Clinical Research Assignment. Level 8 BA.
Pharmaceutical Business Operations.

Part A

Trihexyphenidyl is used to treat the symptoms of Parkinsons Disease (PD) and belongs to a class of drugs called Anticholinergics. Its chemical entity is $C_{20}H_{31}NO$ HC1. Trihexyphenidyl HCI occurs as a white or creamy-white, almost odourless, crystalline powder. It is very slightly soluble in ether and benzene, slightly soluble in water and soluble in methanol. It is administered orally through either 2mg or 5mg strength tablets or 2mg in elixir form. (5ml teaspoon).

PD is a progressive neurological disorder which affects the central nervous system by slowly reducing dopamine generating cells over a number of years. Dopamine is largely responsible for muscle control and its reduction leads to the cardinal symptom Bradykinesia, a slowness of movement. Other motor symptoms include tremor, rigidity, stiffness, vision impairment and non-motor symptoms include poor sleep, fatigue and depression.

The disease is most often detected 4-6 years after onset and generally progresses by 10% year on year. There is no known cure for PD and current treatments are for the symptoms only. Research is underway to find suitable Biomarkers for the detection and treatment of PD and there is no one test to diagnose. For a neurologist to diagnose PD, Bradykinesia must be present and at least one other of the following symptoms:

● Shaking or tremor ● Stiffness or rigidity of the arms, legs or trunk ● trouble with balance and falls.

It is hypothesised that as dopamine neurons die off in the brain, this causes an over-activity of a substance in the brain called acetylcholine. An excess of acetylcholine is thought to cause depression and interferes with voluntary muscular movements. It sends messages that cause muscles to contract, while dopamine moderates these signals to proper levels. As a result, it causes patients with PD to experience an imbalance in these chemical levels, leading to Bradykinesia, involuntary tremors and muscle rigidity amongst many others.

Dopamine inhibits the production of acetylcholine and when the level of dopamine is reduced by the progression of PD, this causes an imbalance between the two substances. Trihexyphenidyl works by restoring this balance and is thus defined as an anticholinergic, which inhibits the production of acetylcholine.

Another drug in the anticholinergic class is Benzatropine, brand name Cogentin. This drug is generally used to control the side effects of antipsychotic treatments, but is also used as second line defence for treating the symptoms of PD.

Trihexyphenidyl is generally used in combination with another drug to control the symptoms of PD and the most common of these is Levodopa.

A direct treatment of dopamine by itself is ineffective because the brains natural defences block it from being used. Levodopa is synthesized in the brain to make dopamine, however by the time it gets to the brain through the digestive and bloodstream mechanism, it is normally broken down and ineffective. To prevent this from happening, Carbidopa is used as a sort of transport mechanism, by preventing peripheral metabolism of levodopa. It also helps to prevent nausea and when ingested in pill form, it gets into the bloodstream through the small intestine, transported to the brain and stored in the neurons when needed for muscle control. Trade names include Sinemet, Madopar and Atamet.

Part B

Study rationale - For the purposes of the trial, Cogentin is being categorised as standard of care for the purpose of comparison in efficacy. For the purposes of this assignment it will be taken that Phase I clinical trials is complete and safety in human has been established. The study is required to determine the improved efficacy of Trihexyphenidyl in reducing tremor over Cogentin.

Study objectives - Trial is at phase II and its primary objective is to determine efficacy.
Safety, tolerability, side effects and other observed benefits during the full implementation of the Unified Parkinsons Disease Rating Scale (UPDRS) are secondary objectives.

Official Biomarkers do not exist for PD, though it should be noted that in 2015, the director for the FDA's Centre for Drug Evaluation and Research, Janet Woodcock, sent three letters acknowledging the work being carried out in regarding biomarkers, by CAMD, the Arizona based Critical Path Institutes Coalition Against Major Diseases.

Study design - Due to the subjective nature of testing, the trial is a three arm, Double blind, Placebo and Comparator Controlled, Parallel group, Crossover trial.

Due to the subjective nature of the data being measured it is required for the trial to be double blind to ensure both patient and investigator are not unduly biased. To further prevent bias, a placebo shall be introduced during the washout phase of the trial, which occurs when the patient will change from being administered Artane to Cogentin and for the parallel group, Cogentin to Artane.
This changeover will take place after 11 weeks, upon which the placebo will be administered for two weeks and the patient then returns to standard of care Cogentin (or the trial drug Artane) for the remaining 11 weeks.

The data being measured is more qualitative in nature and open to subjective interpretation and description from the patient. The Hoehn & Yahr scale is to be used to baseline severity and stage of the disease. The UPDRS is to be exercised by fully trained and qualified professionals in movements disorders.

Parkinson patients are described to be in the 'OFF' when the effects of the drug have worn off and movements are sporadic, involuntary and intensified. The 'ON' state is when the patient has relative normal control over body movements with the aid of medication.

Study Population – Group is stratified by age. Subsets are 30-40 ; 40-50 years ; 50-60 ; 60-70 ; 70-80 ; ≥ 80. Two groups shall be formed and both groups shall have an equal portion of patients from each age bracket. For example, 10 patients are available from the 50-60 age bracket. Five shall go into parallel group A, whilst the remaining 5 will participate in group B and so on.

The purpose of grouping is to establish a correlation of age to efficacy if any. Parkinsons is a progressive disease and therefore time of onset, age, dosage and peak dose may separately or in combination, impact the efficacy of Trihexyphenidyl. It is known that patients over the age of 65 are more sensitive to this drug and therefore the dosage may need to be reduced.

Duration of study - Due to the nature of the disease, there can be a lot of variability in signs and symptoms. Motor fluctuations can be sporadic with varying severity of the disease. The population mix and age can also further add to the variability within the study so it is necessary to have the study conducted over a 6 month period allowing enough time to gather data and assess the impact of all variables to ensure statistical confidence in the results.

Product name	Trihexyphenidyl (Artane)
Study rationale	The study is required to determine if the drug Artane (Trihexyphenidyl) is superior in efficacy compared to standard of care Cogentin (Benzatropine) for reducing tremor in patients with idiopathic Parkinsons Disease.
Study objectives	The primary objective of the trial is determine the efficacy of the drug Trihexyphenidyl in the reduction of tremor in patients on L-Dopa+ with motor fluctuations using the UPDRS rating scales for Parkinson disease. Secondary objectives are all other measures on the UPDRS scale, safety and tolerability.
Study design	This is a stratified, phase II, Three arm, Double blind, Placebo and Comparator Controlled, Parallel group Crossover trial.
Study population Inclusion criteria	500 subjects. Male & Female. Age group ≥ 30. Stratified by age in subsets of 30-40, 40-50, 50-60, 60-70, 70-80 and ≥ 80 years of age. 1. Subject has been fully informed and all questions answered. Ample time has been provided for the patient to fully think through their participation and written consent provided. 2. Subject is able to comply with trial requirements. 3. Subject is over 30 years of age. 4. Subject has idiopathic Parkinsons Disease as indicated by the presence of Bradykinesia and resting tremor. No other cause other Parkinsons Disease is attributable to these symptoms. 5. Subject must be between 2 and 4 on the Hoehn & Yahr scale. This must be observed by the investigator in both the 'On' and 'Off' states. 6. The patient must be on a course of Levodopa in combination with Carbidopa for at least 28 days prior to visit No.2 (Baseline) 7. Patient must score ≥25 points on part III of the UPDRS rating scale in the 'Off' state.
Exclusion criteria	1. Subject has previously participated in this trial or a previous trial with Artane. 2. Is currently participating in another trial or has participated in the trial of another drug within the past 30 days. 3. Subject has PD symptoms due to or caused by other drug treatments or disorders such as Wilson disease. 4. Subject has had deep brain simulation. 5. Subject has dementia or active hallucinations unless these are being treated successfully with no symptoms presenting over the past 28 days.
Geographic area	International
Planned duration of study	6 months

Part C

The primary efficacy variable to be measured is Tremor using the UPRDS scale. The trial is to be run using a combination of Levodopa & Artane in comparison to a combination of Levodopa and Cogentin. Levodopa works to control Bradykinesia, whilst Artane or Cogentin is administered to control tremor. Tremor should be focused upon and measured as closely as possible during this trial.

Following the guidelines on the clinical investigation of medicinal products for PD, it suggests that a clinical trial for PD should depend on the objective of the trial and the guidelines set out four different objectives that may be distinguished:

- Symptomatic relief in early stage PD before L-Dopa+ treatment:
- Symptomatic relief in patients with PD on L-Dopa+ subdivided in:
    - Patients on L-Dopa+ with insufficient control of motor symptoms;
    - Patients on L-Dopa+ with motor fluctuations;
    - Patients with serious unpredictable and rapid changing motor fluctuations.
- Therapies aimed to modify disease progression, late motor complications;
- Treatment aimed to postpone late motor fluctuations;
- Treatment aimed to delay disease progression;
- Substitution of neuronal loss

With the above objectives distinguished it is important to choose the appropriate efficacy variable and the objective a drug should meet in treating that particular variable. Trihexyphenidyl in combination with L-Dopa does not modify, postpone or delay progression and it is not substituting neuronal loss. It falls into the category of 'relief in patients with PD on L-Dopa+', as tremor would be a factor in each of the above subdivisions.

In patients with PD, motor fluctuations can be predictable and unpredictable. It must be understood if these fluctuations are dose or non-dose dependant.
For example, the patient may experience 'delayed on' which is a prolongation of the time it takes for the drug to have an effect which can vary from patient to patient and subgroup to subgroup. Freezing or dyskinesia (abnormal or involuntary movement) during an 'on' phase are less related to the timing of the dosage as they are sporadic and unpredictable.

Predictable motor fluctuations are related to the time of dosing e.g. peak dose dyskinesias. When Levodopa is at its peak concentration it can cause disabling motor fluctuations and dyskinesias which negate the therapeutic benefits of the drug. Controlling the dosage and timing of levodopa are preventative measures associated with the use of the drug.

As part of the trial it will be important to measure the effect of Trihexyphenidyl on predictable motor fluctuations against standard of care Cogentin.

For less predictable motor complications such as freezing, therapy is measured by the duration and frequency of the 'ON' and 'OFF' state, but the primary efficacy variable being measured during this trial is tremor, therefore a measurement of 'ON' and 'OFF' states is a secondary objective.

Patients with PD often use more than one anti-parkinson drug and dose adaptions are normal. To measure the efficacy of the test drug with greater accuracy, the dose of Levodopa should remain constant throughout the trial.

To begin treatment, Trihexyphenidyl is administered in 1mg dose on the first day of treatment and incremented by 2mg for the following 3 to 5 days until a daily maximum of between 6- 15mg per day is reached, patient dependant. On average, a dose is being administered every 3 hours. Dose titration should be finalised before baseline measurements are taken to ensure the optimum dose per patient is reached before the trial drug measurements are begun.

Trihexyphenidyl is absorbed very quickly by the gastrointestinal tract and its therapeutic effect lasts 2-3 hrs, hence the need for almost continuous administration. It is required therefore to measure the effects on the primary efficacy variable on a daily basis. Disruption to the life of the patient is a concern and performing a full UPDRS on a daily basis would be considered overly burdensome.
It would be more appropriate to perform part III of the UPDRS on a daily basis whilst performing a full UPDRS on a weekly basis.

This is to be performed by both investigator and patient for the first two weeks, essentially training and calibrating the patient to keep their own diary record through the UPDRS scale. Upon waking the patient must take the first daily dose and allow 2 hours for therapeutic benefit to take effect.
A UPDRS record may be taken during any part of the day. Sleeping periods disrupt the continuous administration of the drug, therefore morning time will have least therapeutic benefits, patient and circumstance dependant.

Starting week three, the investigator will perform a full weekly UPDRS measurement and monitor the patient diary for any significant drift in calibration.

The primary efficacy variable is to be collected once daily together with the investigator and the patient for the first two weeks. Thereafter it is to be collected once daily by the patient only, through the use of the UPDRS Part III motor fluctuation diary.
Finally, a comprehensive once weekly UPDRS exercise is to be performed by the investigator and patient for a total of six months.

The above instruction is to be repeated across the three arms: Double blind, Placebo and Comparator controlled, Parallel group Crossover trial.

At the end of the six month trial, sufficient data shall have been gathered across the three arms to make a proven comparison of efficacy between Artane and Cogentin.

Part D

Case Report Form

Protocol Number: _____

Title

Comparison of efficacy for Trihexyphenidyl against standard of care Cogentin in subjects with Idiopathic Parkinsons Disease

Participant Number _____

Study group _____

Study site _____

Date of birth _____

Gender _____

Informed consent process Complete: Yes No

General Instructions

- This case report form must be filled out for each patient.
- Answer all questions in block capitals using a black ball point pen
- Measure all responses based

Bias

- Personnel trained and qualified in the use of the UPDRS scale are to perform this evaluation.
- A minimum of two differently trained personnel are to perform the evaluation a bi-weekly basis.

UPDRS

- This scale is to be completed in its entirety once weekly
- UPDRS Part III

Dates and times

- All dates must appear in the format DD-MMM-YYYY e.g. 12-Jun-2016
- All time entries must appear in the 24-hour format e.g. 15.30.

Corrections

- Do not use correction fluids or erasers.
- Neatly put a strike through the error and enter the correct value beside the strike.
- Initial and date the correction

Exclusion/Inclusion criteria

- Subject must have been previously assessed against exclusion/inclusion criteria

Specific Instructions

Rigidity

● Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation manoeuvre. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation manoeuvre such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity.

Postural tremor of the hands

● All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds.

Kinetic tremor of the hands

● This is tested by the finger-to-nose manoeuvre. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose manoeuvres with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose manoeuvre should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen.

Rest tremor amplitude

● This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when sitting quietly, during walking and during activities when some body parts are moving and but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor. As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs also for the lip/jaw. Rate on the maximum amplitude that is seen at any time as the final rating.

Unified Parkinsons Disease Rating Scale – Bradykinesia, Tremor & Severity

Tremor

Over the past week, have you usually had shaking or tremor?

0: Normal: Not at all. I have no shaking or tremor.

1: Slight: Shaking or tremor occurs but does not cause problems with any activities.

2: Mild: Shaking or tremor causes problems with only a few activities.

3: Moderate: Shaking or tremor causes problems with many of my daily activities.

4: Severe: Shaking or tremor causes problems with most or all activities.

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Rigidity

0: Normal: No rigidity.

1: Slight: Rigidity only detected with activation manoeuvre.

2: Mild: Rigidity detected without the activation manoeuvre, but full range of motion is easily achieved.

3: Moderate: Rigidity detected without the activation manoeuvre; full range of motion is achieved with effort.

4: Severe: Rigidity detected without the activation manoeuvre and full range of motion not achieved.

Score

Neck ☐

Rue ☐

Lue ☐

RLE ☐

LLE ☐

SLOWNESS OF MOVEMENT (BODY BRADYKINESIA)

0: Normal: No problems.

1: Slight: Slight global slowness and poverty of spontaneous movements.

2: Mild: Mild global slowness and poverty of spontaneous movements.

3: Moderate: Moderate global slowness and poverty of spontaneous movements.

4: Severe: Severe global slowness and poverty of spontaneous movements.

☐

POSTURAL TREMOR OF THE HANDS

0: Normal: No tremor.

1: Slight: Tremor is present but less than 1 cm in amplitude.

2: Mild: Tremor is at least 1 but less than 3 cm in amplitude.

3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude.

4: Severe: Tremor is at least 10 cm in amplitude.

4: Severe: Tremor is at least 10 cm in amplitude.

☐ R

☐ L

KINETIC TREMOR OF THE HANDS

0: Normal: No tremor.

1: Slight: Tremor is present but less than 1 cm in amplitude.

2: Mild: Tremor is at least 1 but less than 3 cm in amplitude.

3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude.

4: Severe: Tremor is at least 10 cm in amplitude.

Score

☐ R

☐ L

REST TREMOR AMPLITUDE

Extremity ratings

0: Normal: No tremor.
1: Slight.: < 1 cm in maximal amplitude.
2: Mild: > 1 cm but < 3 cm in maximal amplitude.
3: Moderate: 3 - 10 cm in maximal amplitude.
4: Severe: > 10 cm in maximal amplitude. Lip/Jaw ratings

Lip/Jaw ratings

0: Normal: No tremor.
1: Slight: < 1 cm in maximal amplitude.
2: Mild: > 1 cm but < 2 cm in maximal amplitude.
3: Moderate: > 2 cm but < 3 cm in maximal amplitude.
4: Severe: > 3 cm in maximal amplitude.

	Score
Rue	☐
Lue	☐
RLE	☐
LLE	☐
Lip/Jaw	☐

CONSTANCY OF REST TREMOR

0: Normal: No tremor.
1: Slight: Tremor at rest is present < 25% of the entire examination period.
2: Mild: Tremor at rest is present 26-50% of the entire examination period.
3: Moderate: Tremor at rest is present 51-75% of the entire examination period.
4: Severe: Tremor at rest is present > 75% of the entire examination period.

Score ☐

DYSKINESIA IMPACT ON PART III RATINGS

A. Were dyskinesia's (chorea or dystonia) present during examination?	No	Yes
B. If yes, did these movements interfere with your ratings?	No	Yes

HOEHN AND YAHR STAGE

0: Asymptomatic.
1: Unilateral involvement only.
2: Bilateral involvement without impairment of balance.
3: Mile to moderate involvement; some postural instability
but physically independent; needs assistance to recover from pull test.
4: Severe disability; still able to walk or stand unassisted.
5: Wheelchair bound or bedridden unless aided.

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Bibliography

www.ema.europa.eu. (2012). *Guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease*. [online] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129601.pdf [Accessed 28 Jan. 2017].

www.fda.gov. (1998). *Guidance for Industry - E9 Statistical Principles for Clinical Trials*. [online] Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf [Accessed 28 Jan. 2017].

Clinicaltrialsregister.eu. (2017). *Clinical Trials Register*. [online] Available at: https://www.clinicaltrialsregister.eu/ctr-search/search?query=trihexyphenidyl [Accessed 28 Jan. 2017].

www.movementdisorders.org. (2008). *Movement Disorder Society (MDS) sponsored new version of the Unified Parkinsons Disease Rating Scale.*. [online] Available at: http://www.movementdisorders.org/MDS-Files1/PDFs/MDS-UPDRS-Rating-Scales/NewUPDRS7308final.pdf [Accessed 28 Jan. 2017].

RxList. (2009). *Artane (Trihexyphenidyl) Drug Information: Indications, Dosage and How Supplied - Prescribing Information at RxList*. [online] Available at: http://www.rxlist.com/artane-drug/indications-dosage.htm [Accessed 28 Jan. 2017].

Stvincents.ie. (2017). *Hoehn and Yahr Staging of Parkinson's Disease*. [online] Available at: http://www.stvincents.ie/dynamic/File/UPDRS,H&Y,%20S%20&%20E_MedEl_tool.doc [Accessed 28 Jan. 2017].

neurosurgery.mgh.harvard.edu. (2017). *Hoehn and Yahr Staging of Parkinson's Disease, Unified Parkinson Disease Rating Scale (UPDRS), and Schwab and England Activities of Daily Living*. [online] Available at: https://neurosurgery.mgh.harvard.edu/functional/pdstages.htm [Accessed 28 Jan. 2017].

EverydayHealth.com. (2017). *Recognizing the Stages of Parkinson's Disease Progression*. [online] Available at: http://www.everydayhealth.com/parkinsons-disease/parkinsons-disease-progression.aspx [Accessed 28 Jan. 2017].

www.fda.gov. (2015). *The Voice of the Patient*. [online] Available at: http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm498266.pdf [Accessed 28 Jan. 2017].

Factor, D.O.M, S. (2003). *Treating the "off" periods in Parkinson's - Parkinson's Disease Foundation (PDF)*. [online] Pdf.org. Available at: http://www.pdf.org/en/fall03_periods [Accessed 28 Jan. 2017].

Lee, MD, FRCPC, C. (2001). *Levodopa-induced dyskinesia: Mechanisms and management*. [online] Bcmj.org. Available at: http://www.bcmj.org/article/levodopa-induced-dyskinesia-mechanisms-and-management [Accessed 28 Jan. 2017].

Parkinsons.org.uk. (2017). *Levodopa*. [online] Available at: https://www.parkinsons.org.uk/content/levodopa [Accessed 28 Jan. 2017].

Fda.gov. (2016). *Drug Study Designs - Information Sheet*. [online] Available at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm126501.htm [Accessed 28 Jan. 2017].

Thanvi, B., Lo, N. and Robinson, T. (2007). *Levodopa-induced dyskinesia in Parkinson's disease: clinical features, pathogenesis, prevention and treatment*. [online] National Center for Biotechnology Information. Available at: http://www.ncbi.nlm.nih.gov [Accessed 28 Jan. 2017].