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Continuous Delivery of Ropinirole by Subdermal ProNeura™ Implants

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Objective

A subdermal implantable product that can continuously provide dopamine replacement therapy for 6-12 months from a single application.

Background

The cornerstone of symptomatic treatment for Parkinson's disease is dopamine replacement therapy. Frequent dosing with oral dopamine replacement therapy medication, however, is associated with the pulsatile stimulation of dopamine receptors due to peak-trough fluctuations in drug plasma concentrations. This non-physiologic stimulation of brain dopamine receptors contributes to development of serious motor complications and dyskinesias, thus limiting treatment effectiveness. New treatments that provide continuous dopamine replacement therapy appear to be more effective, but current approaches are surgically invasive and associated with potentially serious adverse effects. ProNeura™ is a proprietary subdermal implantable drug delivery system that provides continuous, non-fluctuating therapeutic drug levels for several months from a single application. Efficacious and well-tolerated continuous delivery of buprenorphine using this platform has been demonstrated in a Phase 3 clinical program (Probuphine®) on opioid addiction.

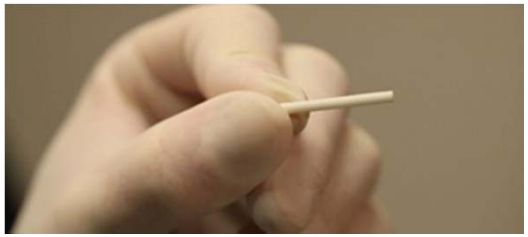

Figure 1. Titan's Proprietary ProNeura Technology

Matchstick-sized non-erodible implants formulated by blending and extruding the drug of choice with the co-polymer, Ethylene Vinyl Acetate (EVA).

The drug is uniformly distributed throughout the EVA matrix and it is released in a continuous, non-fluctuating manner into the interstitial fluids in the subdermal space through dissolution-controlled diffusion following pseudo-zero order kinetics.

- Inserted in a brief, simple, office-based procedure
- Continuous non-fluctuating blood levels of drug seen for several months with low inter-subject variability
- There is no reservoir and, therefore, no risk of drug dumping
- At termination, or if necessary for safety reasons, the implants can be quickly removed in a minor office-based procedure

The lead application of the ProNeura technology is the Probuphine implant (buprenophine HCl/EVA), which delivers non-fluctuating, stable blood levels of buprenorphine in patients for 6 months from a single treatment.

Methods

ProNeura-based implants containing the dopamine agonist, ropinirole (4-[2-(dipropylamino) ethyl]-1,3-dihydro-2H-indol-2-one hydrochloride), were tested for pharmacokinetics (PK) of release in rats and in non-human primates, and motor functions and onset of dyskinesias in MPTP- (1 – methyl – 4 - phenyl - 1,2,3,6 - tetrahydropyridine) induced Parkinsonian monkeys were evaluated in a dose-escalating study with ropinirole implants.

PHARMACOKINETICS OF RELEASE IN THE RAT MODEL

One ropinirole-containing EVA implant was placed subdermally in the dorsal-scapular region of each male Sprague Dawley rat (n=3), and blood samples drawn over a 1 month period and assayed for ropinirole content by LC-MS/MS.

GENERATION OF PARKINSONIAN MONKEYS

Sixteen male cynomolgus macaques received intracarotid artery injections of MPTP. The animals were monitored by two independent raters, one blinded, using an established Clinical Rating Scale (CRS) for primates to determine the severity of the unilateral lesion. Fourteen symptom parameters were scored from 0 (normal) to 3 (severe), and totaled to provide the CRS score for that day's observation. Animals that did not show robust lesions (i.e., CRS scores around 20) (n=11) were given additional intravenous MPTP injections to increase the severity of the lesions and to obtain stable scores (<10-20% deviation) for a period of at least 8 weeks.

CLINICAL AND PK RESPONSES TO TREATMENT

Eight stable Parkinsonian animals were each injected with apomorphine (2 mg/kg, SC) to evaluate their CRS score response to an acute administration of a dopamine agonist with a short half-life.

After a wash-out period of one-week (when the CRS scores reverted to about 20), 4 Parkinsonian animals were each implanted with ropinirole-containing EVA implants in a time-dependent dose-escalating manner. The other 4 Parkinsonian animals served as controls. The implanted animals were sampled over time for the plasma bioanalysis by LC-MS/MS of the pharmacokinetics of ropinirole release, and all of the animals were independently rated for their CRS scores as before.

Results

Continuous non-fluctuating release of ropinirole was observed for a period of several months following implantation and PK studies in rats have been extended to determine the full duration of release. The dose-escalating study with implants in unilateral-lesioned Parkinsonian monkeys demonstrated that motor functions could be significantly improved following treatment, and no onset of dyskinesias was seen. There were also no signs of skin irritation, inflammation or fibrotic capsule formation detected at the implant site in monkeys at study termination.

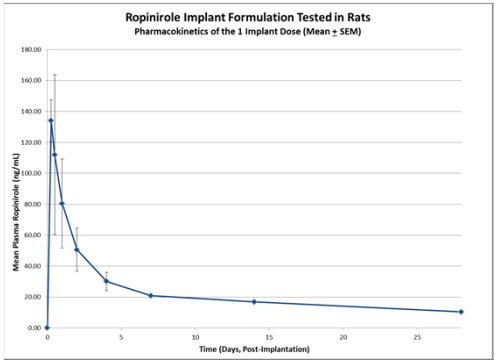

Figure 2. Plasma Release of Ropinirole in Rats (n=3)

Following an initial peak release of ropinirole from the implant surface, the release was stabilized by 1 week post-implantation. At 1 month the mean plasma ropinirole concentration was measured at ~10 ng/mL.

Subsequent implants were washed extensively before gamma-radiation sterilization, to significantly reduce the initial peak release of drug following implantation in Parkinsonian monkeys.

Parameter	Post- MPTP	Apomorphine Injection
Tremor R Arm	2	2
Tremor L Arm	3	3
Freezing	0	0
Locomotion	2	0
Fine Motor R Arm	1	0
Fine Motor L Arm	2	0
Bradykinesia R Arm	1	0
Bradykinesia L Arm	2	0
Posture	2	0
Hypokinesia	1	0
Balance	2	1
Startle Response	2	0
Gross Motor R Arm	0	0
Gross Motor L Arm	2	0
Total CRS Score	**22**	**6**

Table 1. Severity of the Parkinsonian Symptoms in Monkeys

Total CRS scores for a representative Parkinsonian monkey post-MPTP lesioning, and following the apomorphine injection challenge.

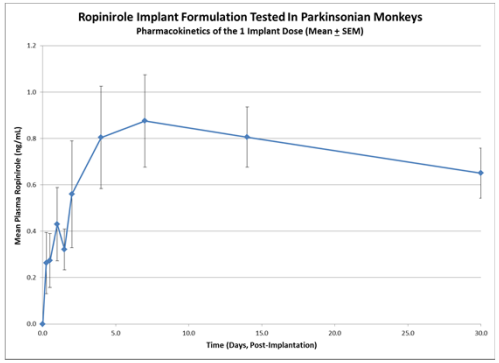

Figure 3. Plasma Release of Ropinirole in Monkeys (n=4)

Stable Parkinsonian monkeys were each surgically implanted with one ropinirole-containing EVA implant, and blood was sampled at designated time points for bioanalysis of plasma ropinirole content. The mean plasma ropinirole concentration attained at this 1 implant dose was just under 1 ng/mL.

After assessing CRS scores for 8 weeks, each animal received 2 additional implants (total no. of implants/animal=3) and sampled for PK and assessed as before for an additional 6 weeks. Each animal then received 5 additional implants (total no. of implants/animal=8), and sampled for PK and monitored for another 8 weeks (Day 58 post-implantation for the 8 implant dose).

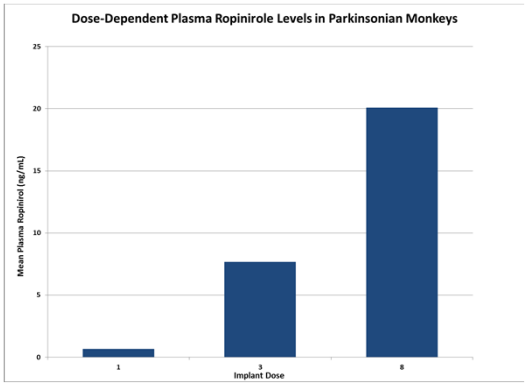

Figure 4. Plasma Ropinirole Following Implant Dose Escalation

With all three implant doses factored, the mean plasma ropinirole concentration attained in Parkinsonian monkeys (n=4) averaged to about 2 ng/mL/implant in this animal model.

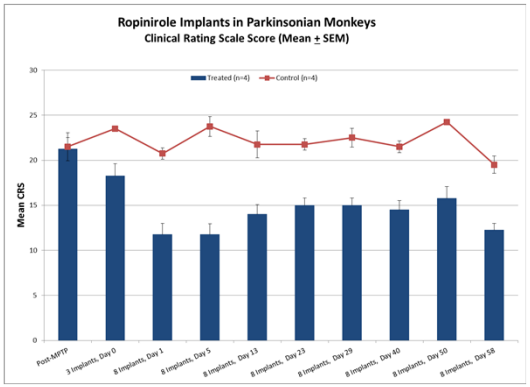

Figure 5. Rating of Parkinsonian Symptoms Following Treatment

Mean CRS scores were assessed for treated (n=4) and control, untreated (n=4) monkeys. Of the 8 implants in each of the treated animals, 1 implant was in place for over 20 weeks and 2 implants were in place for around 16 weeks at the time of study termination (8 implants dose: day 58, post-implantation).

Conclusions

The feasibility of continuous, long-term, non-fluctuating delivery of ropinirole using the ProNeura implant platform has been demonstrated.

These novel subdermal ropinirole implants could significantly improve Parkinson's disease pharmacotherapy and patient compliance, lower caregiver expense, and enhance the quality-of-life in patients, by providing continuous dopaminergic stimulation without the side effects and inconvenience associated with chronic dosing with oral dopamine replacement therapy, or from infusion by external mechanical pumps.