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Stand Alone Protocol

Title: Treatment of hyperprolactinemia with the non-ergoline dopamine agonist Ropinirole: A dose escalation study of efficacy and tolerability.

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Scientific Abstract
Prolactinomas are the most common type of secretory pituitary adenomas. Due to their unique physiology they are generally treated medically, as opposed to surgically, with dopamine agonists that tonically inhibit prolactin. Cabergoline and bromocriptine have been the preferred medications for the treatment of hyperprolactinemia, lowering prolactin levels and promoting tumor shrinkage when applicable. However, concerns have emerged about the long-term safety of these drugs. Data highlighting an association between ergoline dopamine agonists and valvular heart disease has recently been published, and patients and endocrinologists remain uncertain about the cardiac sequelae of their chronic use. Subsequently, there is a need for safer, therapeutic alternatives. Ropinirole, a non-ergoline dopamine agonist FDA approved for treatment of Parkinson's disease (PD) and Restless Leg Syndrome, has been shown to lower prolactin levels in patients with PD and in healthy male volunteers without major side effects. These characteristics make it a potentially useful drug for the treatment of hyperprolactinemia. This pilot study is designed to examine, for the first time, the potential use of the non-ergoline dopamine agonist ropinirole for the treatment of hyperprolactinemia in patients with idiopathic hyperprolactinemia and microprolactinomas (<10mm). The aims of this study are 1) to evaluate the effect of ropinirole on serum prolactin levels and tumor size in patients with hyperprolactinemia, 2) to determine the most effective starting and therapeutic doses for prolactin suppression, 3) to evaluate the tolerability of ropinirole when used chronically for the treatment of hyperprolactinemia and 4) to evaluate the pharmacokinetics/pharmacodynamics of ropinirole in patients with hyperprolactinemia.

Lay Abstract
Prolactinomas are pituitary tumors that make the hormone prolactin, causing elevated levels of prolactin in the blood. These tumors are typically treated with medications as opposed to surgery. Cabergoline and bromocriptine are the medications that are most commonly used to treat prolactinomas. These medications lower prolactin levels and promote tumor shrinkage when applicable. However, both medications are commonly associated with side effects. In addition, concerns have emerged about the long-term safety of these medications because recent data suggests that the use of these medications may be associated with heart valve disease. Subsequently, there is a need for new, safer medications to treat hyperprolactinemia. Ropiniriole is a medication that is currently FDA approved for use in patients with Parkinson's disease and in patients with Restless Leg Syndrome. Ropinirole has been show to lower prolactin levels in patients with Parkinson's disease and in healthy normal individuals with few side effects. It therefore may be a useful medication for the treatment of high prolactin levels and this study aims to investigate this question.

Study Description

1) Study Purpose and Rationale:

Study Purpose: This pilot study is designed to examine, for the first time, the potential use of the non-ergoline dopamine agonist ropinirole for the treatment of hyperprolactinemia in patients with idiopathic hyperprolactinemia and microprolactinomas (<10mm). While ropinirole is currently FDA approved for use in Parkinson's disease (PD) and Restless Leg Syndrome (RLS), its use as a prolactin suppressant has not been systematically evaluated in patients with hyperprolactinemia. This is particularly important given the recent recognition of heart valve abnormalities associated with the ergoline dopamine agonists most commonly used to treat hyperprolactinemia. Therefore the primary aims of this study are 1) to define the clinical pharmacokinetics and pharmacodynamics of ropinirole immediate release and extended release formulations in patients with prolactinomas, 2) to measure the effect of ropinirole at escalating doses on serum prolactin levels, gonadal function, and tumor size in patients with prolactinomas, and 3) to determine the immediate and chronic tolerability of ropinirole in patients with prolactinomas. Given the safety issues associated with the current medications used for the treatment of hyperprolactinemia, alternative therapeutic agents would provide significant clinical benefit. This study will help us to determine whether ropinirole can be safely and effectively used to treat hyperprolactinemia. If ropinirole shows promise, this pilot study will serve as the basis for further experiments exploring its potential therapeutic use. Such exploration will include a prospective study of ropinirole in patients with hyperprolactinemia in the setting of demonstrable pituitary tumors greater than10mms; macroprolactinomas, in order
to evaluate not only its effect of serum prolactin but its impact on tumor size, visual abnormalities, and hypogonadism and hypopituitarism if present.

Rationale: Prolactinomas are the most common type of secretory pituitary adenomas, accounting for 30 to 40 percent of all clinically recognized hypophyseal tumors. There presence can result in hypogonadism and infertility, low bone density, and galactorrhea and in more severe cases can cause headaches, hypopituitarism, and significant visual loss. While the majority of pituitary tumors are surgically managed, prolactinomas are uniquely responsive to medical therapy. The secretion of prolactin is under the tonic inhibitory control of dopamine. Subsequently, the dopamine agonists bromocriptine and cabergoline are first line therapy for the treatment of prolactinomas. Both bromocriptine and cabergoline are ergoline derivatives that lower prolactin levels and promote tumor shrinkage. Although, bromocriptine has been approved to treat prolactinomas since the early 1980s and normalizes serum prolactin levels in 59-79% of patients, side effects including nausea, postural hypotension, nasal stuffiness, and headache limit its use [1]. In a double-blind randomized controlled trial of cabergoline versus bromocriptine for the treatment of hyperprolactinemia in 459 women, the longer acting dopamine agonist cabergoline proved to be more effective at normalizing prolactin levels (83% normalized v. 59%) and was associated with fewer side effects [2]. Since this trial, cabergoline has been the preferred agent for the treatment of prolactinomas, that is until recent concerns emerged about its long-term safety.

Several case reports highlight a potential causal relationship between the use of ergotamine derived dopamine agonists like cabergoline, used to treat PD, and the development of valvular heart disease [3]. Further investigation of this relationship conducted using a nested casecontrol analysis of a population-based cohort comprised of 11,417 subjects who were prescribed anti-Parkinsonian drugs confirmed that the rate of cardiac-valve regurgitation was increased with cabergoline by an incidence-rate ratio of 4.9 (95% CI, 1.5 to 15.6) [4]. Similarly,

when echocardiography was used to assess the prevalence of valvular disease in a cohort of 155 patients with Parkinson's treated with ergot and non-ergot dopamine agonist, clinically significant regurgitation was significantly more frequent in patients taking cabergoline (28.6%) compared to controls (5.6%) [5]. Another independent case-control study in a Japanese PD cohort provides further support for a potential causal relationship between ergot-derived dopamine agonists and drug-induced valvular heart disease, illustrating a higher frequency of valvulopathy (68.8% v. 17.6% controls, $P<0.05$) in patients treated with cabergoline, even after controlling for age, sex, gender, and duration of disease [6]. Notably, there is data to suggest that valvular damage may be dose related as cabergoline doses were significantly higher among those who developed valvulopathy in the latter study [6]. While patients with prolactinomas are typically treated with much lower doses of dopamine agonists than patients with Parkinsons, their treatment courses are often decades longer resulting in potentially similar cumulative dose exposures.

In order to assess the prevalence of cardiac disease in patients with prolactinomas treated with cabergoline, Colao et al performed echocardiographic screening in a cohort of 50 patients receiving cabergoline and found a significantly higher prevalence of moderate tricuspid regurgitation in treated patients than in age and sex-matched controls (54% v. 18%, $P<0.0001$) [7]. Similarly, when Kars et al studied a similar cohort of 78 prolactinoma patients, the frequency of mild tricuspid regurgitation (43% v. 26%, $P=0.05$) and aortic and mitral calcifications was higher in cabergoline treated patients than in healthy controls [8]. While other studies failed to find an increased risk of valvulopathy in prolactinoma patients treated with cabergoline, the mean cumulative dose exposures in these cohorts were less, although admittedly dose-dependency has not been firmly established [9]. Prospective controlled studies are clearly needed to confirm a causative relationship between cabergoline and valvular disease. Nonetheless, both the manufacturer (Pfizer) of cabergoline and the UK Department of Health have issued advisories regarding the risk of cardiac valvular disease with cabergoline use. Additionally, some authors have recommend avoiding its use entirely, in spite of its efficacy and tolerability and endocrinologist and patients alike remain concerned about the potential cardiac effects of the long-term drug treatment that prolactinomas often necessitates.

The potential mechanism of ergoline mediated valvulopathy is thought to involve the serotonergic system. Cabergoline has a high affinity for the serotonin 5-hydroxytryptamine (5HT) receptor subtype 5HT-2B, much like fenfluramine which was withdrawn from the market because of its association with valvular heart disease. The 5HT-2B receptor is expressed in heart valves and when stimulated mediates mitogenesis and fibroblastic proliferation, and promotes the development of an overgrowth valvulopathy [10]. While, bromocriptine has only partial affinity for the 5HT-2B receptor and is thought to be less valvulopathic, a case report describing triple valvular fibroplasia and severe tricuspid regurgitation in a Parkinson's patient treated with high dose bromocriptine for 30 months has been published [11]. Overall, agonism at the 5HT-2B receptor does not appear to be a class effect of dopamine agonists. Data from a large population-based cohort of treated Parkinson's patients did not identify an increased risk of valvular regurgitation in patients treated with non-ergoline dopamine agonists like pramipexole and ropinirole [4].

Ropinirole is a dopamine D2/D3 receptor agonist, with little activity at other receptor subtypes while pramipexole has high specificity for the D2 receptor, but also has affinity for the beta-adrenergic receptor. Notably, both medications have negligible in vitro activity at the 5HT-2B

receptor [10]. Due to concerns about valvular heart disease, these drugs have now replaced ergoline dopamine agonists as the preferred therapy for the treatment of Parkinson's disease.

While they are FDA approved solely for the treatment of Parkinson's and RLS, both ropinirole and pramipexole have the ability to lower serum prolactin levels. In a placebo controlled dose rising study evaluating the effects of ropinirole on serum prolactin levels in 14 healthy male volunteers, statistically significant decreases in mean serum prolactin levels, comparable to those seen with bromocriptine, were observed with all doses (0.8mg to 2.5mg), with maximum prolactin suppression occurring with a dose of 1.0mg [12]. Ropinirole had only minimal side effects resulting in mild brief nausea without vomiting in 4/14 subjects at doses greater than 1.25mg and in postural hypotension six hours after 1.25mg doses in 2/14 subjects (although similar symptoms did not occur at higher doses -1.85mg and 2.5mg). Additionally, there were no drug related changes in hematologic and biochemical safety parameters. In a randomized double-blind fourfold crossover Phase I tolerability study of pramipexole in 12 healthy male volunteers, single oral doses of pramipexole also induced significant reductions in serum prolactin levels, but most subjects reported feeling markedly sedated following pramipexole use and nausea, dizziness and vomiting were common (5/12 subjects) [13]. When the relative impact of ropinirole, pramipexole, and bromocriptine on prolactin levels was evaluated in 18 Parkinson's patients taking therapeutic doses of these medications, bromocriptine and ropinirole had a greater impact on prolactin levels than pramipexole [14]. Although neither drug is currently FDA approved for the treatment of hyperprolactinemia, given ropinirole's prolactin lowering capacity, its relatively benign side effect profile, and its lack of 5HT-2B agonist activity it may represent a promising new therapeutic option for the treatment of prolactinomas. We have subsequently designed this pilot study to investigate its efficacy and tolerability in a cohort of patients with idiopathic hyperprolactinemia and microprolactinomas.

2) Study Design and Statistical Analysis:

In order to establish the PKPD profile of ropinirole for the treatment of hyperprolactinemia and to evaluate the safety, tolerability, and effect of ropinirole on serum prolactin levels in 21 patients with hyperprolactinemia who have either no tumor or a microadenoma (<10mm) on pituitary MRI, this pilot study includes the following: 1) A forced titration dose-response study of ropinirole's effect on PRL concentrations in patients with microprolactinomas. The PKPD data obtained from the forced titration dose-response study will be used a) to identify a reasonable starting dose for ropinirole in the treatment of microprolactinomas, b) to establish an appropriate drug titration plan, and c) to establish the time course of ropinirole's effect on PRL concentrations in order to determine the necessary daily dosing schedule for both immediate release and extended release ropinirole. 2) A prospective open-label 24-week outpatient dose escalation trial of ropinirole for the treatment of microprolactinomas in order to evaluate the long-term effects of ropinirole on serum PRL levels, gonadal function, and tumor size and to establish the medication's safety and tolerability in patients with microprolactinomas. 3) Lastly, subjects who have achieved normal PRL levels during the initial open-label 24-week trial can be studied for an additional 24 weeks using the previously determined dose of ropinirole in order to assess the extended effect on serum PRL levels (measured q2 months), gonadal function, and tumor size as measured by MRI one year after initial dosing.

Study Procedures:

Screening visit includes 1) physical exam, 2) visual field testing, 3) hematologic and biochemical screening labs, 4) baseline PRL confirming PRL > 40ng/ml and ruling out macroprolactinemia.

Eligible subjects who provide written informed consent will be enrolled for treatment with ropinirole. This investigational drug will be handled in accordance with the CUMC Research Pharmacy procedures and the relevant policies outlined in NYP policy P168, Version 4Investigational Drugs: Use and Control, will be followed.

Six subjects will undergo the dose-response forced titration study. Each subject will receive up to 4 doses of ropinirole in total, each on a separate occasion. 2 doses of ropinirole will be the immediate release formulation and 1 dose of extended release ropinirole will be given in order of increasing dose at a dose ranging from 0.5mg to 2.5mg. Doses will be administered in the inpatient CRC and subjects will then remain for 24hr frequent blood sampling and monitoring. Blood will be drawn for PRL at the time of IV placement (T=-60 minutes) and then 30 minutes after IV placement (T=-30 minutes). Blood will then be drawn for PRL and ropinirole immediately prior to ropinirole dose (T=0 minutes) then q30 minutes x 6 hrs, and then q2hrs x 10 hrs and q4hrs x 8 hrs thereafter. Pulse rate, blood pressure and adverse events (AE) will be evaluated q15 minutes for 1 hr after drug administration and then at each blood draw. AEs will be coded according to a standardized nomenclature developed from those previously reported to occur with ropinirole. Standardized meals will be provided. Safety labs will be done prior to and following admission.

Twenty subjects will be enrolled in a 24-week outpatient prospective dose-escalation trial of ropinirole for the treatment of microprolactinomas, following completion of the PK/PD analysis. An initial dose of ropinirole ranging from 0.25mg to 1.0mg will be given and the dose will then be up-titrated over the course of 4 weeks to the dose determined by our PKPD study to acutely and tolerably achieve max PRL suppression. The 0.25mg starting dose will be utilized for subjects previously known to have experienced side effects with dopamine agonists. A q4 week decision cascade will dictate subsequent dosing such that the ropinirole dose will be increased if PRL is greater than or equal to 20 ng/ml. Once a daily dose of 2.0mg is reached subjects can be transitioned to the once daily extended release formulation given lowest dose available is 2mg tab. Subjects will be contacted by telephone or email for safety and AE surveillance at least one-time between in person evaluations. If a subject reports a severe AE at a dose, the subject will be moved to the next lower dose for 2 weeks. If a subject reports no severe AEs and the PRL level is < 20 ng/ml, the subject will repeat the same dose for the next two-week period. If the subject reports no severe AEs and the PRL level is greater than or equal to 20 ng/ml, the subject will move to the next higher dose for the following treatment period. At the end of each study period (week 2 (+/- 3 days), 4 (+/-1 week), 8 (+/-1 week), 12 (+/-1 week), 16 (+/-1 week), 20 (+/-1 week), 24 (+/-1 week)) subjects will return to the CRC for 1) physical exam; 2) completion of questionnaire pertaining to side effects, inter-current illness, galactorrhea, menstrual cycles (in female subjects), libido, and erectile function (in male subjects); 3) medication compliance evaluation included in questionnaire; 4) urine collection in order to measure urine-HCG in pre-menopausal participants 5) a single blood draw to measure PRL, ropinirole, gonadotropins and sex steroids. Safety labs will be checked at week 2, 4, 12 and 24. Blood samples for PRL and ropinirole will be processed immediately or will be centrifuged and frozen at -80 degrees Celsius until analyzed. Visits can be added or removed at the discretion of the investigator. For participants that live far away requiring a flight or extended trip by car, bus or train, the investigator may opt to allow up to 3 of the visits to be performed remotely. A remote visit would include a survey by phone, local labs and a dose adjustment if necessary. If a participant is experiencing side effects or has an unexpected lab value, the investigator may request that a participant make additional visits for safety monitoring or get a repeat lab, travel will be reimbursed for safety visits. At week 24, radiologic tumor assessment using high

resolution MRI will be performed if applicable. Subjects who have achieved PRL normalization and/or tumor shrinkage or stabilization will have the option of remaining on ropinirole for an additional 6 months, during which labs for PRL and gonadal function will be measured q2 months. Subjects who have completed the study will be titrated off ropinirole in accord with an individualized medication titration scheme provided by the principal investigator.

Radiologic tumor assessment by MRI will be repeated in this cohort 1 year after the original study start date if applicable. All MRI scans completed as part of the study will be read by a credentialed radiologist as soon as possible but no later than two weeks following receipt of the image. The credentialed radiologist will give notice to the principal investigator if the credentialed radiologist believes that there is an incidental finding of clinical significance such as brain tumors, aneurysms, subdural fluid collections, arachnoid cysts and asymptomatic brain infarcts. "Reporting of Incidental Findings in Research" form will be included on each subject following review of the study MRI sequences. Prospective population based data from a large cohort of subjects undergoing brain MRI suggests an overall prevalence of incidental findings of approximately 10% [15]. The prevalence of findings was: aneurysms (1.8%), subdural fluid collections (less than 0.1%), arachnoid cysts (1.1%), asymptomatic brain infarcts (7.2%) cavernous angioma (0.4%) benign tumors (1.6%), malignant pituitary tumors (less than 0.1%), metastases (less than 0.1%), subdural hematoma (less than 0.1%), Chiari I malformation (0.9 %), major vessel stenosis (0.5%), fibrous dysplasia (less than 0.1%), vestibular schwannomas (0.2%).

In regards to our protocol, it should be noted that the inclusion criteria include that subjects must have a prolactinoma less than 1.5cm and ≥ 5mm from the optic chiasm on pituitary MRI. As such, the investigators will have reviewed a baseline MRI on all subjects prior to the start of the study. It would be quite unusual for a new incidental finding to arise spontaneously during the 6-12 month time period of the study given the natural history of the majority of potential incidentalomas.

Assays: PRL will be measured by two-site chemiluminescent enzyme immuonometric assay using the Immulite 1000 Immunoassay Analyzer. The median adult serum PRL is 9.4ng/ml (95% range 1.9-25 ng/ml). To screen for macroprolactinemia on all baseline PRL samples, serum samples will be incubated with polyethylene glycol and then centrifuged; the supernatant is then reanalyzed for PRL. The Immulite 1000 Analyzer will also be used to measure total testosterone, estradiol, beta- HCG, FSH, and LH. Ropinirole will be measured in plasma using a highly sensitive assay that uses liquid chromatography coupled to tandem mass spectrometry with electrospray ionization in the positive-ion mode (LC-ESI-MS/MS).

Statistical Analysis: Power calculation - 6 subjects tested at 3 doses provides capacity to estimate the true mean to within, approximately, 0.4 of a standard deviation. This level of precision is adequate to the objective of estimating the shape of the PKPD relationship between ropinirole dose, uptake, distribution and clearance. PK/PD Analysis: Initially non-compartmental analysis (NCA) of the ropinirole serum concentration data will be performed using Phoenix WinNonlin Pharmacokinetic-Pharmacodynamic software. The area under the serum concentration time curve between time 0 and time T (AUC0-T,rop), maximum concentration reached (Cmax), time at which maximum concentration is reached (Tmax) and the terminal halflife (t½rop) are the non-compartmental pharmacokinetic parameters that will be calculated for each patient at each dose level. Linearity of pharmacokinetics will be confirmed by investigating the relationship between dose and the pharmacokinetic parameters. The area

under the PRL concentration time curve between time 0 and time T (AUC0-T,PRL), the nadir and the half-life (t½PRL) describing the wearing off of the effect, are the pharmacodynamic parameters that will be calculated. Non-compartmental PKPD relationships will be investigated using exploratory regression and correlation analysis. Subsequently, a fully integrated PKPD model will be developed for ropinirole as previously described. Parameters of the model will be calculated from the data collected during the forced titration dose-response study and will be refined using data from prospective dose-escalation trial.

Power calculation: Simon's two-stage design (40) is used assuming acceptance of the treatment and progression to a Phase III study if ROP's efficacy is comparable to available therapy and 68% subjects exhibit PRL < 25ng/ml after 6 months of ROP treatment (3) and setting a floor for rejection of the treatment if 40% of subjects or less achieve PRL < 25 ng/ml, with the understanding that while not all patients respond to standard therapy, at less than 40% efficacy standard therapy would be preferred. The floor for rejection of 40% also holds for people who have side effects with standard therapy, but would not be expected to accept less than 40% efficacy for an alternative treatment with better tolerability. Based on these parameters a sample size of 20 subjects will be utilized. Specifically, the null hypothesis that the true response rate is 40% will be tested against a one-sided alternative. In the first stage, 14 patients will be accrued. If there are 7 or fewer responses in these 14 patients, the study will be stopped. Otherwise, 6 additional patients will be accrued. The null hypothesis will be rejected if 12 or more responses are observed in 20 patients, yielding a type I error rate of 5% and power of 80% when the true response rate is 68%. The probability of early stopping for futility is 85%. Linear mixed models for repeated measures will be used to determine the rate of decline of PRL levels and the rate of change in gonadotropin and sex hormone levels within each dose grade. A utility function relating PRL-lowering efficacy to toxicity increasing AE frequency will be developed to determine the dose at peak utility where maximal efficacy is obtained without elevating toxicity (44). Changes in tumor size will be evaluated by paired t-test.

3) Study Drug:

The oral non-ergoline dopamine agonist ropinirole (4-[2-(dipropylamino)ethyl]-1, 3-dihydrp-2Hindol-2-one, monochloride) will be used in this pilot study. Both the immediate and the extended release formulations of this drug are FDA approved for the treatment of idiopathic PD and RLS. Drug safety has therefore been established for use in adults with normal hepatic function and creatinine clearance greater than 30, and in the geriatric population, at doses that are approximately 10 times higher than the doses that will be studied in this pilot protocol. When used for treatment of Parkinson’s disease the recommended starting dose is 0.25mg TID for the immediate release or 2mg/day for the extended release. Up-titration for both formulations occurs on a weekly basis to a maximum dose of 24mg/day. When used for restless leg syndrome the starting dose is 0.25mg QHS and weekly 0.5mg dose escalation is recommended to a maximum dose of 4mg/day for treatment of symptoms. Based on the starting dose guidelines for these indications and the Phase 1 pilot data from Acton et al [12], that revealed statistically significant prolactin suppression starting at 0.8mg and FDA data suggesting prolactin suppression at 0.2mg doses in normal men. The lowest dose administered to hyperprolactinemic subjects in the forced titration study will be 0.25mg. In the Phase 1 study performed by Acton et al. the maximum single ropinirole dose administered was 2.5mg and accordingly the maximum single dose administered for the 24hr forced titration study will be 2.5mg. For the purposes of the 24 week outpatient dose escalation trial the minimum dose will be 0.25mg and the maximum dose will be 6mg/day.

4) Study Instruments: N/A

5) Study Subjects:

Study subjects referred directly from the CUMC Neuroendocrine unit. This unit provides a multidisciplinary (neuroendocrinology, neurosurgery, and neuroradiology) evaluation of patients with pituitary and hypothalamic disorders. Of the approximately 1000 patient visits per year, 30% are for patients with a diagnosis of prolactinoma or hyperprolactinemia. Subjects will also be referred from the Neurosurgery practices of Drs. Bruce (CUMC) and Post (Mt. Sinai Hospital) and from the General Endocrine Clinic at CUMC. **Inclusion criteria:** 1) Men and women aged 18-80 years; 2) All subjects must have elevated prolactin levels greater than normal at the time of enrollment in the study. 3) Subjects must have no evidence of other abnormal pituitary hormone hypersecretion. 4) Subjects must have either a non-detectable tumor on pituitary protocoled MRI or a tumor < 1.5cm in greatest diameter and ≥ 5mm from the optic chiasm. If an MRI performed by the patient's primary endocrinologist is not available, patients may have a baseline MRI as part of the study; 5) Subjects must have normal renal and liver function; 6) Premenopausal female subjects must agree to use barrier contraception. **Exclusion criteria –** 1) Subjects taking other medications known to interfere with prolactin secretion and metabolism including metoclopramide, cimetidine, typical and atypical anti-psychotics, CYP1A2 inducers, methyldopa, reserpine, verapamil and ciprofloxacin are not eligible. Subjects who are euthyroid on stable doses of levothyroxine will not be excluded; 2) Subjects who have used dopamine agonists less than 4 weeks prior to start of the study are excluded; 3) Subjects who have visual field abnormalities, previous radiation; 4) Subjects who drink more than 2 alcoholic beverages per day; 5) Pregnant women are not eligible.

Note that data from the screening visit which will evaluate all the above can be used as information for the baseline visit so long as the basline visit is scheduled 4 weeks or less from the screening visit.

6) Recruitment:

Potential subjects will be individuals referred from CUMC NEU and from the Neurosurgery practices of Drs. Bruce (CUMC) and Post (Mt. Sinai Hospital) and from the General Endocrine clinic at CUMC. Individuals who meet inclusion/exclusion criteria will be asked by their physician if they are interested in participating in a research study. Those who express interest will be given more information about the study by the principal investigator, co-investigator or study coordinator. A brochure outlining the studies will also be circulated to those patients interested in obtaining further information. A recruitment letter and brochures will also be sent to other practicing endocrinologists in the Columbia University medical community. Once a participant has determined she or he is interested in participating in the study, the participant will enter the pre-screening phase. At this time, the study team will ask the potential participant questions about their relevant medical history (MRI history, prolactin levels, previous and current medication, etc) to determine if a participant is likely eligible.

7) Informed Consent Process:

Consent for participation will be obtained by one of the study investigators using a consent form requiring signature. All questions raised by the potential participant will be answered verbally and in full by the consenting investigator.

8) Confidentiality of Study Data:

All paper study data will be kept in a study binder in a locked office accessible only by the study team. Data that is transferred from the paper study binder to an electronic format will be kept on a password protected computer (with a strong password per CUMC encryption guidelines) accessible only by members of the study team. In addition, all participants will be coded and labeled with a study code. The key for this study code will be kept on a password protected computer accessible only by the study team.

9) Privacy Protections:

In accord with privacy protection mandates all subjects will complete a HIPAA form prior to participation.

10) Potential Risks:

Potential risks related to blood drawing include soreness and bruising at the puncture site or catheter insertion site. Occasionally people feel lightheaded or faint. There is a small risk of infection whenever blood is drawn or a catheter (tube) is placed in a vein. The amount of blood taken at any one time is approximately half a tablespoon to one tablespoon. This amount is not expected to pose any risks to subjects.

The risks of ropinirole include potential side effects. Some patients with Parksinon's disease and Restless Leg Syndrome taking ropinirole report fatigue, dizziness, nausea, vomiting, fainting, viral infections. Leg swelling, palpitations, high blood pressure, flushing, sweating, headache, diarrhea or constipation, confusion, difficulty concentrating, abdominal pain, dry mouth have been reported by less than 10% of people taking this medication.

There have been no risks associated with an MRI as long as the patient has no imbedded metal artifacts. Some patients do feel claustrophobic being inside the scanner or uncomfortable due to the loud noise produced during normal operation. Earplugs are given to help reduce the noise.

11) Data and Safety Monitoring:

An independent endocrinologist who is experienced in both clinical medicine and research and who is not associated with the study, will be appointed for the purposes of Data Safety Monitoring. She will be immediately notified of all moderate-severe adverse events and will conduct a thorough evaluation of the potential relationship between all events and the study drugs/procedures. This independent Data Safety Monitoring appointee has the power to stop the study at any time, if she concludes that participants are being subjected to unnecessary risks. For the purposes of the pilot study, the Data Safety Monitoring physician will conduct an independent safety analysis after every 5 patients enrolled, until the completion of the study.

12) Potential Benefits:

There are no direct benefits to participating. However, if interested subjects can learn the results of their medical tests. Benefits to society potentially include the development of a new therapy for hyperprolactinemia and prolactinomas.

13) Alternatives:

The alternative is not to participate in this research study. This will have no bearing on an individual's medical treatment at this hospital.

14) Research at External Sites:
N/A

15) Columbia as Lead Institution:
N/A

16) Cost to Subjects:
None.

17) Compensation:
We will follow the Human Subjects Research Reimbursement/Compensation to Study Participants policy (http://www.cumc.columbia.edu/dept/irb/policies/documents/CompensationReimbursementPolicy.041205.Final.doc). If SSNs are collected they will not be used for purposes other than reporting to the IRS.

Subject Compensation
The 6 subjects recruited for the 24-hour inpatient pharmacokinetic aspect of the study will receive $300 for each 24-hour visit, for a total of $900 for three completed 24-hour visits. Each of the 15 subjects who participate in the outpatient dose escalation study will be compensated $585 for their time and effort. The 10 subjects who elect to continue in the additional 24-week cohort will receive $100 for their time.

We will follow the Human Subjects Research Reimbursement/Compensation to Study Participants policy (http://www.cumc.columbia.edu/dept/irb/policies/documents/CompensationReimbursementPolicy.041205.Final.doc) and will collect social security numbers from all subjects qualifying for compensation of $600 or more for the purposes of IRB reporting. SSNs will not be used for purposes other than reporting to the IRS.

Compensation Justification
The 24-hour inpatient study visit will require placement of an IV and initial blood draw, followed by 21 additional blood samples and an overnight stay. Subjects will receive $21 for the IV placement and initial blood draw, followed by $9 for each subsequent blood sample; and will then receive $90 for the overnight hospital stay. The compensation for each 24-hour visit is therefore $300, or a total of $900 for all three completed visits.

The 15 outpatient subjects participating in the dose escalation component will have 8 visits consisting of a physical exam, questionnaire, and blood draw plus a final MRI at the conclusion of the study. They will be compensated $65 per visit for Visits 1-7 and $130 for Visit 8, for a total of $585 for completion of the entire study.

The second 24-week cohort will return to the CRC q2 months for 30-minute office visits and blood draws and a final MRI at the conclusion of the 6 months. They will be compensated $100 in total, $25 for visits 1 and 2 which consist of blood draws and physical exams, and $50 for the final visit which includes an MRI, blood draw, and physical exam.

All potential subjects will also have their blood drawn for screening purposes prior to participation in the study but will not be compensated for this.

18) Minors as Research Subjects:

Minors will not be recruited.

19) Radioactive Substances:

Radioactive substances will not be used in this protocol.

20) References:

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