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Effects of COMPOUND XXX on Parkinson Symptoms in MPTP-Treated Macaques

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This study was conducted under the terms of an Agreement between **CLIENT** and NeuroDetective International, Inc., **dated**, as subsequently amended. This study was conducted in the laboratory of Dr. Jay Schneider, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Introduction

The protocol for this study was designed to assess effects of a proprietary compound supplied by **CLIENT**, designated COMPOUND XXX, on motor aspects of parkinsonism in non-human primates with MPTP-induced parkinsonism. The protocol also allowed comparison of the efficacy of COMPOUND XXX with an optimal (single) dose of levodopa and an optimal (single) dose of the dopamine agonist quinpirole.

1 Methods

1.1 Pilot Study

Prior to the main study, a pilot study was conducted to compare different modes of drug administration of COMPOUND XXX in cynomolgus monkeys. Following drug administration, blood samples were obtained for analysis of plasma levels of COMPOUND XXX.

Animals/Dose:

Two adult male cynomolgus monkeys (5-8 kg) were used. Each animal received two formulations of COMPOUND XXX, both formulations containing a dose of 3 mg/kg COMPOUND XXX base (corresponding to 3.426 mg/kg COMPOUND XXX·HCl·H_2O using correction factor 1.142).

Formulation 1:

An appropriate amount of COMPOUND XXX·HCl·H_2O in powder form was weighed and placed into a glass vial. Then, 10% citric acid was added, followed by dilution with a gradually added 10% sucrose solution. The result was a final volume of 15 ml.

Example: For a monkey weighing 5 kg, 17.115 mg COMPOUND XXX·HCl·H_2O (corresponding to 15 mg COMPOUND XXX base) would be placed into a 20 ml glass vial. Then, 78 µl of 10% citric acid solution (COMPOUND XXX:citric acid molar ratio = 1:1.2) would be added, with continuous stirring, to yield a suspension. Immediately thereafter, 14.922 ml of 10% sucrose solution would be gradually added to the suspension of COMPOUND XXX and stirred until a clear solution was obtained. The final concentration would then be 1 mg/ml for COMPOUND XXX base and 0.35 mg/ml for citric acid.

Maximum achievable concentration with this formulation is 6 mg/ml. In the two actual dosings, this formulation was prepared fresh, and, based on visual inspection, appeared to be stable at least for 2 hours.

Formulation 2:

For the second formulation, a standard, commercial brand marshmallow was divided into halves, and the solid drug (powder form) of COMPOUND XXX HCl H2O was placed between the halves. The marshmallow was then squished back together.

Example: For a 5 kg monkey, 17.115 mg COMPOUND XXX HCl H2O would be placed into the marshmallow. The correction factor would be 1.141 (i.e., 1.142 g COMPOUND XXX HCl H2O corresponding to 1 g COMPOUND XXX base).

Blood sampling:

Blood samples of at least 1.0 ml were withdrawn from each animal's femoral vein, and placed into sampling tubes containing Li-heparin as anticoagulant, and kept on ice. Within 30 minutes following withdrawal of the blood samples, the samples were centrifuged at approximately 3000 rpm for 10 minutes at 4°C. The resulting plasma fractions were stored at approximately □20°C until shipment to sponsor.

Treatment procedure:

The two monkeys first received 3 mg/kg COMPOUND XXX in Formulation 1. At 2 hours post-dosing, the 1 ml blood samples were obtained. Following a 3-day washout period, the same two monkeys received 3 mg/kg COMPOUND XXX in Formulation 2. At 2 hours post-dosing, the 1 ml blood samples were again obtained.

1.2 Monotherapy Study

1.2.1 Experimental Design:

Using standard methodology, six adult male cynomolgous macaque monkeys were administered the neurotoxin MPTP (0.075-0.20 mg/kg), two to three times per week, in order to induce motor deficits typical of Parkinson's disease. Monkeys exhibiting stable Parkinsonian symptoms were then tested for response to COMPOUND XXX, as well as to levodopa and the dopamine agonist quinpirole.

To assess drug effects on Parkinsonian symptoms, animals were observed and rated on a previously validated non-human primate Parkinson rating scale, shown below:

NON-HUMAN PRIMATE PARKINSON RATING SCALE (0-54)

Subgroup 1: Generalized Behaviors (0-33)

1.1a. Appetite:
0 - Normal
1 - Up to 30% food left in cage from previous feeding
2 - Up to 65% food left in cage from previous feeding
3 - Greater than 65% food left in cage from previous feeding

1.1b. Response To Offered Food
0 - Responds to offered food
1 - Inconsistent response to offered food
2 - Little interest in offered food
3 - No interest in offered food

1.2 Overall Activity
0 - Normal amount of movement
1 - Mild hypokinesia; decrease in spontaneous movement
2 - Moderate hypokinesia; sparse movement
3 - Severe hypokinesia; essentially no spontaneous movement; tends to remain in one place

1.3 Appearance
0 - Normal
1 - Mild but noticeable decrease in self-maintenance
2 - Moderate decrease in self-maintenance
3 - Severe lack of self-maintenance

1.4 Posture
0 - Normal
1 - Minor flexing or stooping
2 - Moderate flexing or stooping; head and upper body almost parallel to floor of cage
3 - Severe flexing or stooping; head lowered to feet

1.5 Balance
0 - Normal
1 - Mild loss on arising or movement
2 - Moderate loss on arising or movement; occasionally falls or supports self to keep from falling
3 - Frequent and severe loss of balance; falls

1.6 Climbing
0 - Climbing observed with no delays in initiation/execution
1 - Mild, deficit in ability to climb and support weight
2 - Moderate deficit in ability to climb and support weight; tends to 'slide down'
3 - Absence of any climbing behavior

1.7 Tremor (resting/intention; if present, note body part)
0 - Absent
1 - Slight and intermittent
2 - Slight and persistent or moderate and intermittent
3 - Moderate/Severe and persistent

1.8 Freezing During Movement
0 - Absent
1 - Occasional freezing for brief periods
2 - Occasional freezing for prolonged periods or frequent freezing for brief periods
3 - Prolonged and 'frequent freezing

1.9 Facial Expression
0 - Normal
1 - Slight but noticeable diminution of facial expression
2 - Moderate hypomimia
3 - Severe, masked fixed faces

1.10 Defense Reaction
0 - Normal
1 - Mild, noticeable reduction in reaction or slowed reaction, but can be provoked to react
2 - Moderate reduction in reaction; can produce facial display but not body reaction
3 - Little to no response

Sub-group 2: Specific Motor Functions (0-21)

2.1a. Upper Limb Movement (L/R)
0 - Normal
1 - Noticeable decrease of limb use
2 - Moderate decrease of limb use
3 - Severe decrease of limb use

2.1b. Lower Limb Movement (L/R)
0 - Normal
1 - Noticeable decrease of limb use
2 - Moderate decrease of limb use
3 - Severe decrease of limb use

2.2a. Range of Upper Limb Movement (L/R)
0 - Normal
1 - Mild reduction, but able to extend limb almost completely
2 - Moderate reduction in range of motion with some usage difficulty; exhibits definite flexor posturing of limbs at rest
3 - Severe reduction; flexor posturing of limbs at rest

2.2b. Range of Lower Limb Movement (L/R)
0 - Normal
1 - Mild reduction, but able to extend limb almost completely
2 - Moderate reduction in range of motion with some usage difficulty; exhibits definite flexor posturing of limbs at rest
3 - Severe reduction; flexor posturing of limbs at rest

2.3 Fine Motor Skills
0 - Normal
1 - Noticeable clumsiness and decrease in ability to grasp food or rewards; occasional dropping of food; may use side of hand to grasp food
2 - Moderate decrease in ability to grasp and handle food; ,drops food often; uses two hands or brings mouth to hand
3 - Unable to consistently grasp, hold or manipulate food: may bring mouth directly to food

2.4 Eating
0 - Normal
1 - Mild slow chewing and/or occasional pauses
2 - Mild slow chewing with frequent pauses or moderate slow chewing with occasional pauses
3 - No effective eating on own

Each numerical rating for each item came from two raters, who were blind to treatment condition of each animal. For each animal, the rating for each item was the mean of the two raters' evaluations.

Based on results of the pilot study, all subsequent studies with COMPOUND XXX used formulation 2 (powder administered in marshmallow).

All drugs were prepared fresh each day immediately prior to administration. Levodopa was administered as levodopa methyl ester by intramuscular injection given 30 minutes after administration of benserazide. An ascending dose-response procedure was used as follows for the studies with COMPOUND XXX:

1st Dose:

Day1: 6.0 mg/kg p.o. COMPOUND XXX

Day2: 6.0 mg/kg p.o. COMPOUND XXX plus behavioral assessment 2 hrs after drug

Day3: 6.0 mg/kg p.o. COMPOUND XXX plus blood sampling 2 hrs after drug

2nd Dose:

Day1: 12.0 mg/kg p.o. COMPOUND XXX

Day2: 12.0 mg/kg p.o. COMPOUND XXX plus behavioral assessment at 2, 4 and 6 hrs after drug administration

Day3: 12.0 mg/kg p.o. COMPOUND XXX plus blood sampling 2 hrs after drug

3rd Dose:

Day1: 24.0 mg/kg p.o. COMPOUND XXX

Day2: 24.0 mg/kg p.o. COMPOUND XXX plus behavioral assessment 2 hrs after drug

Day3: 24.0 mg/kg p.o. COMPOUND XXX plus blood sampling 2hrs after drug

Levodopa (20 – 35 mg/kg)/benserazide (5 – 8.8 mg/kg):

Day1: Optimal dose/animal plus behavioral assessment 1 hr after drug

Quinpirole:

Day1: 0.15 mg/kg plus behavioral assessment 30 min and 1 hr after drug

2 Results

2.1 Pilot Study

The dose used for the pilot study was 3.0 mg/kg COMPOUND XXX base (corresponding to 3.426 mg/kg COMPOUND XXX·HCl·H_2O using correction factor 1.142).

Formulation 1 (COMPOUND XXX in 10% Sucrose Water):

Drug was prepared as described in Methods and administered to 2 animals. Drug solution was prepared fresh and administered within 10 minutes of preparation. The drug went completely into solution with no drug particles visible. Drug preparation and administration information is shown in Table 1.

Drug was administered to both animals in their home cages without incident. Both animals readily drank the drug solution from a syringe. No drug solution dripped out of the animal's mouths. Animals were observed every 30 minutes post drug administration. No adverse events were noted at any time. At approximately 10 minutes post drug administration, animal Ez1 appeared a little anxious with rapid eye movements and increased eye blinks but this was no longer apparent by 30 minutes post drug. Animal Hu1 picked up food and began eating it at approximately 10 minutes post drug administration, but then appeared to have uncharacteristically rapid jaw movements. This was no longer apparent by 30 minutes post drug administration. Parkinson symptom ratings were recorded before, and at 120 minutes after, drug administration. No significant changes in Parkinson symptoms were observed in either animal at any time post drug administration (Table 2). Two hours after drug administration, animals were anesthetized with ketamine HCl and blood was drawn and plasma obtained and frozen as described in Methods.

Formulation 2 (COMPOUND XXX in Marshmallow):

Drug was prepared as described in Methods and administered to 2 animals. A marshmallow was broken apart and the solid drug (powder) of COMPOUND XXX was placed inside the marshmallow and then it was squished back together. Drug preparation and administration information is shown in Table 3.

Drug was administered to both animals in their home cages without incident. Both animals readily grasped and ate the marshmallow. No drug/marshmallow dropped out of the animal's mouths. Animals were observed every 30 minutes post drug administration. No adverse events were noted at any time. Parkinson symptom ratings were recorded before, then at 60 and 120 minutes after, drug administration. No significant changes in Parkinson symptoms were observed in either animal at any time post drug administration (Table 4). Two hours after drug administration, animals were anesthetized with ketamine HCl and blood was drawn and the plasma fraction obtained and frozen as described in Methods.

Summary:

Two modes of COMPOUND XXX drug administration (i.e., drug dissolved in sucrose water or solid drug hidden in marshmallow) were assessed in 2 Parkinsonian cynomolgus monkeys. Animals readily consumed both preparations. Neither preparation resulted in any adverse events. Neither preparation resulted in any significant change in Parkinsonian symptoms.

2.2 Monotherapy Study

The various doses of COMPOUND XXX were administered successively to all animals, in an ascending-dose manner. Each dosing was separated by a week from the subsequent dosing. Baseline ratings on the Parkinsonsim scale were obtained just prior to each drug dosing. Following the last behavioral evaluation, blood samples were obtained and stored for shipping to the sponsor, as described in Methods.

Dose 1 (6.0 mg/kg):

6 mg/kg COMPOUND XXX base (corresponding to 6.852 mg/kg COMPOUND XXX·HCl·H_2O using correction factor 1.142) was administered first, using formulation 2 (the marshmallow), upon request of the sponsor following results of the pilot study. Drug was administered on Days 1, 2, and 3, with behavioral ratings obtained on Day 2 and blood draws obtained on Day 3, at 2 hrs following drug administration. Although the protocol called for behavioral observations to be made only at 2 hrs post-dosing, the animals were in fact observed qualitatively at approximately 30 min intervals

post-dosing, with formal Parkinsonism ratings obtained at both 1 and 2 hrs post drug administration.

All animals quickly ate the COMPOUND XXX containing marshmallow, with no observed drug loss. No adverse events were noted at any time post-dosing. Parkinson symptom ratings are shown in Table 5. The percent improvement from baseline ratings (pre-dosing) is noted in parentheses. The group had a mean rating at baseline of 21.7 ± 1.6. At 60 min. post drug administration, the mean rating for the group improved to 17.0 ± 1.5 (i.e., lower numbers mean less impairment in the observed abnormal behaviors). Improvements in symptoms ranged from 15% to 31%. At 120 min post drug administration, the mean rating for the group remained stable, at 16.8 ± 1.4. Percent improvement in individual symptoms that compose the scale ranged from 20% to 30%. Repeated measures analysis of variance indicated a significant effect of treatment ($F = 64.52$, $p < 0.0001$). Pairwise comparisons (Student-Newman-Keuls test) showed significant differences between baseline and 60 min ratings ($p < 0.001$) and baseline and 120 min ratings ($p < 0.001$) and no difference between 60 and 120 min ratings.

These data suggest that COMPOUND XXX at 6 mg/kg had a mild and statistically significant symptomatic benefit in all animals. The effect observed at 60 min after drug administration was not substantially different from the effect observed at 120 min post drug administration. The symptoms that appeared to improve most were climbing ability, decrease in freezing during movement, and facial expression/eye blink rate.

Dose 2 (12 mg/kg):

12 mg/kg COMPOUND XXX base (corresponding to 13.704 mg/kg COMPOUND XXX·HCl·H_2O using correction factor 1.142) was administered next in marshmallow, on Days 1, 2, and 3, with behavioral ratings obtained on Day 2 and blood draws obtained on Day 3 (2 hrs after drug administration). Behavioral observations were recorded at 2, 4 and 6 hrs after drug administration, following the request of the sponsor after the results of Dose 1 were available.

All animals quickly ate the COMPOUND XXX containing marshmallow, with no observed drug loss. No adverse events were noted at any time. Parkinson symptom ratings are shown in Table 6. The percent improvement from baseline ratings is noted in parentheses. The group had a mean rating at baseline of 20.2 ± 1.2. At 2 hrs post drug administration, the mean rating for the group improved to 14.2 ± 0.9. Improvements in individual symptoms ranged from 26% to 32%. At 4 hrs post drug administration, the mean rating for the group remained stable at 16.0 ± 1.3. Improvements in individual symptoms ranged from 13% to 29%. At 6 hrs post drug administration, the mean rating for the group again remained stable, at 17.0 ± 1.5. Improvements in individual symptoms ranged from 9% to 29%. Repeated measures ANOVA showed that there was a significant effect of treatment ($F = 60.89$, $p < 0.0001$). Post hoc comparisons (Student-

Newman-Keuls test) showed that observations at 2 ($p < 0.001$), 4 ($p < 0.001$) and 6 hrs ($p < 0.001$) were all significantly different from baseline. The ratings at 2 hrs were significantly different from those at 4 hrs ($p < 0.01$) and 6 hrs. ($p < 0.001$). Parkinson ratings at 4 and 6 hrs were also significantly different from one another ($p < 0.05$). Animals did not quite return to baseline by the 6 hr post-dosing observation time.

The percent change from baseline at 2 hrs following administration of the 12 mg/kg dose was significantly greater than the percent change from baseline at 2 hrs following administration of the 6 mg/kg dose ($t = 3.77$, df=10, $p < 0.0037$).

These data suggest that COMPOUND XXX at 12 mg/kg had a mild/moderate symptomatic benefit in all animals, an improvement that was (at 2 hrs post-dosing) significantly greater than that seen with 6 mg/kg. The symptoms that appeared to improve most were limb movements, decrease in freezing during movement, and fine motor skills. One animal (Hu1) showed transient dystonic posturing of the right lower extremity (foot) at the 2 hr post-dosing observation time. This was not seen in this animal at other observation times, nor was it seen in any other animals.

Dose 3 (24 mg/kg):

24 mg/kg COMPOUND XXX base (corresponding to 27.408 mg/kg COMPOUND XXX·HCl·H_2O using correction factor 1.142) was administered next in marshmallow on Days 1, 2, and 3, with behavioral ratings obtained on Day 2, and blood draws obtained on Day 3 (2 hrs after drug administration). Behavioral observations were taken at 2 hrs only after drug administration, following the sponsor's request.

All animals ate the COMPOUND XXX containing marshmallow with no observed drug loss. No adverse events were noted at any time. Parkinson symptom ratings are shown in Table 7. The percent improvement from baseline ratings is noted in parentheses. The group had a mean rating at baseline of 21.0 ± 1.6. At 2 hrs post drug administration, the mean rating for the group improved to 13.0 ± 1.6. Percent improvements in individual symptoms ranged from 36% to 44%.

Using a paired *t* test, there was a statistically significant difference between baseline ratings and ratings taken 2 hrs after administration of 24 mg/kg COMPOUND XXX ($t = 15.492$, df=5, $p < 0.0001$).

The percent change from baseline at 2 hrs after administration of the 24 mg/kg dose was significantly greater than the percent change from baseline at 2 hrs after administration of the 12 mg/kg dose ($t = 2.98$, df=10, $p < 0.0138$).

These data suggest that COMPOUND XXX at 24 mg/kg had a moderate symptomatic benefit, and significantly greater than that seen with either 6 or 12 mg/ COMPOUND XXX at 2 hr post-dosing. The symptoms that appeared to improve most were limb movements, climbing ability and defense reactions. No adverse reactions were observed.

Levodopa:

Two weeks following the last dose of COMPOUND XXX, levodopa methyl ester was administered by intramuscular injection to all animals 30 minutes after administration of benserazide. The optimal dose of levodopa was determined for each animal and ranged from 20 mg/kg to 35 mg/kg. Behavioral observations were recorded at 1 hr after levodopa administration (a time which previous studies in this lab has shown to reflect the peak effect of levodopa).

No adverse events were noted after levodopa administration. Parkinson symptom ratings are shown in Table 8. The percent improvement from baseline ratings is noted in parentheses. The group had a mean baseline rating of 22.3 ± 1.2. At 1 hr post-dosing, the mean rating for the group improved to 11.8 ± 0.5. Improvements in individual symptoms ranged from 41% to 54%. Using a paired *t* test, there was a statistically significant difference between baseline ratings and ratings taken 1 hr after administration of levodopa ($t = 11.864$, df=5, $p < 0.0001$).

These results suggest that the therapeutic response observed with COMPOUND XXX was similar to, but not quite as good as, that observed following optimal dosing with levodopa. Levodopa generally produced a greater increase in overall activity (in addition to improving overall limb usage and decreasing freezing), compared to that observed with COMPOUND XXX.

Quinpirole:

One week following testing with the optimal dose of levodopa, quinpirole was administered to all animals by intramuscular injection. The optimal dose of quinpirole had been previously determined for these animals (0.15 mg/kg). Behavioral ratings were obtained at 30 min and 1 hr following dosing with quinpirole.

No adverse events were noted after quinpirole administration. Parkinson symptom ratings are shown in Table 9. The percent improvement from baseline ratings is noted in parentheses. The group had a mean baseline rating of 21.8 ± 2.0. At 30 min post drug administration, the mean rating for the group improved to 12.8 ± 1.2. Improvements in symptoms ranged from 35% to 56%. At 1 hr post drug administration, the mean rating for the group improved to 10.2 ± 1.1. Improvements in individual symptoms ranged from 43% to 67%. Repeated measures ANOVA showed that there was a significant effect of treatment ($F = 52.28$, $p < 0.0001$). Post hoc comparisons (Student-Newman-Keuls test) showed that the Parkinsonism

ratings at 30 min ($p < 0.001$) and 1 hr ($p < 0.001$) post-dosing were significantly different from baseline. Ratings at 30 min and 1 hr after drug administration were also significantly different from each other ($p < 0.05$).

COMPOUND XXX vs. Levodopa vs. Quinpirole:

The percent improvement in symptoms following treatment with COMPOUND XXX (2 hr observation), levodopa (1 hr observation) and quinpirole (1 hr observation) were also compared. Repeated measures ANOVA showed that there was a significant effect of treatment ($F = 4.76$, $p < 0.04$). Post hoc comparisons (Student-Newman-Keuls test) showed that the response to COMPOUND XXX (24 mg/kg) was significantly less than the response to quinpirole ($p < 0.05$). The levodopa and quinpirole responses were not significantly different from each other.

These results suggest that the therapeutic response obtained with COMPOUND XXX was not as robust as that obtained with the dopamine D2/D3 agonist quinpirole. Quinpirole generally improved posture, overall limb usage and fine motor skills, and decreased freezing.

A further analysis of variance was conducted to compare the maximal percent change produced by COMPOUND XXX at both 12 and 24 mg/kg vs. the maximal response by levodopa vs. the maximal response by quinpirole. This analysis showed a significant overall effect of treatment ($F(3,5) = 12.90$, $p < 0.0002$). Pairwise post hoc comparisons showed that quinpirole ($p < 0.001$), levodopa ($p < 0.01$) and COMPOUND XXX at 24 mg/kg ($p < 0.05$) all produced significantly more improvement than COMPOUND XXX at 12 mg/kg. COMPOUND XXX at 24 mg/kg was less effective than quinpirole ($p < 0.01$) but not significantly different from levodopa ($p > 0.05$) in its maximal effect.

3 Conclusion

The results of the current study indicate the COMPOUND XXX, at the doses used, is well tolerated by non-human primates and can produce mild to moderate improvement in symptoms in monkeys made Parkinsonian from exposure to the neurotoxin MPTP. The extent of this improvement approached that obtained with levodopa, but was less than that seen with the dopamine D2/D3 agonist quinpirole.

Table 1. Pilot study drug preparation and administration Formulation 1.

	Animal Hu1	*Animal Ez1*
Animal weight	8.2 kg	6.1 kg
Amount drug given	28.13 mg	21 mg
Vehicle	128.1 µl citric acid solution	95.6 µl citric acid solution
	14.87 µl 10% sucrose solution	14.9 µl 10% sucrose solution
Time Drug Administered	1:25 pm	1:30 pm
Time Blood Sampled	3:25 pm	3:30 pm

Table 2. Pilot study Parkinsonian ratings after Formulation 1 administration.

	Animal Hu1	*Animal Ez1*
Pre-administration rating	26	24
Post 120 minutes	23	24

Table 3. Pilot study drug preparation and administration Formulation 2

	Animal Hu1	*Animal Ez1*
Animal weight	8.1 kg	6.1 kg
Amount drug given	27.8 mg	21 mg
Vehicle	1 marshmallow (approx. 7 g)	1 marshmallow (approx. 7 g)
Time Drug Administered	9:20 am	9:25 am
Time Blood Sampled	11:20 am	11:25 am

Table 4. Pilot study Parkinsonian ratings after Formulation 2 administration.

	Animal Hu1	*Animal Ez1*
Pre-administration rating	25	24
Post 60 minutes	25	26
Post 120 minutes	24	25

Table 5. Parkinsonian ratings in response to 6.0 mg/kg COMPOUND XXX

	Animal Hu1	*Animal Ez1*	*Animal Pa1*	*Animal Be1*	*Animal St1*	*Animal An1*
Pre-administration rating	22	27	25	20	16	20
Post 60 minutes	17 (22%)	22 (22%)	19 (24%)	16 (20%)	11 (31%)	17 (15%)
Post 120 minutes	17 (22%)	22 (22%)	19 (24%)	14 (30%)	13 (19%)	16 (20%)

Table 6. Parkinsonian ratings in response to 12.0 mg/kg COMPOUND XXX

	Animal Hu1	*Animal Ez1*	*Animal Pa1*	*Animal Be1*	*Animal St1*	*Animal An1*
Pre-administration rating	21	22	23	22	17	16
Post 2 hrs	15 (29%)	15 (32%)	17 (26%)	15 (32%)	12 (29%)	11 (31%)
Post 4 hrs	18 (14%)	17 (23%)	20 (13%)	17 (23%)	12 (29%)	12 (25%)
Post 6 hrs	19 (10%)	18 (18%)	21 (9%)	19 (14%)	12 (29%)	13 (19%)

Table 7. Parkinsonian ratings in response to 24.0 mg/kg COMPOUND XXX

	Animal Hu1	*Animal Ez1*	*Animal Pa1*	*Animal Be1*	*Animal St1*	*Animal An1*
Pre-administration rating	22	22	27	22	16	17
Post 2 hrs	13 (41%)	14 (36%)	20 (26%)	12 (45%)	9 (44%)	10 (41%)

Table 8. Parkinsonian ratings in response to optimal levodopa dosing.

	Animal Hu1	*Animal Ez1*	*Animal Pa1*	*Animal Be1*	*Animal St1*	*Animal An1*
Pre-administration rating	24	26	24	22	19	19
Post 1 hr	13 (46%)	13 (50%)	11 (54%)	13 (41%)	11 (42%)	10 (48%)

Table 9. Parkinsonian ratings in response to optimal quinpirole dosing

	Animal Hu1	*Animal Ez1*	*Animal Pa1*	*Animal Be1*	*Animal St1*	*Animal An1*
Pre-administration rating	23	27	27	21	18	15
Post 30 min	15 (35%)	12 (56%)	17 (37%)	13 (38%)	11 (39%)	9 (40%)
Post 1 hr	12 (48%)	10 (63%)	13 (52%)	12 (43%)	6 (67%)	8 (47%)