0%
4	109	94.0%	120	96.0%
6	107	92.2%	118	94.4%
8	105	90.5%	116	92.8%
10	101	87.1%	112	89.6%
12	95	81.9%	110	88.0%
16	85	73.3%	109	87.2%
20	82	70.7%	106	84.8%
24	79	68.1%	105	84.0%
≥28*	3	7.5%	5	20.0%

* Patients who completed the study outside the week 24 window. ≥ 197 days

Data source: SAS Table 5.5.2a and SAS Appendix 5.5 in Appendix B

4.2.3 Withdrawal Reason

The number and percent of patients by treatment group and by reason for withdrawal are presented in Table 8.

A total of 57 of 241 patients in the intention to treat population were withdrawn prior to completing the six month study; 37 in the ropinirole group and 20 in the placebo group. The difference in withdrawal rates was statistically significant (Fisher's exact test, p = 0.004).

Forty (40) patients were withdrawn because of adverse experiences, including disease progression. A greater percentage of ropinirole treated patients were withdrawn due to adverse experiences compared to placebo treated patients (23% vs 10%, respectively). This difference was statistically significant (Fisher's exact test, p=0.009). An imbalance in the number of patients withdrawing due to adverse experiences was observed between the selegiline strata (14 selegiline patients and 26 non-selegiline patients), and study treatment: (*27 patients in the ropinirole group* - 16 non-selegiline vs 11 selegiline; and *13 patients in the placebo groups* - 10 non-selegiline vs 3 selegiline).

Table 8 The number (%) of randomized patients who completed the study or were withdrawn by the reason for study withdrawal - Intention to Treat Population

Study Conclusion Reason	Ropinirole (n=116)		Placebo (n=125)	
	N	%	n	%
Completed Study	79	(68.1)	105	(84.0)
Reason for Discontinuation				
Adverse Experiences Including Intercurrent Illness	27	(23.3)	13	(10.4)
Lack of Efficacy	1	(0.9)	2	(1.6)
Protocol Violation, including Non-Compliance	5	(4.3)	2	(1.6)
Lost to Follow-Up	0	(0.0)	1	(0.80)
Patient Withdrawn at SmithKline Beecham's Request	1	(0.9)	0	(0.0)
Other Reasons	3	(2.6)	2	(1.6)
TOTAL WITHDRAWN	37	(31.9)	20	(16.0)

Data source: SAS Table 5.5.1a and SAS Appendix 5.5 in Appendix B

Five (5) patients were withdrawn for other reasons; 3 in the ropinirole group and 2 in the placebo group. Two of the three ropinirole treated patients (PID054.008.00004

Table 14 History of Parkinson's disease by selegiline strata - Intention to Treat Population

	Ropinirole Non-Selegiline (n=58)		Placebo Non-Selegiline (n=64)		Ropinirole Selegiline (n=58)		Placebo Selegiline (n=61)	
Hoehn & Yahr	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Stage I	7	(12.1)	5	(7.8)	8	(13.8)	7	(11.5)
Stage I.5	7	(12.1)	14	(21.9)	10	(17.2)	11	(18.0)
Stage II	20	(34.5)	19	(29.7)	21	(36.2)	25	(41.0)
Stage II.5	15	(25.9)	16	(25.0)	14	(24.1)	13	(21.3)
Stage III	9	(15.5)	10	(15.6)	5	(8.6)	5	(8.2)
Duration of Disease (months)								
Mean + SD	18.8 ± 19.7		18.2 ± 17.8		30.4 ± 19.7		27.5 ± 19.8	
Min, Max	2, 105		1, 71		3, 78		1, 95	

Data source: SAS Table 5.1.5.1b, SAS Table 5.1.6.1b and SAS Appendix 5.1 in Appendix B

4.5 Presenting Conditions and Medical History

Active Conditions

Frequently reported presenting medical conditions included *hypertension* (15.5% in the ropinirole group and 11.2% in the placebo group); *arthropathy* (10.3% in the ropinirole group and 9.6% in the placebo group); and *constipation* (7.8% in the ropinirole group and 11.2% in the placebo group). No other condition occurred in more than 10% of patients in either treatment group. There were no important differences observed between the two treatment groups in the incidence of any one condition. The number and percent of patients with active conditions are presented in SAS Table 5.2.2a. Individual presenting conditions by patient are included in SAS Appendix 5.1 in Appendix B.

Previous Conditions

Previous medical conditions were reported for 195 of the 241 randomized patients (80.9%); 91 of 116 patients (78.4%) in the ropinirole group treatment group and 104 of 125 patients (83.2%) in the placebo group. Conditions categorized in the WHO disease classification as *Operations* were the most frequently reported in 151 of 241 patients (62.7%); 71 of 116 patients (61.2%) in the ropinirole treatment group and 80 of 125 patients (64.0%) in the placebo group. *Female genital operation* (17.8%), *nose/mouth operation* (13.7%), and *appendix operation* (12.0%) were the most

Statistical Methods

Dichotomous response variables were analyzed using logistic regression. The ratio of absolute motor score to baseline motor score was analyzed at endpoint using weighted linear regression. Percentage change from baseline in total motor score was analyzed using analysis of covariance. The incidence of adverse experiences in the two treatment groups were compared using Fishers exact test.

Patient Disposition and Key Demographic Data

	Ropinirole N (%)		Placebo N (%)	
Patient Disposition				
Total Number Screened	268			
Randomized	116	(100)	125	(100)
Completed Study	79	(68.1)	105	(84.0)
Withdrawn from Study	37	(31.9)	20	(16.0)
Intention to Treat Population	116	(100)	125	(100)
Efficacy Evaluable Population	95	(81.9)	102	(81.6)
Selegiline Strata	58	(50)	61	(48.8)
Non-Selegiline Strata	58	(50)	64	(51.2)
Demographic Characteristics				
Male	70	(60.3)	80	(64.0)
White	110	(94.8)	119	(95.2)
Mean Age (years) ± SD	62 ± 10.6		63.6 ± 10.7	
Duration of Parkinson's Disease (months)	24.6 ± 20.5		22.8 ± 19.3	

Table 16 Total daily dose of study medication (mg) by week - Intention to Treat Population

Time Interval (week)		Ropinirole	Placebo
1	Mean (mg) ± SD	0.75 ± 0.0	0.76 ± 0.1
	Range		
	n	110	120
2	Mean (mg) ± SD	1.5 ± 0.2	1.5 ± 0.2
	Range		
	n	104	118
3	Mean (mg) ± SD	2.1 ± 0.4	2.2 ± 0.3
	Range		
	n	104	114
4	Mean (mg) ± SD	2.9 ±0.3	3.0 ± 0.4
	Range		
	n	108	118
6	Mean (mg) ± SD	5.3 ± 1.1	5.4 ± 1.1
	Range		
	n	104	115
8	Mean (mg) ± SD	7.5 ±1.8	7.8 ± 1.9
	Range		
	n	103	114
10	Mean (mg) ± SD	10.7 ± 4.2	12.0 ± 4.0
	Range		
	n	103	109
12	Mean (mg) ± SD	14.0 ± 6.2	16.8 ± 5.5
	Range		
	n	91	105
16	Mean (mg) ± SD	15.9 ± 7.2	19.3 ± 6.6
	Range		
	n	90	107
20	Mean (mg) ± SD	16.9 ± 7.1	20.8 ± 5.6
	Range		
	n	77	106
24	Mean (mg) ± SD	17.8 ± 7.1	21.0 ± 5.7
	Range		
	n	79	105

Table 16 Total daily dose of study medication (mg) by week - Intention to Treat Population

Time Interval (week)		Ropinirole	Placebo
≥28	Mean (mg) ± SD	18.4 ± 7.8	18.4 ± 9.4
	Range		
	n	4	4
Endpoint*			
	Mean (mg) ± SD	15.7 ± 8.3	19.6 ± 7.1
	Range		
	n	115	123

Zero dose represents a dose interruption on the day prior to the CGI assessment

*Endpoint is the last pre-tapering dose of study medication.

Data source: SAS Table 5.3.1a and SAS Appendix 5.3.1 and 5.3.2 in Appendix B

A total of 76 ropinirole patients (66%) and 101 placebo patients (81%) in the intention to treat population were titrated to at least 15 mg of study medication (SAS Table 5.3.2a). The maximum dose of study medication was 24 mg in both treatment groups. However, there was a difference in the continued upward titration of study medication between the treatment groups. The mean dose of study medication at endpoint for ropinirole patients was 15.67 ± 8.3 mg compared to 19.58 ± 7.1mg in the placebo group.

Efficacy Results

There was a statistically significant treatment difference in favor of the ropinirole treatment group for both the primary and secondary efficacy parameters.

ITT Population	Ropinirole (n=116)		Placebo (n=125)		Treatment Difference (95% CI)
Primary Efficacy Parameter					
Mean Percentage Change in Motor Score	-21.52		+3.57		-22.99 (-33.85, -12.13)
Regression Coefficient for Total Motor Score	0.756*		1.026		
Secondary Efficacy Parameters					**Odds Ratio****
Responder: ≥30% reduction in Motor Score	50/107	(47%)	23/118	(19.5%)	4.45 (2.26, 8.78)
Patient Improvement on CGI (score of 1 or 2)	38/115	(33%)	15/123	(12%)	4.06 (2.00, 8.22)
Patients Requiring l-Dopa Rescue	13/116	(11%)	36/125	(29%)	0.30 (0.14, 0.61)
Patients with Insufficient Therapeutic Response	14/116	(12%)	37/125	(30%)	0.31 (0.15, 0.63)

* significantly improved over placebo $p<0.001$

** CI's for odds ratio do not include 1 which implies a significant treatment difference

Safety Results

A total of 111 ropinirole treated patients (95.7%) and 113 placebo patients (90.4%) reported one or more adverse experiences.

Most Frequently Reported Adverse Experiences	Ropinirole	Placebo
Nausea	52.6%	21.6%
Dizziness	36.2%	18.4%
Somnolence	36.2%	18.4%
CNS Adverse Experience		
Confusion	6.0%	1.6%
Hallucinations	1.7%	0.0%

A total of 35 patients reported serious adverse experiences: 22 patients in the ropinirole group and 13 patients in the placebo group. One patient from the ropinirole treatment group died (unknown cause) approximately nine months after completing the study.

Table 17 - Percentage Change from Baseline in Total Motor Score of the UPDRS Intention to Treat Population

	Mean ± SD (n)			
	Week 4	Week 12	Week 24	Endpoint
Ropinirole	-6.3 ± 37.6	-25.6 ± 35.6	-29.6 ± 45.6	-21.5 ± 45.4
	(106)	(93)	(68)	(107)
Placebo	-3.7 ± 37.5	-3.5 ±37.2	4.7 ± 55.2	3.57 ± 47.8
	(114)	(101)	(70)	(118)

Data source: SAS Table 6.1.2a and SAS Appendix 6.1 in Appendix C

Adjusted means (± SE) for the percentage change from baseline to endpoint in motor score were -19.0 (± 4.1) for the ropinirole treatment group and +4.0 (± 3.9) for the placebo treatment group utilizing a model including terms of treatment, center grouping, selegiline strata and the treatment by selegiline interaction. The estimated treatment difference between ropinirole and placebo was statistically significant (-22.99, 95% CI:-33.85, -12.13). The distribution of residuals was slightly skewed in this analysis with one extreme outlier. The outlier had little effect on the fit of the model or in the direction or size of the treatment difference so the analysis was conducted with the outlier included.

There was a significant treatment by selegiline strata interaction which indicated that there was a difference in the treatment effect within strata. In the selegiline strata, the mean percentage change at endpoint in the ropinirole treatment group was -28.2 compared to +11.5 in the placebo treatment group. In the non-selegiline strata, the mean percentage change at endpoint was -14.7 in the ropinirole group and -4.1 in the placebo group (SAS Table 6.1.2.1a). Based on these results, the placebo treatment group concomitantly treated with selegiline experienced a worsening of motor impairment during the study. In contrast, the placebo treatment group not concomitantly treated with selegiline experienced a slight improvement in motor function.

The analysis of the efficacy evaluable population provided similar results (SAS Table 6.1.2b and SAS Table 6.1.2.1b).

Study 54

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>
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     1
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 26 054.002.00280    5  20.000  47.500 180.000 180.000
135 054.013.00071    4   0.000  50.000 250.000 250.000
212 054.023.00042    3  33.333  33.333 133.333 133.333
>
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0 = MP
1 = PBO

STUDY 54

BEFORE REMOVAL OF 6 PATIENTS

	Selegiline	Non-Selegiline
Ropinirole	-28	-14
Placebo	11	-4

AFTER REMOVAL

	Selegiline	Non-Selegiline
Ropinirole	-28	-24
Placebo	2	-4

Dose at first response

Table 20 presents the number and percent of patients who were responders and the total daily dose at which they first met criteria for response. In both treatment groups, response criteria were first met most frequently at a total daily dose of less than 4.0 mg or at a total daily dose greater than 20 mg. The majority of responders ended the trial at a total daily dose greater than 20 mg (66% ropinirole, 74% placebo, SAS Table 6.2.2a) indicating that responders continued to titrate upward on study medication even after a substantial improvement in motor score was achieved. Similar results were seen in the separate selegiline strata (SAS Table 6.2.2.1a, SAS Table 6.2.3.1a). The dose profile at first response and at endpoint was similar in the efficacy evaluable population (SAS Table 6.2.2b, SAS Table 6.2.2.1b, SAS Table 6.2.3b, SAS Table 6.2.3.1b).

Table 20 Number and Percent of Patients with a 30% Reduction on Total Motor Score of the UPDRS (Responder) by Total Daily Dose of Study Medication at Which They First Responded Intention to Treat Population

	Treatment Group			
	Ropinirole		Placebo	
Dose (mg)	n	%	n	%
<4.0	16	15.0	12	10.2
4.0-8.0	5	4.7	0	0.0
8.0-12.0	2	1.9	1	0.9
12.0-16.0	2	1.9	0	0.0
16.0-20.0	5	4.7	1	0.9
20.0-24.0	20	18.7	9	7.6

Data Source: SAS Table 6.2.3a, SAS Appendix 6.2 in Appendix C

Patient Improvement (Score of 1 or 2 on CGI Improvement Item)

Thirty-three percent (38/115) of ropinirole patients and 12% (15/123) of placebo patients achieved a CGI improvement item score of 1 or 2 at endpoint (SAS Table 6.3.1a). There was a significant treatment effect favoring ropinirole over placebo (odds ratio :4.06, 95% CI: 2.00,8.22). In the selegiline stratum, 37.9% (22/58) ropinirole treated patients and 11.5% (7/61) placebo treated patients achieved improvement on the CGI and in the non-selegiline stratum, 28% (16/57) of ropinirole treated patients and 13% (8/62) of placebo treated patients were improved on the CGI (SAS Table 6.3.1.1a, SAS Appendix 6.3 in Appendix C). There was no significant interaction between selegiline strata and treatment. Therefore, the treatment effect was similar in both selegiline strata.

dose, 6 hours later for the second (afternoon) dose, and 6 hours later for the third (evening) dose.

The initial dose of ropinirole was 0.25mg tid and of bromocriptine, 1.25mg od (taken in the evening). The dose of study medication could be increased at weekly intervals, but the investigator was to titrate to and maintain an optimal dose for each patient according to that individual's clinical response. Dose level 5 was defined as the minimum expected therapeutic dose and the dose could be adjusted throughout the study. The dosing schedule for bromocriptine is in accordance with that of the datasheet. The dosing guideline provided to the investigator is shown in Table 2.

Table 2 Dosing guideline

Dose level	Treatment					
	ropinirole dose (mg)		bromocriptine dose (mg)			
	unit (tid)	daily	morning	afternoon	evening	daily
1	0.25	0.75	placebo	placebo	1.25	1.25
2	0.5	1.5	placebo	1.25	1.25	2.5
3	0.75	2.25	placebo	2.5	2.5	5.0
4	1.0	3.0	2.5	2.5	2.5	7.5
5	1.5	4.5	2.5	2.5	5.0	10.0
6	2.0	6.0	2.5	5.0	5.0	12.5
7	2.5	7.5	5.0	5.0	5.0	15.0
8	3.0	9.0	5.0	5.0	7.5	17.5
9	4.0	12.0	5.0	7.5	7.5	20.0
10	5.0	15.0	7.5	7.5	10.0	25.0
11	6.0	18.0	10.0	10.0	10.0	30.0
12	7.0	21.0	10.0	10.0	13.3	33.3
13	8.0	24.0	13.3	13.3	13.3	39.9

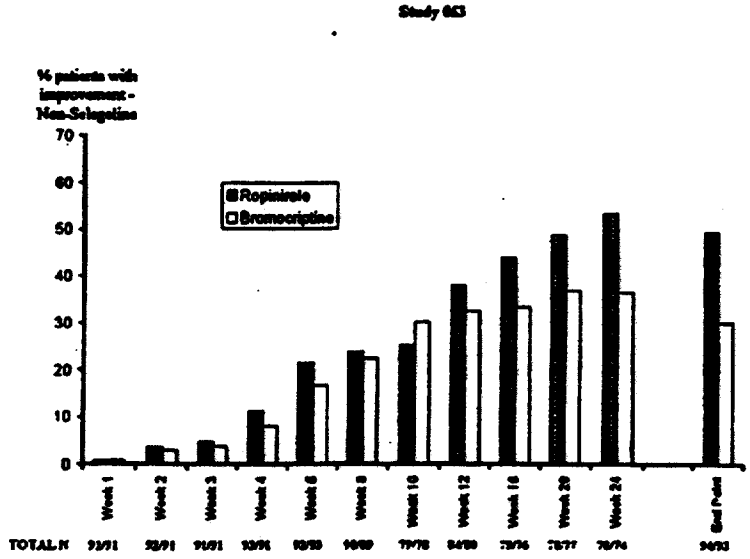
Data source: Appendix E of the protocol in Appendix A of this report

3.5.3 Methods of Blinding

The study used a double dummy technique to maintain blinding. Ropinirole tablets, either active or placebo, were supplied in a securitainer and bromocriptine capsules, either active or placebo, were supplied in blister packs. The securitainers and blister packs contained sufficient double-blind medication for each inter-visit period.

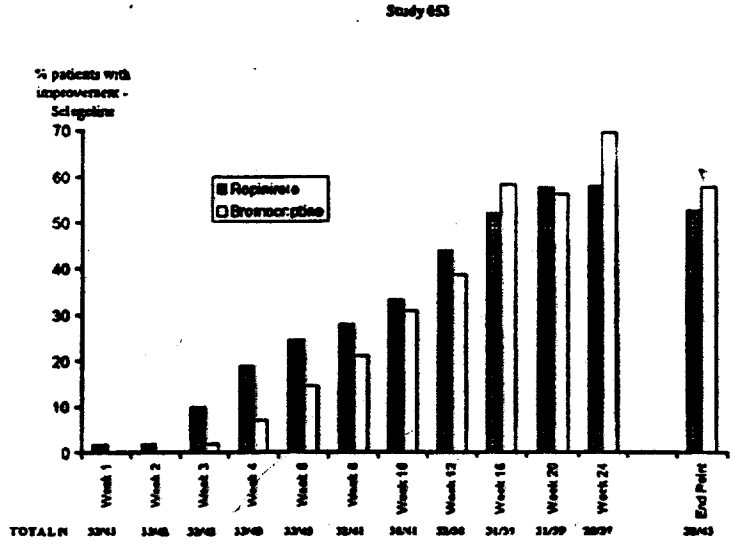
The investigator was permitted to break the study blind only in the event of a serious adverse experience which he felt could not be adequately treated without knowledge

Figure 5.1.3.3a CGI improvement by visit in Study 053 - non-selegiline subgroup



Source: Study Report CPMS-053 SAS Figure 2

Figure 5.1.3.3b CGI improvement by visit in Study 053 - selegiline subgroup



Source: Study Report CPMS-053 SAS Figure 1

Table 7 - The percentage of patients still in the study at each week.

Week	Ropinirole	Placebo
1	97.9 (100.0)*	96.3 (100.0)
2	95.8 (100.0)	88.9 (100.0)
3	94.7 (100.0)	88.9 (100.0)
4	94.7 (100.0)	83.3 (100.0)
6	91.6 (100.0)	83.3 (100.0)
8	88.4 (100.0)	81.5 (97.6)
10	87.4 (100.0)	77.8 (92.9)
12	85.3 (98.6)	75.9 (90.5)
16	85.3 (98.6)	70.4 (83.3)
20	83.2 (95.8)	64.8 (78.6)
24	79.0 (93.1)	64.8 (78.6)
≥28**	77.9 (91.7)	64.8 (78.6)

* The numbers in parentheses represent those patients included in the efficacy evaluable population.
**Represents patients who completed or withdrew from the trial outside the week 24 window.
Data Source: SAS tables 5.5.2a, 5.5.2c; Appendix B (SAS appendix 5.5)

5.2.3. Reason For Withdrawals

The number (%) of patients who completed the study and the number and reason for withdrawals are presented in Table 8. The cumulative percentage of patients withdrawn during the study by reason are displayed in Table 9. A larger percentage of placebo treated patients withdrew from the study compared to ropinirole treated patients. This difference was not statistically significant (Fisher's exact test, p=0.088). The most common reason for withdrawal was adverse experience, with a similar percentage of patients withdrawing in both treatment groups. Approximately 15% of placebo treated patients withdrew due to insufficient therapeutic effect, compared to 4.2% ropinirole treated patients. Survival curves of time to withdrawal are presented in SAS figures 5.5.1a and 5.5.2a.

The number of patients who completed the study and the number and reason for withdrawals for the forced l-dopa reduction ITT and efficacy evaluable populations are presented in SAS tables 5.5.1b and 5.5.1c, respectively. This data is also displayed by week for the ITT, forced l-dopa reduction ITT and efficacy evaluable populations in SAS tables 5.5.2.2a, b, c, respectively. The number of patients withdrawing by selegiline strata is displayed for the ITT population in SAS table 5.5.1.1a.

activities of daily living scores of the UPDRS scale all indicated that patients were mildly to moderately impaired in these areas at the start of the study. There were no notable differences in any baseline scores between the ropinirole and placebo groups.

Table 13 - Parkinson's disease rating scales at baseline (Mean ± SD)

ITT Population	Ropinirole	Placebo
Percentage of Awake Time Spent "Off"	39.3 ± 23.3 (n=90)	43.4 ± 21.6 (n=53)
Modified Schwab & England ADL Score Patient	75.6 ± 13.0 (n=88)	77.5 ± 13.7 (n=49)
Modified Schwab & England ADL Score Family	73.3 ± 14.9 (n=56)	74.5 ± 14.3 (n=28)
Modified Schwab & England ADL Score Clinician	74.5 ± 14.1 (n=87)	76.9 ± 13.6 (n=49)
Total UPDRS Mental Score	1.7 ± 1.7 (n=89)	1.5 ± 1.5 (n=49)
Total UPDRS Activities of Daily Living	13.3 ± 5.3 (n=88)	12.2 ± 5.6 (n=47)
Total UPDRS Motor Score "Off"	37.0 ± 14.0 (n=47)	35.3 ± 12.0 (n=26)
Total UPDRS Motor Score "On"	19.7 ± 9.9 (n=81)	18.0 ± 10.8 (n=41)

Data Source:SAS tables 6.3.1a, 6.6.1a, 6.7.1a, 6.8.1a, 6.9.1a, 6.9.3a, 6.9.5a; Appendix C (SAS appendices 6.3, 6.6, 6.7, 6.8, 6.9)

5.5. Presenting Conditions and Medical History

The most common presenting conditions, those with an incidence of >5%, are presented in Table 14. The most common presenting conditions in the ropinirole group included insomnia (13.7%), depression (12.6%), and headache (11.6%). The most common presenting conditions for the placebo group included insomnia (20.4%), constipation (14.8%), depression (13.0%) and arthropathy (13.0%). There were no major differences in frequency of presenting conditions or in medical history (SAS table 5.2.1a) between treatment groups.

SKF 101468 : Study 036 (C7104)

Table 6.1.2a
Number (%) Of Patients Responding (20%) To Therapy At Endpoint
By Treatment Group And Dose
Intention To Treat

	Treatment Group			
	Ropinirole		Placebo	
	N	%	N	%
Total Daily Dose Of Ropinirole (mg)				
4	1	9.1	0	0
5	0	0	1	25.0
6	2	18.2	1	25.0
8	4	36.4	1	25.0
10	4	36.4	1	25.0
Total	11	100.0	4	100.0

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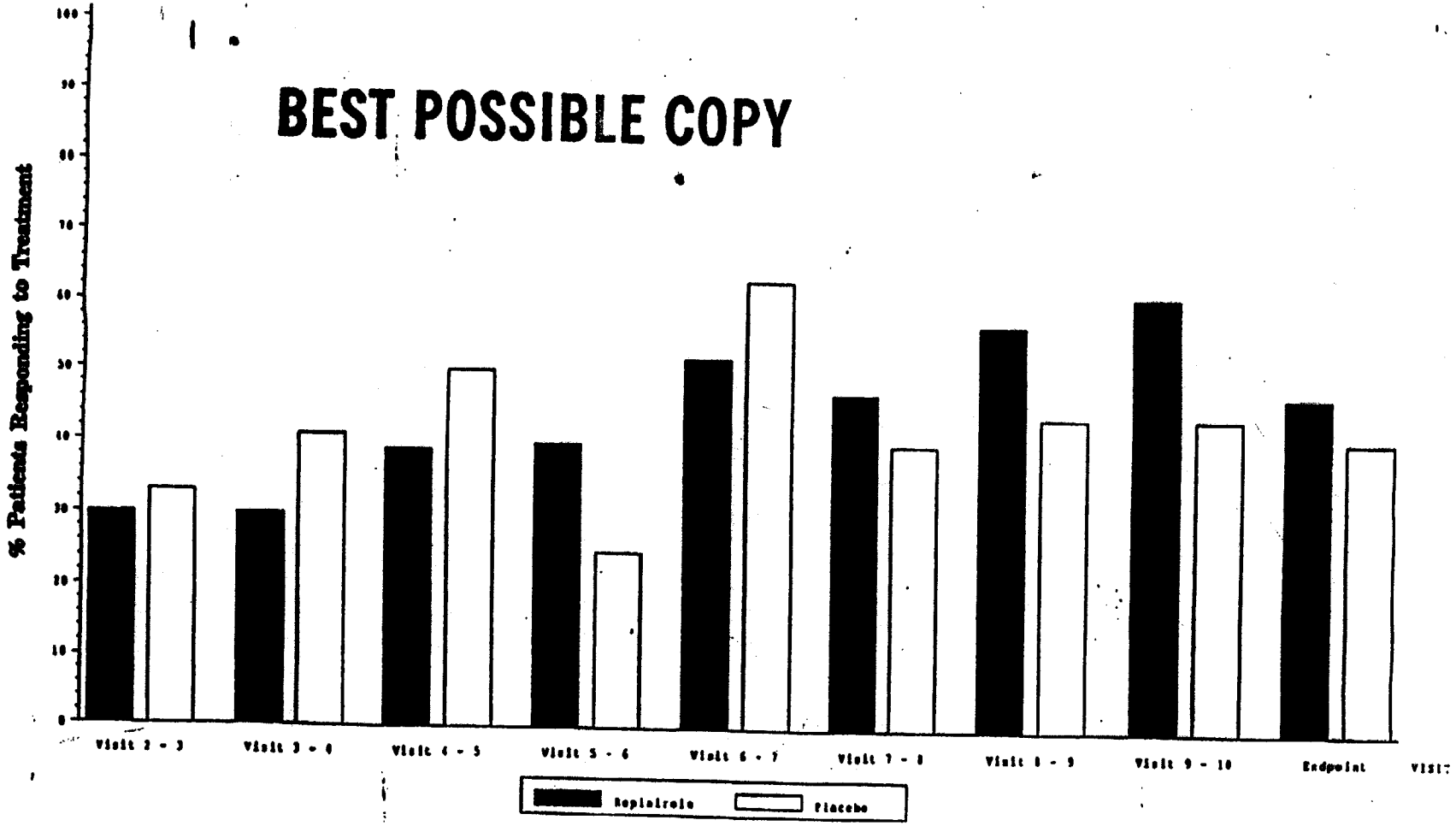
SK&F 101468 : Study 038 (C7105)
Dose Ranging Placebo Controlled

Figure 6.1.1a
Bar Chart Showing Percentage Of Patients
Responding To Treatment
Intention To Treat



SASUSER2:[STATS_GROUP.SK101468.C7105]DIARY_GRAPH_177.SAS (27SEP95:18:13)

SK&F 101468: Study 038 (C7105)
Dose Ranging Placebo Controlled

Figure 6.1.2a
Mean (Standard Error Of The Mean) Amount Of Time Spent Off
Intention To Treat

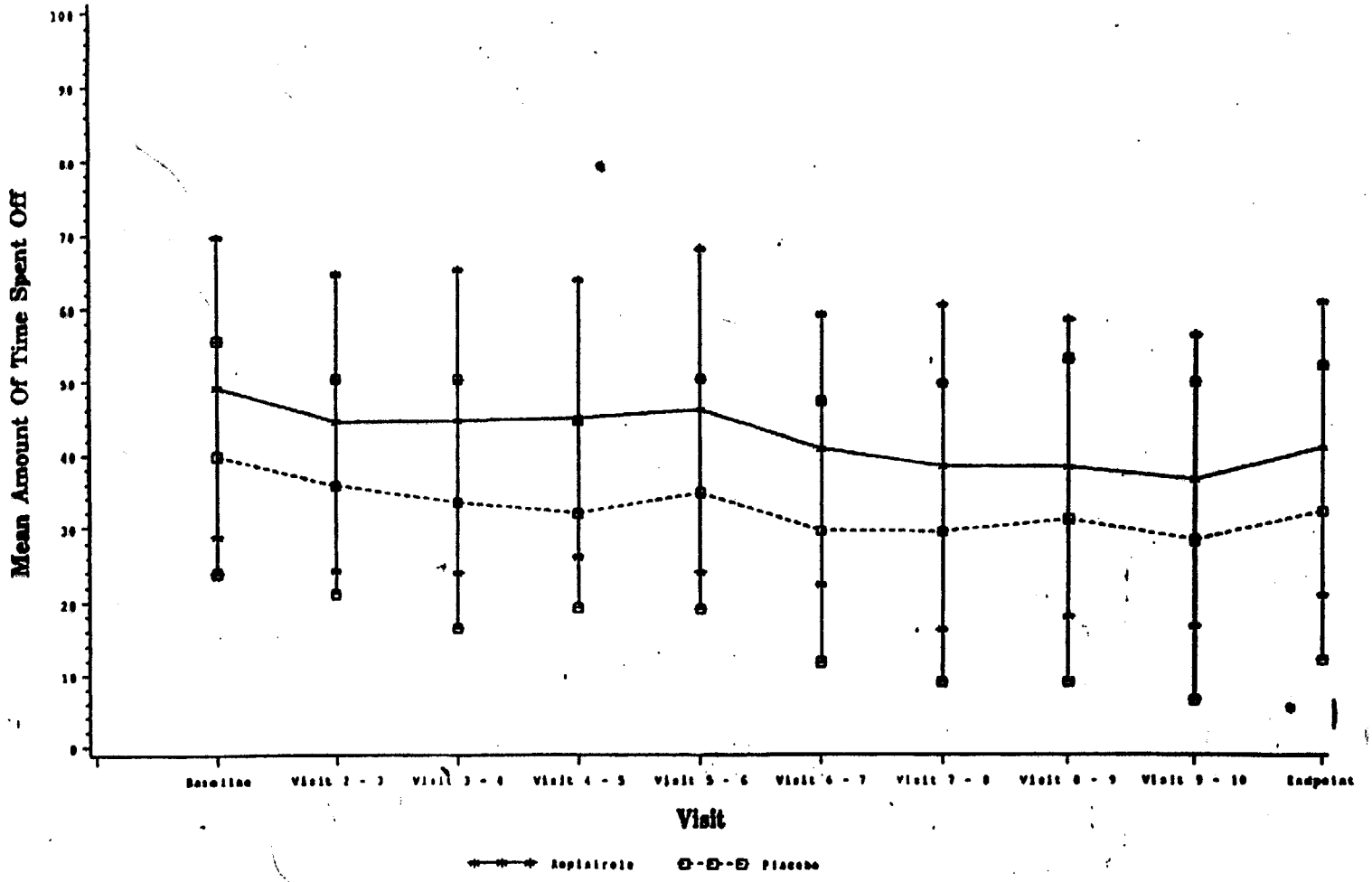


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Table 3. Dosing Regimen

	Securitainer	Screen	Treatment								Follow-up
Visit Number		1	2	3	4	5	6	7	8	9*	10
Week		1	1	2	3	4	5	6	7	8	9
Group 1 (placebo)	1 2	-	P P	P P	P P	P P	P P	P P	P P	P P	-
Group 2 0.5mg bid	1 2	-	P P	P P	P P	P 0.5	P 0.5	P 0.5	P 0.5	P 0.5	-
Group 3 1.0mg bid	1 2	-	P P	P P	P 0.5	P 1.0	P 1.0	P 1.0	P 1.0	P 1.0	-
Group 4 2.0mg bid	1 2	-	P 0.5	P 1.0	0.5 1.0	1.0 1.0	1.0 1.0	1.0 1.0	1.0 1.0	1.0 1.0	-

* 1 dose only during study visit
P Placebo

4.8 Coded Medication Supplies

Ropinirole (SK & F 101468) and matching placebo was supplied as white, pentagonal tiltab tablets. Active ropinirole tablets contained 0.5 mg or 1.0 mg active drug substance. All study medication was packaged in securitainers, each containing 16 tablets. This was sufficient to provide study medication for 1 week. The IPO numbers for placebo tablets were 90152 (pts numbers 1-120) and 91124 (pts numbers 121-200). The IPO numbers for 0.5 mg ropinirole tablets were 90150 (pts numbers 1-120) and 91125 (pt numbers 121-200). The IPO numbers for 1.0 mg ropinirole tablets were 90151 (pt numbers 1-120) and (91126 (pt numbers 121-200).

4.9 Scales for Assessment of Parkinson Symptoms

The severity of Parkinson symptoms were assessed by the Unified Parkinson's Disease Rating Scale (UPDRS). The 42-item UPDRS contains a section for rating severity of alterations in: (1) mentation, behavior and mood, (2) activities of daily living, (3) motor functions, and (4) complications of therapy. This scale also includes the modified Hoehn & Yahr staging scale and the Modified Schwab & England Activities of Daily Living Scale.

The severity of motor symptoms was assessed at each visit both prior to administration and 2 hours post-dosing by the motor examination section of

Table 8. Parkinson's Disease Rating Scales at Baseline (Mean ± SD)

	Placebo	1.0 mg	2.0 mg	4.0 mg
Percentage of Awake Time Spent "off"	39.1 ± 15.4 (n=31)	38.6 ± 21.9 (n=31)	39.2 ± 16.4 (n=30)	43.0 ± 12.2 (n=29)
Total UPDRS Motor Score	19.2 ± 8.6 (n=31)	17.4 ± 8.8 (n=31)	16.5 ± 7.2 (n=29)	15.7 ± 6.8 (n=30)
Total UPDRS Mental Score	2.4 ± 1.6 (n= 31)	1.7 ± 1.5 (n=32)	1.8 ± 1.7 (n=31)	2.1 ± 2.0 (n=30)
Total UPDRS Activities of Daily Living Score	13.1 ± 4.7 (n=31)	12.0 ± 6.1 (n=32)	12.2 ± 5.0 (n=31)	11.1 ± 4.4 (n=30)
Modified Schwab & England ADL Score Patient	72.9 ± 14.7 (n=31)	77.2 ± 13.8 (n=31)	76.5 ± 15.0 (n=31)	79.2 ± 8.9 (n=30)
Modified Schwab & England ADL Score Family	66.7 ± 16.4 (n=21)	75.4 ± 16.0 (n=18)	72.8 ± 16.6 (n=19)	76.6 ± 10.0 (n=19)
Modified Schwab & England ADL Score Clinician	71.3 ± 15.3 (n=31)	76.3 ± 13.4 (n=32)	74.8 ± 14.0 (n=31)	78.9 ± 8.8 (n=30)

Table 12. Percentage Change from Baseline in Proportion of Awake Time Spent "Off"

	Treatment Group															
	Placebo				1 mg				2 mg				4 mg			
	n	median	mean	s.d.	n	median	mean	s.d..	n	median	mean	s.d.	n	median	mean	s.d.
Titration																
Week 1	31	1.0	0.0	30.0	29	-2.5	0.8	40.6	30	-0.2	5.6	35.5	29	-2.6	1.9	35.1
Week 2	31	-0.8	6.2	50.3	29	-5.1	35.9	181.4	30	-6.7	3.4	45.3	29	-12.7	-6.9	51.1
Week 3	30	2.0	4.1	46.5	29	2.6	44.9	213.2	28	-7.7	1.5	44.7	28	-9.8	-10.0	43.7
Study Dose																
Week 1	30	-7.9	-4.9	52.8	28	-6.6	51.4	269.4	30	-9.8	-0.9	49.7	28	-14.4	-7.1	51.8
Week 2	30	-4.9	2.2	48.8	26	-12.8	42.7	243.1	28	-4.8	-3.6	43.7	28	-20.8	-15.6	53.2
Week 3	29	-8.4	-2.1	57.6	26	-9.1	81.7	329.2	27	-12.1	-8.6	45.3	28	-24.9	-18.7	66.2
Week 4	28	-11.3	6.1	70.0	26	4.3	73.1	347.7	27	-5.1	-3.2	55.2	28	-18.1	-9.6	47.3
Endpoint	30	-11.3	6.1	67.9	28	4.3	67.8	335.2	30	-5.4	-5.6	54.0	28	-18.1	-9.6	47.3

P-Values GLM with ranks		
	Treatment	Linear
Study Dose		
Week 1	0.983	0.710
Week 2	0.272	0.077
Week 3	0.183	0.044
Week 4	0.634	0.366
Endpoint	0.607	0.308

Table 14. Percentage Change from Baseline in Total UPDRS Motor Examination Score*

		Treatment Group														
		Placebo				1 mg				2 mg				4 mg		
		n	median	mean	s.d.	n	median	mean	s.d.	n	median	mean	s.d.	n	median	mean	s.d.
Baseline	Pre	31	0.0	0.0	(0.0)	31	0.0	0.0	(0.0)	29	0.0	0.0	(0.0)	30	0.0	0.0	(0.0)
	Post	31	-7.1	-10.7	(26.5)	31	0.0	2.2	(56.3)	29	-8.7	5.4	(50.3)	30	-13.2	-0.2	(70.1)
Titration																	
Week 1	Pre	30	-0.7	-0.8	(41.7)	29	-13.0	10.7	(86.2)	29	0.0	12.9	(60.7)	30	-10.1	-3.7	(32.7)
	Post	31	-8.3	0.5	(59.3)	29	-8.7	-0.3	(57.7)	29	-15.4	41.7	(282.5)	29	-23.3	-20.3	(45.4)
Week 2	Pre	30	-2.6	12.1	(64.2)	29	-14.3	-1.4	(79.7)	28	-5.6	53.9	(323.8)	30	-23.6	-18.2	(40.8)
	Post	30	-17.3	-4.1	(49.0)	29	-9.5	-4.5	(54.2)	29	0.0	5.7	(57.3)	30	-33.9	-23.7	(64.9)
Week 3	Pre	30	-22.0	-2.0	(49.4)	28	-18.4	-8.6	(54.4)	29	-4.5	60.4	(374.7)	29	-25.0	-20.0	(33.3)
	Post	30	-20.6	-6.8	(56.8)	28	-26.8	-15.1	(48.6)	29	-9.1	18.0	(155.7)	28	-21.6	-23.0	(33.4)
Study Dose																	
Week 1	Pre	30	-15.5	5.7	(74.7)	26	-18.3	-13.5	(60.2)	29	-8.7	13.7	(85.4)	28	-23.3	-18.4	(30.2)
	Post	29	-7.1	6.9	(60.3)	26	-20.1	4.8	(94.0)	29	-14.3	8.9	(104.2)	28	-34.3	-33.4	(30.4)
Week 2	Pre	30	-21.1	1.7	(69.5)	25	-19.2	-21.0	(26.5)	27	-19.0	25.1	(199.3)	29	-23.1	-21.6	(28.9)
	Post	30	-27.0	-5.5	(46.7)	26	-28.7	-7.1	(65.0)	27	-18.2	-14.8	(53.3)	29	-36.7	-21.9	(48.8)
Week 3	Pre	29	-10.5	14.2	(81.8)	25	-25.0	-3.5	(71.6)	27	-18.2	55.1	(330.7)	29	-15.8	-12.2	(37.6)
	Post	29	-25.0	-11.0	(58.0)	25	-13.3	-2.1	(89.2)	25	-23.8	3.9	(127.7)	29	-37.5	-28.0	(38.6)
Week 4	Pre	21	-16.7	-7.7	(37.9)	20	-19.0	-10.0	(43.0)	24	-5.8	7.1	(480.7)	26	-13.9	6.1	(60.1)
	Post	21	-20.8	-21.4	(34.6)	19	-22.7	8.9	(125.5)	24	-18.6	20.0	(169.8)	26	-38.2	-19.9	(55.5)
Endpoint	Post	30	-20.9	-12.3	(56.8)	26	-26.1	-2.6	(109.4)	29	-18.2	15.2	(155.2)	29	-36.4	-20.7	(54.6)

* Table 8 contains baseline UPDRS motor scores

Appendix 16 in Appendix C contains the listing of Clinician Global Evaluation at each week by patient and by treatment group.

Table 16. Number (%) of Patients Responding to Treatment with a CGE Score of 1 or 2 (Marked or Mild/Moderate Improvement)

	Placebo responder/ n	%	1mg responder/ n	%	2mg responder/ n	%	4mg responder/ n	%
Titration								
Week 1	4/31	12.9	7/31	22.6	6/31	19.4	5/29	17.2
Week 2	8/31	25.8	9/30	30.0	8/31	25.8	14/30	46.7
Week 3	13/30	43.3	8/30	26.7	10/31	32.3	12/29	41.4
Study Dose								
Week 1	12/30	40.0	6/29	20.7	15/31	48.4	17/29	58.6
Week 2	14/30	46.7	9/26	34.6	12/29	41.4	19/30	63.3
Week 3	14/29	48.3	9/25	36.0	11/28	39.3	17/29	58.6
Week 4	16/29	55.2	8/25	32.0	10/29	34.5	19/28	67.9
Endpoint	16/30	53.3	8/28	28.6	10/31	32.3	19/29	65.5

6.2.5 Abnormal Involuntary Movements

At each study visit, patients were observed for the presence of abnormal involuntary movements. For patients who demonstrated abnormal movements, the severity of the movements was rated according to the Abnormal Involuntary Movement Scale (AIMS). The number of patients who were scored for abnormal involuntary movements at each week is presented in Table 17. There were baseline differences across the treatment groups in the numbers of patients who exhibited abnormal movements. The placebo group had the lowest percentage and the 4 mg ropinirole treatment group had the highest percentage of patients with abnormal movements. The proportion of patients with abnormal movements changed little during the course of the trial. In the placebo and the 1 mg ropinirole groups, there was a small decline in the proportion of patients who exhibited abnormal movements by study dose week 4.

Appendix 17 in Appendix C contains a listing of patients who exhibited involuntary movements at any study visit by patient and by treatment group.