CONFIDENTIAL

STATISTICAL ANALYSIS PLAN FOR PROTOCOL 204503

Assessment of cognitive function and mobility in

Individuals with pain

BIOSTATISTICS DEPARTMENT

GLAXOSMITHKLINE CONSUMER HEALTHCARE

INVENTIV HEALTH CLINICAL

PPD

PPD (Statistician)

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Glossary

AE	Adverse Event
ANCOVA	Analysis of Covariance
AST	Attention Switching Task
BMI	Body Mass Index
BPI	Brief Pain Inventory
CRF	Case Report Form
CANTAB	Cambridge Cognition Cognitive Assessments
GCP	Good Clinical Practice
GRF	Ground Reaction Force
GSKCH	GlaxoSmithKline Consumer Healthcare
HPL	Human Performance Lab
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention to Treat
mITT	Modified Intention to Treat
OTC	Over-the-Counter
OTS	One Touch Stockings of Cambridge
RTI	Reaction time
SAE	Serious Adverse Event
SWM	Spatial Working Memory
SRT	Simple Reaction Time
SAP	Statistical Analysis Plan
RVP	Rapid Visual information Processing
RVPA	Rapid Visual information Processing A prime

1 Introduction

This document describes the statistical methods and data presentations to be used in the summary and analysis of the final data from Protocol 204503.

This statistical analysis plan will be finalized and approved prior to database freeze and unblinding.

2 Objectives

Objectives	Endpoints
Primary	
• To investigate within-subject cognitive changes in individuals with everyday pain compared to pain-free performance.	• Subject level change from pain-free state in cognition as measured by cognitive function assessment (CANTAB and Axon Sports) in the pain state.
Secondary	
• To investigate within-subject mobility changes in individuals with everyday pain compared to pain-free performance.	• Subject level change from pain-free state in mobility as measured by gait, time to standing and grip force score in the pain state.
Exploratory	
• Investigate the relationship between pain type and intensity with cognitive function and mobility.	• Correlation between pain intensity and each cognitive assessment for each pain type at Visit 2 Pre and Visit 2 Post. • Correlation between pain intensity and each mobility assessment for each pain type at Visit 2 Pre and Visit 2 Post.
• To investigate the effects of OTC treatment (paracetamol +/- caffeine and placebo) on cognitive function and mobility in individuals with everyday pain.	• Effect of intervention on change from pain-state assessment in cognition as measured by cognitive function assessment (CANTAB and Axon Sports) to post-treatment assessment period. • Effect of intervention on change from pain-state assessment in mobility as measured by gait score, time to standing score and grip

	strength to post-treatment assessment period.

3 Study Design

Overall Design
This parallel, assessor blind, placebo-controlled, stratified, randomised study will recruit approximately 65 male and female participants with everyday pain (as assessed by the Brief Pain Inventory – Short Form questionnaire). They will be recruited from GSK employees or by a Clinical Research Organisation, screened for eligibility and the assessment will be at The Human Performance Lab (HPL).
Visit 1 - Screening Visit
After initial screening via email/telephone subjects will be invited for a screening visit at the HPL at a suitable time. The below activities will be conducted during the screening visit in the following order: **1. Informed Consent** **2. Subject Eligibility assessments (in any order)** - Demographics - Brief Pain Inventory - short form **(SEE APPENDIX 2)** - Pain Recurrence Question (see Appendix 3) - General Medical History - GP name and contact details collected - Current/concomitant medication - Height, Weight and BMI measurements - Physical exam and vital signs - Pregnancy test (women of childbearing potential only) - Subject eligibility (Confirm subject satisfies all entry criteria relevant to screening Visit 1 prior to progression to familiarization activities) **3. - Familiarization activities (in any order)** - Cognitive testing practice session (Axon Sports and CANTAB cognitive assessment) - Mobility assessments practice session (Gait, Time to standing, Grip Force) - Inclusion/Exclusion criteria Letter to GP sent via email or next day delivery post on same day as screening visit. GP

letter to include summary of the study and request that GP contact the site if any reason known that the subject should not participate.

Visit 2 - Pain state assessment

A minimum of 7-days and a maximum of 28-days later, a pain-state assessment will be performed. The following assessments will be conducted in the order written:

- Brief Pain Inventory - short form **(SEE APPENDIX 2)**
- Pregnancy test (females of child bearing potential only)
- Urine drug screen and alcohol breath test
- General Medical History
- GP letter response reviewed if received
- Current/concomitant medication
- Physical exam and vital signs
- Pain State Question (see appendix 4)
- Subject Eligibility
- Inclusion/Exclusion criteria
- **Pre-treatment** Cognitive testing (Axon Sports and CANTAB cognitive assessment)
- **Pre-treatment** Mobility assessments (Gait, Time to standing, Grip Force)
- Stratification and Randomization to OTC medication
- Subject will be stratified to one of four strata according to their pain type and then randomized accordingly to one of the three treatment groups.
- Supervised OTC medication given on site
- **Post-treatment (1hr ± 15 mins)** Brief Pain Inventory - short form **(SEE APPENDIX 2)**
- **Post-treatment** Cognitive testing (Axon Sports and CANTAB cognitive assessment)
- **Post-treatment** Mobility assessments (Gait, Time to standing, Grip Force)
- Physical exam and vital signs
- Adverse Events

Visit 3 - Pain-free state assessment

Subjects will be requested to return a minimum of 2-days and a maximum of 30-days post Visit 2 once they are pain-free for another assessment (visit 3). In order to be pain-free participants must rate their pain as 0 in response to Question 6 on Brief Pain Inventory – Short Form **(SEE APPENDIX 2).** If after 30 days their score is still >0 in response to Question 6 on Brief Pain Inventory – Short Form then only their pain state

and post-intervention data will be used in analysis and will not be required for further follow-up.

The following assessments will be conducted in the order written:

- Urine drug screen and alcohol breath test
- Brief Pain Inventory - short form **(SEE APPENDIX 2)**
- Current/concomitant medication
- Cognitive testing (Axon Sports and CANTAB cognitive assessment)
- Mobility assessments (Gait, Time to standing, Grip Force)
- Adverse events
- Study conclusion/Medical sign-off

4 Sample Size Determination

This is an exploratory study, the sample size calculation is not based on any formal formulations. A sufficient number of subjects will be screened in order to randomize approximately 65 subjects to obtain 20 subjects per treatment group for a 5 week analysis.

5 Data Considerations

5.1 Analysis Populations

All Subject: The population of All Subjects includes all subjects that are screened for entry into the study.

Safety Population: Safety population will include subjects who are randomized and received at least one dose of study treatment.

Safety population summaries will be presented by actual treatment received.

Intent-to Treat Population (ITT): ITT population will include subjects who are randomized, receive at least one dose of study treatment and provide at least one post-baseline assessment of efficacy.

Modified Intent-to-Treat (mITT) Population: All the subjects those who are randomized, received at least one dose of study treatment and have at least one post-baseline assessment without any violation of study inclusion-exclusion criteria will be included in the mITT population.

Primary population for efficacy assessment will be considered as mITT.

All mITT population summaries and analyses will be presented by treatment randomized.

Efficacy analysis will be performed on the cognitive performance (as measured by individual scores from the Axon Sports Priming Application and each of the CANTAB tasks – RTI, OST, AST, SWM and RVP) and mobility (as measured by individual scores from gait, time to standing and grip force assessments) for mITT populations.

A blinded data review will be performed before database lock to identify protocol violations (Important protocol are listed below). The protocol violations deemed to have potential to affect efficacy measures will lead to the exclusion of subjects from mITT population or the exclusion of the affected data from mITT analysis. The review listings will include, but will not be necessarily limited to, the following:

- Violations of Inclusion or Exclusion Criteria;
- Current / Concomitant Medications;
- Treatment Non-Compliance;
- Protocol Deviations;
- Visit schedule not followed as required in protocol, i.e.

  Visit 2 (Pre-Treatment) (schedule or re-schedule) not within 7-28 days of Visit 1

  Visit 2 (Post Treatment) – Same day within 45-75 (1 hr +/- 15 min) minutes as Visit 2 (Pre Treatment), i.e. anything that is not fall within 45-75 (1 hr +/- 15 min) minutes should be listed.

  Visit 3 (schedule or re-schedule) not within 2 - 30 days of Visit 2 (NONCOMPLIANCE WITH VISIT SCHEDULE).
- Subjects deviating from the protocol in any other major way, as determined by blinded review of the CRF comments pages.
- Listing of all efficacy variables falling outside Mean +/- 3 SD will be produced for each time points.

Details of blinded review listings will be given in the Review Listing Requirement document. Protocol violations will be identified between the statistician and Clinical Research Scientist or designee, ahead of study unblinding.

5.2 Subgroups/Stratification

There will be four strata in this study based on pain type. Subject will be stratified according to the Pain Type (I.e. Joint, Back, Headache and Period).

Stratum 1: Person feels the pain in the knee or hip joint at baseline

Stratum 2: Person feels the pain in the upper or lower back at baseline
Stratum 3: Person has headache at baseline

Stratum 4: Person (Female only) having menstrual period related pain at baseline

5.3 Time Windows

The study schedule should be followed as per protocol. Deviations from the study schedule with respect to visit timings will be reviewed on a case-by-case basis. Required time windows are presented in Section 5.1.

6 Demographics and Baseline Characteristics

6.1 Subject Disposition

The subject disposition summary will present the number of screened subjects, the number of screening failures and the number of subjects randomized. The number and percentage of subjects, in the Safety and mITT populations will also be presented with percentages based upon the total number of subjects randomized.

The number and percentage of subjects completing the study and not completing the study, including a breakdown of the reasons for not completing the study, will also be presented with percentages based upon the total number of subjects randomized.
A separate summary table of major protocol violations will be produced indicating the number and percentage of subjects with each violation. Percentages will be based on the mITT population

6.2 Demographics

Descriptive statistics (number of subjects, mean, and standard deviation, median, minimum and maximum for continuous variables, and frequency and percentage for categorical variables) will be provided for demographic data. These data include age, gender, race and BMI, and will be presented for the Safety and mITT population.

6.3 Baseline Characteristics

Number and percentage of subjects in each stratum (stratified by pain type) will be summarized by treatment group and will be presented for the Safety and mITT population.

7 Treatment Compliance and Concomitant Medications

7.1 Treatment Compliance

Assessment of treatment compliance will be based on comments reported on the CRF comments page. Treatment compliance will be reviewed during blinded review and a listing will be produced for evaluation of protocol violations only. Treatment compliance will be neither tabulated nor listed. However Treatment compliance will be checked during blinded review.

7.2 Concomitant Medications

A listing of concomitant medications will be produced.

8 Efficacy Analysis

8.1 Determination of Efficacy Measure

8.1.1 Determination Cognitive Function Assessments:

- **Axon Sports:** The Axon Sports Priming Application is a computerized test performed on a tablet device that measures cognitive performance, namely psychomotor speed. The main outcome measure is simple reaction time (SRT) (msec), error (msec) and error adjusted SRT (msec). Subject level change from pain-free state (Visit 3) in error adjusted SRT at pain state (Visit 2 [Pre-treatment & Post treatment) will be used as efficacy variable.

- **Reaction Time (RTI):** In this five-choice reaction time task the participant holds down a button at the bottom of the screen until a yellow spot appears in one of the five circles at the top of the screen. They must then release the button and touch inside the circle where the yellow spot appeared as quickly as they can. The key outcome measure for this task is median five-choice reaction time (the median duration between the onset of the stimulus and the release of the button. Calculated for correct, assessed trials where the stimulus could appear in any one of five locations). Subject level change from pain-free state (Visit 3) in

median five choice reaction time at pain state (Visit 2 [Pre-treatment & Post treatment) will be used as efficacy variable.

- **One Touch Stockings (OTS):** This task is a measure of executive function and takes approximately 10 minutes to complete. The participant is shown two displays containing three colored balls. The displays are presented in such a way that they can easily be perceived as stacks of colored balls held in stockings or socks suspended from a beam. This arrangement makes the 3-D concepts involved apparent to the participant, and fits with the verbal instructions. There is a row of numbered boxes along the bottom of the screen. The test administrator first demonstrates to the participant how to use the balls in the lower display to copy the pattern in the upper display, and completes one demonstration problem, where the solution requires one move. The participant must then complete three further problems, one each of two moves, three moves and four moves. Next the participant is shown further problems, and must work out in their head how many moves the solutions to these problems require, and then touch the appropriate box at the bottom of the screen to indicate their response. The main outcome variable is the OTS problems solved on first choice which is the number of assessment problems on which the first box choice made was correct. Subject level change from pain-free state (Visit 3) in number of assessment problems on which the first box choice made was correct at pain state (Visit 2 [Pre-treatment & Post treatment) will be used as efficacy variable.
- **Attention Switching Task (AST):** This task is a measure of executive attention and takes approximately 8 minutes to complete. The test displays an arrow which can appear on either side of the screen (right or left) and can point in either direction (to the right or to the left). Each trial displays a cue at the top of the screen that indicates to the participant whether they have to press the right or left button according to the "side on which the arrow appeared" or the "direction in which the arrow was pointing". Some trials display congruent stimuli (e.g. arrow on the right side of the screen pointing to the right) whereas other trials display incongruent stimuli which require a higher cognitive demand (e.g. arrow on the right side of the screen pointing to the left). The main outcome is the AST congruency cost (median; msec) which is the difference between the median latency of response (from stimulus appearance to button press) on the trials that were congruent versus the trials that were incongruent. It is calculated by subtracting the median congruent latency (in msec) from the median incongruent latency. This measure is complex in sense in that close to zero indicates less variation in latencies across congruent and incongruent trials. A positive score indicates that the subject is faster on congruent trials and a negative score indicates that the subject is faster on incongruent trials.
- **Spatial Working Memory (SWM):** This task is a measure of working memory and takes approximately 6-7 minutes to complete. The task involves a number of colored squares (boxes) being shown on the screen. The aim of this test is to find one blue token in each of a number of boxes by process of elimination and use these to fill up an empty column on the right hand side of the screen. The

number of boxes gradually increases up to a maximum of eight boxes to search and the color and position of the boxes change from trial to trial. The main outcome variable is the SWM between errors and is defined as times the subject revisits a box in which a token has previously been found. This is calculated for 12 tokens.

- **Rapid Visual information Processing:** This task measures attention and takes approximately 7 minutes to complete. A white box appears in the center of the computer screen, inside which digits, from 2 to 9, appear in a pseudo-random order, at the rate of 100 digits per minute. Participants are requested to detect target sequences of digits (for example, 2-4-6, 3-5-7, 4-6-8) and to register responses using the press pad. The main outcome variable is RVPA' (Aprime) and it is the signal detection measure of sensitivity to the target, regardless of response tendency (the expected range is 0.00 to 1.00; bad to good). In essence, this metric is a measure of how good the subject is at detecting target sequences.

8.1.2 Determination Mobility Function Assessments:

- **Gait:** Subjects will perform a walking assessment in comfortable walking shoes (subjects own) to measure gait parameters (contact phase, stride length and walking speed over 5-10m for each foot). An athletic movement analysis system (Optojump, Microgate) will be utilized. Differences in contact phase (s), stride length (cm) and walking speed over 5-10m (meters/second) and their within-test variability will be analyzed between baseline (pain state), post-intervention and pain-free follow-up assessments.

  The system will be set up over a 15m length of track with only the 5-10m section measured and analyzed. Subjects will be instructed to walk the 15m length a minimum of 6 times (3 practice and a minimum of 3 test walks) always entering the 15m length with the same foot first. The foot (left or right) entering the 5-10m section first will be recorded by visual assessment of the Opto jump operator for the test walks. Test walks will be repeated until there are 3 walks in which the subject has entered the 5-10m section with the same foot first. Parameters will be averaged based on the 3 test walks in which this occurs.

- **Time to Standing:** Time to standing provides a simple assessment of physical mobility. From a seated position with arms crossed so that the right hand is placed on the left shoulder and the left hand on the right shoulder, participants will stand to a fully erect stature in as short a time as possible. Time to standing will be derived from the force plate data and ground reaction force (GRF) during the movement analyzed using a force plate (AMTI) interfaced with a computer. Subjects will conduct the movement 3-times.

- **Grip Force:** This task is a measure of grip strength. The subject holds the dynamometer in their dominant hand and the arm is swung from above the head to by the side of the body. If the dominant arm or hand is painful then the non-

dominant hand will be used. Subjects will be instructed to assert maximum effort during the squeezing motion and maintain it for about 4 seconds using a metronome. Subjects will conduct the movement 4-times (1 practice effort and 3 test efforts) and there will be a 1-minute recovery period between each effort. The handle of the dynamometer is adjusted if required - the base should rest on first metacarpal (heel of palm), while the handle should rest on middle of four fingers. The results from 3 test efforts will be recorded, with the average grip strength being used for data analysis.

8.2 Primary Efficacy Analysis

Subject level change from pain-free state (Visit 3) in cognition as measured by cognitive function assessment (CANTAB and Axon Sports) in the pain state (Visit 2 Pre-treatment & Visit 2 Post treatment) will be considered as the primary efficacy variable.

Efficacy variable corresponding to the each cognitive function assessment and are as follow,

Reaction Time (RTI) – Subject level change from pain-free state in median five-choice reaction time (RTIFMDRT) will be used as efficacy variable

Rapid Visual information Processing (RVP) – Subject level change from pain-free state in signal detection sensitivity to the target (RVPA) will be used as efficacy variable

Attention Switching Task (AST) – Subject level change from pain-free state in the AST congruency cost (median) (ASTCCMD) will be used as efficacy variable

Spatial Working Memory (SWM) – Subject level change from pain-free state in the SWM Between errors (SWMBE) will be used as efficacy variable

One Touch Stockings of Cambridge (OTS) – Subject level change from pain-free state in the number of assesments problems on which the first box choice made was correct (OTSPSFC) will be used as efficacy variable

Axon Sports Priming Application– Subject level change from pain-free state in error adjusted SRT will be used as efficacy variable.

Detailed descriptions for each assessment are presented in Section 8.1.1 of SAP.

A two-sided paired t-test will be used to analyse the primary efficacy endpoints that are not ‘time-related’ (RVP, SWM and OTS) For the ‘time-related’ variables (RTI, AST and Axon Sports), the non-parametric method using Wilcoxon Sign Rank test will be

employed at visit 2 Pre-treatment and visit 2 Post treatment. All tests will be two-sided with an alpha level of 0.05. The 95% CI and the p-value will also be presented.

The assumption of normality of residuals will be investigated and if violated, an appropriate data transformation or non-parametric method will be used. If there is the presence of an outlier influencing the residuals then this may be examined through a sensitivity analysis.

8.2 Secondary Efficacy Analysis

Gait:

For gait analysis, subject level change from pain-free state (Visit 3) in contact phase (s), stride length (cm) and walking speed assessments at pain state (Visit 2 pre-treatment & Visit 2 Post treatment) will be used as secondary efficacy variables. For each of these parameters the average of the 3 recorded test walks will be used to compute subject level assessment. If a subject is missing any test assessments, then data from the available assessments will be used to compute the average.
A two-sided paired t-test will be used to analyse the secondary efficacy endpoints stride length and Wilcoxon sign rank test will be used to analyse the secondary efficacy endpoints Contact phase (s) and walking speed at Visit 2 Pre-treatment and Visit 2 Post-treatment.
For the parametric analysis, assumption of normality of residuals will be investigated and if violated, an appropriate data transformation or non-parametric method will be used. If there is the presence of an outlier influencing the residuals then this may be examined through a sensitivity analysis.

Time to standing:

For time to standing analysis, subject level change from pain-free state (Visit 3 - Baseline) in time to standing (s) and ground reaction force (GRF) at pain state (Visit 2 pre-treatment & Visit 2 Post treatment) will be used as secondary efficacy variables. For both of these parameters the average of the 3 recorded sit to stand tests will be used to compute subject level assessment. If a subject is missing any test assessments, then data from the available assessments will be used to compute the average.
A two-sided paired t-test will be used to analyse the secondary efficacy endpoints ground reaction force and Wilcoxon sign rank test will be used to analyse the secondary efficacy endpoints time to standing at Visit 2 Pre-treatment and Visit 2 Post-treatment.
For the parametric analysis, assumption of normality of residuals will be investigated and if violated, an appropriate data transformation or non-parametric method will be used. If there is the presence of an outlier influencing the residuals then this may be examined through a sensitivity analysis.

Grip Force:

For the grip force analysis, subject level change from pain-free state (Visit 3 -Baseline) in grip force at pain state (Visit 2 pre-treatment & Visit 2 Post treatment) will be used as secondary efficacy variables. For this parameter the mean of the three recorded grip force tests will be used to compute subject level assessment. If a subject is missing any test assessments, then data from the available assessments will be used to compute the average.
A two-sided paired t-test will be used to analyse the secondary efficacy endpoints grip force at Visit 2 Pre-treatment and Visit 2 Post-treatment.
Assumption of normality of residuals will be investigated and if violated, an appropriate data transformation or non-parametric method will be used. If there is the presence of an outlier influencing the residuals then this may be examined through a sensitivity analysis.

9 Safety Analysis

The safety profile of the study treatments will be assessed with respect to adverse events (AEs). All safety data will be reported for the All Subject.

Non treatment-emergent adverse events (TEAEs) are defined as AEs occurring after providing written informed consent but prior to administration of study medication. Treatment emergent adverse events are defined as AEs that start during the treatment period after the first administration of the study medication.

The causality of TEAEs will be classified as related or unrelated. The intensity of TEAEs will be rated as mild, moderate, or severe.

All AEs will be reviewed by the Clinical Research Scientist or Designee prior to database freeze and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The following summary tables and listings will be presented by treatment group.

- Listing of all AEs (including Non-treatment emergent)
- Listing of Non Treatment-Emergent Adverse Events
- Table of treatment emergent AEs by SOC and Preferred Term
- Treatment emergent treatment related AEs by SOC and Preferred Term

- Listing of serious AEs. (if there are none a null listing will be produced; If there are more than 5 treatment emergent serious AEs (SAEs) a table will be produced instead by SOC and PT)

- Non-serious treatment emergent AEs by SOC and PT (only produced if there are more than 5 SAEs).

- Listing of incidents (if there are none a null listing will be produced)

No inferential analyses will be performed to compare treatments with respect to safety. All subjects screened will be included in the listing of AEs

10 Interim Analysis

No interim analyses are planned for this study.

11 Topline Summary

No topline summary is planned for this study.

12 Changes to Planned Analysis

This study is terminated early due to serious breaches of GCP guidelines observed during a GSKCH internal audit. The minimum requirement of 8 subject per strata was not met because of early termination so following exploratory analyses will not conducted as specified in the protocol.

1) Compare treatment effect for post treatment visit.

2) Correlation analysis between pain intensity with cognitive and mobility assessments for each pain type

13 References

Allen GJ, Hartl TL, Duffany S, Smith SF, VanHeest JL, Anderson JM, Hoffman JR, Kraemer WJ, Maresh CM. Cognitive and motor function after administration of hydrocodone bitartrate plus ibuprofen, ibuprofen alone, or placebo in healthy subjects with exercise-induced muscle damage: a randomized, repeated-dose, placebo-controlled study. *Psychopharmacology (Berl)*, 2003; **166**(3): 228-33.

Arnold LM, Goldenberg DL, Stanford SB, Lalonde JK, Sandhu HS, Keck PE Jr., Welge JA, Bishop F, Stanford KE, Hess EV, and Hudson JI. Gabapentin in the Treatment of Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. *Arthritis & Rheumatism*, 2007; **56**(4): 1336–1344.

Cleeland CS. *The Brief Pain Inventory User Guide*; 2009.

For more references related to this study please refer section 11 of the protocol.

Appendix 1 Study Schedule

Procedure	Visit 1 Screening	Min of 7-days and max. of 28-days	Visit 2 Pain-state assessment		Recovery Period (min of 2-days and max. 30-days)	Visit 3
			Pre-treatment Assessment	Post-treatment assessment (1 hr ± 15 mins post dosing)		Pain-free assessment
Informed Consent	X					
Demographics	X					
GP name and contact details collected	X					
GP Letter response reviewed if received[1]			X			
Brief Pain Inventory – Short Form	X		X	X		X
Pain Recurrence Questionnaire	X					
Pain State Question	X		X			
General Medical History[2]	X		X			
Current / Concomitant medication	X		X	X		X
Height and Weight measurements	X					
Inclusion / Exclusion Criteria	X		X			
Subject Eligibility	X		X			
Physical Examination/ Vital Signs[3]	X		X	X		
For women of child bearing potential: Pregnancy test	X		X			
Urine drug screen and alcohol breath test			X			X
Cognitive testing (Axon Sports & CANTAB Cog Assessment)[4]	X (Practice)[5]		X	X		X
Mobility assessments (Gait, Time to standing, Grip Force)	X (Practice)[5]		X	X		X
Stratification and Randomization to OTC medication			X			
Supervised OTC medication given			X			
Adverse Events	X[6]		X	X		X
Study conclusion						X

Proceed with completion of visit 2 unless GP letter response received advising against participation.

2. General Medical history and GP letter response if received.

3. The physical exam post-treatment assessment will be a brief physical exam

4. The cognitive tests will be conducted in the following order at visit 2 and visit 3: Axon Sports Priming Application, CANTAB battery (RTI, OTS, AST, SWM, and RVP)

5. COGNITIVE TESTING AND MOBILITY ASSESSMENTS AT VISIT 1 ARE PART OF FAMILIARIZATION TASKS

6. AES WILL BE COLLECTED FROM TIME OF SIGNATURE OF CONSENT FORM FOR ALL SUBJECTS WHO ARE ELIGIBLE AT ASSESSMENT FAMILIARIZATION STAGE (AFTER CONFIRMED ELIGIBILITY BUT PRIOR TO FAMILIARIZATION TASKS)

Appendix 2 List of Tables, Figures & Listings

Use following footnotes for treatment labels in all the TLFs wherever corresponding treatments are appearing:

Treatment 1: Panadol Extra Advance (500mg paracetamol +65mg caffeine)

Treatment 2: Panadol Advance (500mg paracetamol)

Placebo: Placebo to match Paracetamol 665mg- MFC51220B

Table No.	Table Title (including population)	Standard	Template
9.1.1	Subject Disposition – All Screened Subjects	X	
9.1.2	Protocol Violations Deemed to Affect Efficacy – ITT Population	X	
9.2.1.1	Demographic Characteristics – Safety Population	X	
9.2.1.2	Demographic Characteristics – mITT		9.2.1.1
9.2.2.1	Baseline Stratification – Safety Population		App 3
9.2.2.2	Baseline Stratification – mITT Population		9.2.2.1
9.3.1.1	Summary Statistics of Pain intensity – mITT Population		App 3
9.3.1.2	Summary Statistics of Pain intensity for each Pain Type – mITT Population		9.3.1.1

9.3.1.3	Summary Statistics of Cognitive function assessment – mITT Population		App 3
9.3.1.4	Summary Statistics of Cognitive function assessment for each Pain Type – mITT Population		
9.3.1.5	Statistical Analysis of Cognitive function from Pain free assessment – mITT Population		App 3
9.3.1.6	Statistical Analysis of Cognitive function from Pain state (V2 Pre-treatment) assessment – mITT Population.		9.3.1.5
9.3.1.7	Summary Statistics of Pain intensity – mITT Population		9.3.1.1
9.3.1.8	Summary Statistics of Pain intensity for each Pain Type – mITT Population		9.3.1.1
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9.3.2.4	Statistical Analysis of Mobility function from Pain state (V2 Pre-treatment) assessment – mITT Population		9.3.1.2
9.4.1	Listing of Adverse Events – Safety Population	X	
9.4.2	Listing of Non Treatment-Emergent Adverse Events – Safety Population	X	
9.4.3	Treatment Emergent Adverse Events by SOC and PT – Safety Population	X	
9.4.4	Treatment Emergent Treatment Related Adverse Events by SOC and PT – Safety Population	X	

9.4.5	Listing of incidents (Note-if there are none a null listing will be produced) ─ Safety Population	X	
9.4.6	Listing of Adverse Events ─ All Subjects	X	
9.4.7**	Listing of Serious Adverse Events ─ Safety Population	X	
9.4.8**	Listing of Serious Adverse Events ─ All Subjects	X	
9.4.9***	Table of non-serious AEs by SOC and PT ─ Safety Population	X	

**If there are none, a null listing will be produced. If there are more than 5 SAEs a table will be produced by SOC and Preferred Term.

*** Only produced if there are > 5 Non SAE's

Figure Number	Figure Title	Template
9.1.1	Axon Sports (error Adjusted Simple reaction time) by Time and Treatment – mITT Population	App 3
9.1.2	Reaction Time by Time and Treatment – mITT Population	9.1.1
9.1.3	Rapid Visual information Processing (RVP) by Time and Treatment – mITT Population	9.1.1
9.1.4	Attention Switching Task (AST) by Time and Treatment – mITT Population	9.1.1
9.1.5	Spatial Working Memory (SWM) by Time and Treatment – mITT Population	9.1.1
9.1.6	One Touch Stockings of Cambridge (OTS) by Time and Treatment – mITT Population	9.1.1
9.1.7	Gait score [contact phase] by Time and Treatment – mITT Population	9.1.1
9.1.8	Gait score [Stride phase] by Time and Treatment – mITT Population	9.1.1
9.1.9	Gait score [Walking Speed] by Time and Treatment – mITT Population	9.1.1

9.1.10	Time to Standing [Time to standing] by Time and Treatment – mITT Population	9.1.1
9.1.11	Time to standing [Ground reaction force] by Time and Treatment – mITT Population	9.1.1
9.1.12	Grip Force [Walking Speed] by Time and Treatment – mITT Population	9.1.1
9.2.1	Scatter plot of pain intensity Vs Axon Sports (error Adjusted Simple reaction time) by Visit– mITT Population	App 3
9.2.2	Scatter plot of pain intensity Vs Reaction Time by Visit – mITT Population	9.2.1
9.2.3	Scatter plot of pain intensity Vs Rapid Visual information Processing by Visit – mITT Population	9.2.1
9.2.4	Scatter plot of pain intensity Vs Attention Switching Task by Visit – mITT Population	9.2.1
9.2.5	Scatter plot of pain intensity Vs Spatial Working Memory by Visit – mITT Population	9.2.1
9.2.6	Scatter plot of pain intensity Vs One Touch Stockings of Cambridge by Visit – mITT Population	9.2.1

Listing No.	**Listing Title**	**Standard**	**Template**
2.1	Randomization Details – All Randomized Subjects	X	
2.2	Previous and Concomitant Medication ─ Safety Population	X	
2.3	Subject Disposition – All Randomized Subjects		App 3
2.4	Data listing Cantab Assessments –All randomized subjects		App 3
2.5	Data listing Mobility Assessments – All randomized subjects		2.4
2.6	Brief pain inventory (BPI) listings- All randomized subjects		App 3

Appendix 3 Templates for Tables, Figures & Listings

Protocol: 204503 Program Run Date: DDMMMYYYY

Table 9.2.2.1
Visit 2 (Pre-treatment) pain state Stratification
Safety Population

Study Population: Safety Population (N=XXX)

	Treatment 1 (N = XXX) N (%) Mean (SD)	Treatment 2 (N = XXX) N (%) Mean (SD)	Placebo (N = XXX) N (%) Mean (SD)	Overall (N=XXX) N (%) Mean (SD)
VISIT 2 (PRE-TREATMENT) PAIN TYPE				
KNEE OR HIP JOINT	XX (XX.X) XX.XX (XX.XXX)	XX (XX.X) XX.XX (XX.XXX)	XX (XX.X) XX.XX (XX.XXX)	XX (XX.X) XX.XX (XX.XXX)
UPPER OR LOWER BACK	XX (XX.X) XX.XX (XX.XXX)	XX (XX.X) XX.XX (XX.XXX)	XX (XX.X) XX.XX (XX.XXX)	XX (XX.X) XX.XX (XX.XXX)
HEADACHE	XX (XX.X) XX.XX (XX.XXX)	XX (XX.X) XX.XX (XX.XXX)	XX (XX.X) XX.XX (XX.XXX)	XX (XX.X) XX.XX (XX.XXX)
PERIOD	XX (XX.X) XX.XX (XX.XXX)	XX (XX.X) XX.XX (XX.XXX)	XX (XX.X) XX.XX (XX.XXX)	XX (XX.X) XX.XX (XX.XXX)

(Page X of Y)

1] Mean and standard deviation were computed on pain intensity based on Visit 2 pre-treatment.

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Protocol: 204503 Program Run Date: DDMMMYYYY

Table 9.3.1.1
Summary Statistics of Pain intensity
Modified Intent to Treat Population

Study Population: Intent to Treat (N=XXX)

	Treatment 1 (N=XX)	Treatment 2 (N=XX)	Placebo (N=XX)	Overall (N=XX)
VISIT 2 (PRE TREATMENT)				
N (NON-MISSING)	XXX	XXX	XXX	XXX
MEAN	X.XX	X.XX	X.XX	X.XX
SD	X.XXX	X.XXX	X.XXX	X.XXX
SE	X.XXX	X.XXX	X.XXX	X.XXX
MEDIAN	X.XX	X.XX	X.XX	X.XX
MINIMUM	X.X	X.X	X.X	X.X
MAXIMUM	X.X	X.X	X.X	X.X
....				
VISIT 2 (POST TREATMENT)				
N (NON-MISSING)	XXX	XXX	XXX	
MEAN	X.XX	X.XX	X.XX	
SD	X.XXX	X.XX	X.XXX	
SE	X.XXX	X.XXX	X.XXX	
MEDIAN	X.XX	X.XX	X.XX	
MINIMUM	X.X	X.XX	X.X	
MAXIMUM	X.X	X.XX	X.X	
VISIT 3 (PAIN FREE STATE) (SAME AS POST TREATMENT)				

(NOTE TO PROGRAMMER: 1. OVERALL IS ONLY POPULATED FOR VISIT 2 (PRE TREATMENT) 2. FOR TABLE 9.3.1.2 AND 9.3.1.8 SIMILAR SUMMARY NEED TO BE PRODCUED FOR EACH PAIN TYPE)

PPD

Protocol: 204503 Program Run Date: DDMMMYYYY

Table 9.3.1.3
Summary Statistics of Cognitive function assessment
Modified Intent to Treat Population

Study Population: Intent to Treat (N=XXX)

	Treatment 1 (N=XX)	Treatment 2 (N=XX)	Placebo (N=XX)	Overall (N=XX)
AXON SPORTS				
VISIT 2 (PRE TREATMENT)				
N (NON-MISSING)	XXX	XXX	XXX	XXX
MEAN	X.XX	X.XX	X.XX	X.XX
SD	X.XXX	X.XXX	X.XXX	X.XXX
SE	X.XXX	X.XXX	X.XXX	X.XXX
MEDIAN	X.XX	X.XX	X.XX	X.XX
MINIMUM	X.X	X.X	X.X	X.X
MAXIMUM	X.X	X.X	X.X	X.X
....				
VISIT 2 (POST TREATMENT)				
N (NON-MISSING)	XXX	XXX	XXX	
MEAN	X.XX	X.XX	X.XX	
SD	X.XXX	X.XX	X.XXX	
SE	X.XXX	X.XXX	X.XXX	
MEDIAN	X.XX	X.XX	X.XX	
MINIMUM	X.X	X.XX	X.X	
MAXIMUM	X.X	X.XX	X.X	
VISIT 3 (PAIN FREE STATE) (SAME AS POST TREATMENT)				
REACTION TIME				
(SAME LAYOUT AS AXON SPORTS)				
....				
ONE TOUCH STOCKINGS				
(SAME LAYOUT AS AXON SPORTS)				
....				
ATTENTION SWITCHING TASK				
(SAME LAYOUT AS AXON SPORTS)				
....				
SPATIAL WORKING MEMORY				
(SAME LAYOUT AS AXON SPORTS)				
....				
RAPID VISUAL INFORMATION PROCESSING				
(SAME LAYOUT AS AXON SPORTS)				

....

(NOTE TO PROGRAMMER: 1. OVERALL IS ONLY POPULATED FOR VISIT 2 (PRE TREATMENT) 2. FOR TABLE 9.3.1.4, 9.3.1.10, 9.3.2.2 AND 9.3.2.6 SIMILAR TABLES NEED TO BE PRODCUED FOR EACH PAIN TYPE)

PPD

Protocol: 204403 Program Run Date: DDMMMYYYY

Table 9.3.1.5

Statistical Analysis of Cognitive function from Pain free assessment

Modified Intent to Treat Population

Study Population: Intent to Treat (N=XXX)

		Treatment 1 (N=XX) Change from Baseline	Treatment 2 (N=XX) Change from Baseline	Placebo (N=XX) Change from Baseline
AXON SPORT				
VISIT 2 (PRE TREATMENT)	N	XX	XX	XX
	MISSING	XX	XX	XX
	MEAN	X.XX	X.XX	X.XX
	SD	X.XXX	X.XXX	X.XXX
	SE	X.XXX	X.XXX	X.XXX
	MEDIAN	X.XX	X.XX	X.XX
	MINIMUM	XX	XX	XX
	MAXIMUM	XX	XX	XX
	Test statistics [1]	XX.XX	XX.XX	XX.XX
	95% CIs [1]	(X.XX,X.XX)	(X.XX,X.XX)	(X.XX, X.XX)
	P-VALUE [1]	0.XXXX	0.XXXX	0.XXXX
VISIT 2(POST TREATMENT)				
(SAME AS PRE-TREATMENT)				
.....				
REACTION TIME (SAME LAYOUT AS AXON SPORTS)				
....				
ONE TOUCH STOCKINGS				

(SAME LAYOUT AS AXON
SPORTS)
....
ATTENTION SWITCHING TASK
(SAME LAYOUT AS AXON
SPORTS)
....
SPATIAL WORKING MEMORY
(SAME LAYOUT AS AXON
SPORTS)
....

RAPID VISUAL INFORMATION
PROCESSING
(SAME LAYOUT AS AXON
SPORTS)
....

[1] From two sided paired t test for changes from baseline (Visit 3 Pain Free State).

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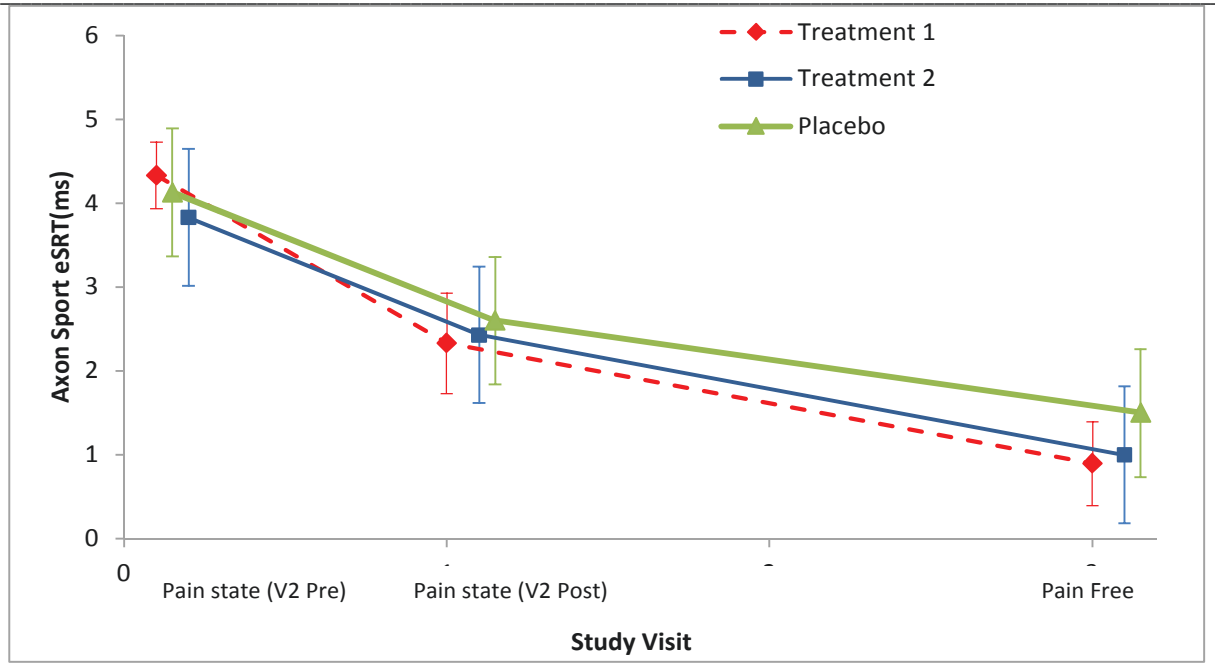
Programming note:

[1] For time related cognitive (AST, RTI & Axon Sports) and mobility assessments (Gait [contact phase and walking Speed], Time to standing) footnote 1 will be changed to:
From two sided signed rank test for changes from baseline (Visit 3 Pain Free State).
[2] Table 9.3.2.3– include statistical analysis of mobility parameter Gait [Stride length, Contact phase and walking speed], Time to Standing [Time to standing and Ground reaction force] and Grip Force for mITT population.
[3] For **Table 9.3.1.6, 9.3.1.10, 9.3.2.4:**
a) Please use the same format of the able. These tables will have output for only Visit 2(Post treatment).
b) Footnote non time related assessments will changed to
[1] From two sided paired t test for changes from baseline (Visit 2 Pre-treatment Pain state)
For time related assessments it will be
[1] From two sided signed rank test for changes from baseline (Visit 2 Pre-treatment Pain state)

Protocol: 204503 Program Run Date: DDMMMYYYY

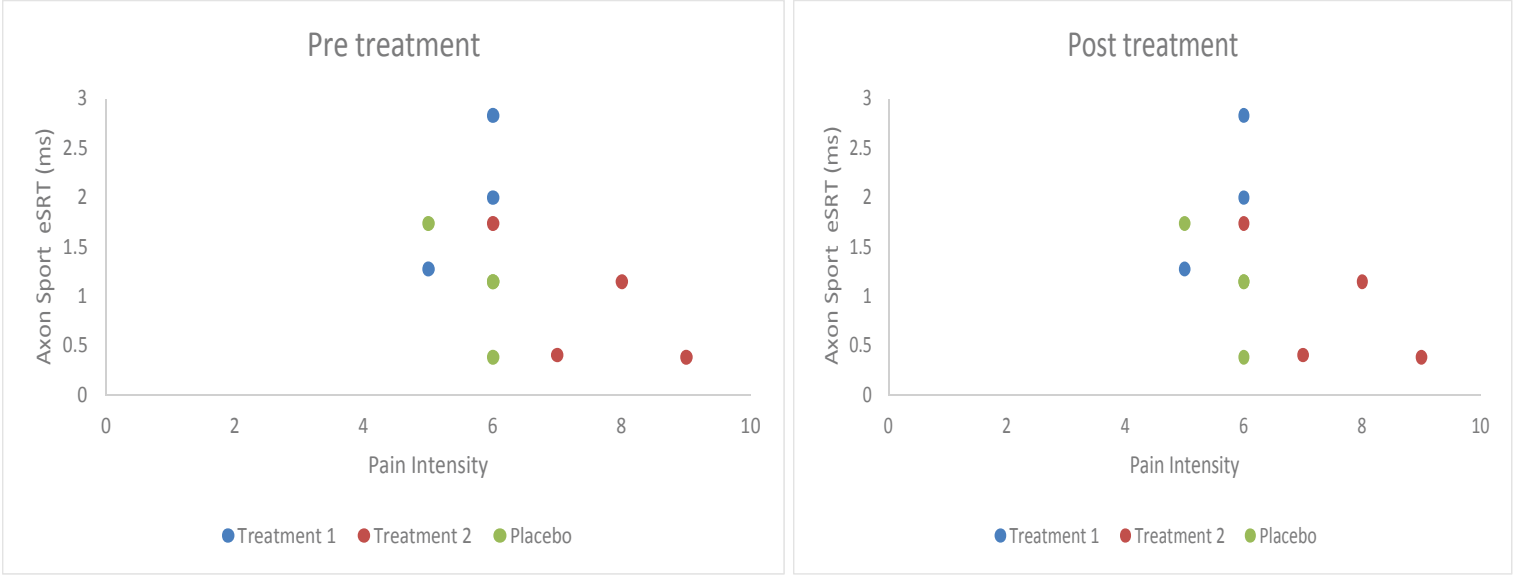
Figure 9.1.1
Axon Sports (error Adjusted Simple reaction time) by Time and Treatment (Raw Mean ± SE)
Modified Intent to Treat Population



Values are Raw mean ± SE
V2 Pre - Visit 2 Pre Treatment V2 Post - Visit 2 Pre Treatment V3 - Visit 3
(Note to programmer: (1) Use different symbols and line-styles for three treatments. (2) (1) Add 'Pain state (V2 Pre)', 'Pain state (V2 Post)' and 'Pain Free (V3)' to X-axis.

Protocol: 204503 Program Run Date: DDMMMYYYY

Figure 9.2.1
Scatter plot of pain intensity Vs Axon Sports (error Adjusted Simple reaction time) by Time
Modified Intent to Treat Population



(Note to programmer: (1) Create similar scatter plot for remaining cognitive assessments. (2) Use different symbols and colour for three treatments.

Protocol: 204503 Program Run Date: DDMMMYYYY

Data Listing 2.3
Subject Disposition
All Randomized Subjects

Center/ Subject	Age/ Sex/ Race	Screening date	Randomization Date	Treatment	Start/End of treatment	Completion/ discontinuation date	Treatment completer? #	Subject completed? $	If applicable, reason for discontinuation

Sex: F= Female; M= Male.

Race: AMI=American Indian or Alaska Native; ASN= Asian; BLK= Black or African American; HAW= Native Hawaiian or other Pacific Islander; MUR= Multi-racial; OTH= Other; WHT= White.

A subject is considered 'treatment completer' after completion of the Visit 2 pre-treatment dosing.

$ A subject is considered completed after completion of the Visit 3 assessments. A subject who withdraws study treatment prematurely and who completes the end of study assessments is considered completed but not 'treatment completer'.

Protocol: 204503 Program Run Date: DDMMMYYYY

Data Listing 2.4
Cantab Assessments
All Randomized Subjects

Endpoint	Assessment Variable	Subject ID	Visit	Treatment	Actual Value

Actual values are based on subject level assessment.

Programming note: 1) For Cantab Endpoint – Assesment variable are median five-choice reaction time (RTIFMDRT), Signal detection sensitivity to the target (RVPA), AST congruency cost (median) (ASTCCMD), SWM Between errors (SWMBE), The number of assessments problems on which the first box choice made was correct (OTSPSFC), Error adjusted SRT for RTI, RVP, AST, SWM, OTS and Axon sports respectively.

2) Please create a same data listing (2.5) For Mobility Endpoint Gait [Stride length, Contact phase and walking speed], Time to Standing [Time to standing and Ground reaction force] and Grip force

Protocol: 204503 Program Run Date: DDMMMYYYY

Data Listing 2.6
Brief pain inventory (BPI)
All Randomized Subjects

Subject ID	Treatment	Visit 1 (Screening)	Visit 2 (Pre-Treatment)	Visit 2 (Pre-Treatment)	Visit 3 (Pain Free)

Actual values are based on subject level assessment.

SIGNATURE PAGE

SAP 204503

Date	Signed By
29-Mar-2017 10:43:01	PPD
Justification	clinical research approval

Date	Signed By
30-Mar-2017 08:58:53	PPD
Justification	Biostatistics Approval

Date	Signed By
Justification	

Date	Signed By
Justification	

Date	Signed By
Justification	

Date	Signed By
Justification	