Clinical Protocol

204503

CONFIDENTIAL

SUMMARY INFORMATION

Title:	Assessment of cognitive function and mobility in individuals with pain
Protocol Number:	204503
Sponsor:	GlaxoSmithKline Consumer Healthcare (UK) Trading Limited St. George's Avenue, Weybridge, Surrey, KT13 0DE, UK Tel: PPD
Product Name:	Paracetamol and Caffeine combination tablet Paracetamol tablet
Development Phase:	IV

Expert Advice Outside of Normal Working Hours:	Tel: PPD

Key Protocol Authors:	
PRIMARY CONTACT **Clinical Study Manager:**	PPD, PHD GSKCH, ST. GEORGE'S AVENUE WEYBRIDGE, SURREY KT13 0DE - UK Tel: PPD Fax:
Biostatistician:	PPD
Clinical Research Lead:	PPD
New Product Research Lead:	PPD
Other Protocol Authors:	
Clinical Supplies:	PPD
Data Manager:	PPD
Medically Qualified Person:	Dr PPD

Chief Investigator	Dr. PPD **DANI HRISTOVA**
Principal Investigator:	Dr. **DANI HRISTOVA**
Study Coordinator	PPD, PhD
Study Site Name & Address:	GSK Human Performance Lab Unit 2 Brentside Executive Park Great West Road Brentford Middlesex United Kingdom TW8 9DA
Study Site Telephone Number:	PPD

EudraCT Number:	2015-002330-42

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol and any amendments and according to the current ICH GCP guidelines.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.
- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

Investigator Name:	Dr PPD **Dani Hristova**
Investigator Qualifications:	**MBBS**~~, PhD, MRCP~~
Investigator Signature:	
Date of Signature/ Agreement:	DD/MMM/YYYY

Table of Content

PROCESS FOR AMENDING THE PROTOCOL

Protocol modifications to ongoing studies which could potentially adversely affect the safety of subjects or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated, or subject selection criteria are considered major/substantial amendments and must be made only after appropriate consultation between an appropriate representative of GSKCH and the investigator.

Details of amendments to the protocols should be recorded on the following page. Protocol modifications must be prepared by a representative of GSKCH. All changes must be justified in the Reason for Amendment section of the following Protocol Amendment Page. Approval of amendments will be made by the original protocol signatories or their appropriate designees.

All major/substantial protocol modifications must be reviewed and approved by the appropriate IEC in accordance with local requirements, before the revised edition can be implemented.

All non-substantial/ minor/ administrative amendments should be submitted to the IEC as per country specific requirements. In some countries pre-approval of a minor amendment is not required and will just be held on file by the sponsor and investigator.

PROTOCOL AMENDMENT PAGE

Details of all amendments should be recorded in the table below. Affected sections should be listed in the table; the actual amendment/ change should be made in the relevant section of the main protocol.
To highlight the change, the following features will be used:
To **add** text: Use of **CAPITAL LETTERS, BOLD AND UNDERLINE**
To **delete** text: Use of Strikethrough e.g. ~~strikethrough~~

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.:1	Non-Substantial/Minor ☒	The primary purpose of this amendment is to update the SAE reporting information. Other clarification and consistency changes have also been made.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☒ Yes ☐ No	• Summary Information – Key Protocol Authors • Schedule of Events • Protocol Synopsis • Section 6.1.6 Pain State Question • Section 6.2.5 Physical Exam / Vital Signs • Section 7.4 Reporting Adverse Events	Signature:
Protocol Version No.:5.0	Substantial/ Major ☐				Date:

				and Serious Adverse Events • Section 12.3 Appendix 3 • Section 12.4 Appendix 4 • Section 12.5 • Appendix 5	
Amendment No.:2 **Protocol Version No.:6.0**	Non-Substantial/Minor ☐ Substantial/ Major ☒	The purpose of this amendment is to update a change in Chief and Principal Investigator. Two other updates were made to ensure consistency between protocol sections with regard to time frame of collection of adverse events and to ensure consistency between protocol sections with respect to time frame of restriction of prohibited medications.	Informed Consent ☒ Yes ☐ No Safety Statement ☐ Yes ☒ No CRF ☒ Yes ☐ No	• Summary Information – Key Protocol Authors • Principal Investigator Protocol Agreement Page • Schedule of Events • Protocol Synopsis • Section 3.1 Study Design • Section 3.2 Subject Restrictions • Section 4.2 Exclusion Criteria	Signature: Date:

SCHEDULE OF EVENTS

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

1. 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, 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)

PROTOCOL SYNOPSIS FOR STUDY 204503

Brief Summary

Pain is a multidimensional, subjective experience, which can have an effect both physically and psychologically. Individuals with chronic pain often report deficits in their mobility and cognitive function is also thought to be affected. Whilst a vast amount of research has been conducted on individuals with chronic or disease specific pain there is very little known about the cognitive and mobility deficit experienced by individuals with everyday pain (pain treatable with Over-the-Counter (OTC) medicine).

The primary focus of this exploratory study will be to investigate the effects of everyday pain on cognition and mobility in otherwise healthy individuals. This study will also evaluate the relationship between specific types and intensity of everyday pain with cognitive function and mobility. Finally, the potential effect of an intervention with paracetamol or paracetamol with caffeine on cognitive function and mobility will be studied on an exploratory basis.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate within-subject cognitive changes in individuals with everyday pain compared to	• Subject level change from pain-free state in cognition as measured by cognitive function assessment (CANTAB and Axon

pain-free performance.	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 change of muscle score to post-treatment assessment period.

Study Design

Overall Design
This parallel, assessor blind, placebo-controlled, stratified, randomized 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 a Clinical Research Organisation, screened for eligibility and assessed 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 (CANTAB and Priming Application)
   - Mobility assessments practice session (Gait, Time to standing, Grip Force
   - Inclusion/Exclusion criteria
4. **ADVERSE EVENTS**
   - **TO BE COLLECTED FROM THE TIME OF SIGNATURE OF THE CONSENT FORM FOR ALL SUBJECTS WHO ARE ELIGIBLE AT ASSESSMENT FAMILIARIZATION STAGE (AFTER CONFIRMED SUBJECT ELIGIBILITY BUT PRIOR TO FAMILIARIZATION TASKS).**

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 (subjects wear eye mask)
- **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 zero in response to Question 6 on Brief Pain Inventory – Short Form. 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

Type and Planned Number of Subjects
A sufficient number of subjects will be screened to randomize approximately 65 subjects to ensure approximately 60 evaluable subjects complete the entire study. This will ensure approximately 20 evaluable subjects per treatment arm.

Diagnosis and Main Criteria for Inclusion
Subjects with everyday pain (treatable with an OTC medicine) will be required for entry to this study. Inclusion criteria for this study includes: consent from the volunteer; aged at least 18 years and in good general health; understands the study and is willing to participate; has a pain rating of ≥ 5 on question 6 of the brief pain inventory - short form (at Visit 2 only).

Product Information

	Test Product 1	Test Product 2	Reference Product 1
Product Name	Panadol® Extra Advance (500mg paracetamol +65mg caffeine) tablets	Panadol® Advance (500mg paracetamol) tablets	Placebo to match Paracetamol 665mg Sustained Release Tablets Panadol Extend Placebo Tablets
Product Formulation Code (MFC)	UK Marketed Product	UK Marketed Product	PPD Placebo Extend Tablet
Dose	2 tablets taken once	2 tablets taken once	2 tablets taken once
Route of Administration	Oral	Oral	Oral
Dosing Instructions	Take medication with 200 mL of water. Eye mask worn by subject.	Take medication with 200 mL of water. Eye mask worn by subject.	Take medication with 200 mL of water. Eye mask worn by subject.

Criteria for Evaluation

- Statistically significant deficit in 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) observed between an individual in pain vs. their pain-free performance.

- Statistically significant deficit in mobility (as measured by individual scores from gait, time to standing and grip force assessments) observed between an individual in pain vs. their pain-free performance.

Statistical Methods

Efficacy

Primary:

- Change from pain-free state in cognition as measured by cognitive function assessment (CANTAB and Axon Sports) in the pain state (pre-treated).

Secondary:

- Change from pain-free state in mobility as measured by gait, time to standing and grip force score in the pain state (pre-treated).

Exploratory:

- Correlate pain type and intensity to cognitive and mobility assessments.

- Effect of intervention on change from pain-state assessment (pretreated) 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 (pretreated) in mobility as measured by gait score, time to standing score and change of muscle function score, to post-treatment assessment period.

A two-sided paired t-test will be used to analyze the primary and secondary efficacy endpoints for all subjects with a significance level α=0.05. For the exploratory efficacy analysis with between treatment comparisons, the mixed effect model with treatment group and pain type as the fixed effect and the baseline value as a covariate will be employed on the change-from-baseline type of variables at Visit 2, 1 hour (± 15 min) post-treatment and at visit 3 for variables other than 'time' related type. For the 'time' related variables (e.g., Reaction Time (RTI), time to standing, etc.) the non-parametric method using Van Elteren's test with stratification factor pain type will be employed at 1 hour post treatment. For the exploratory analysis a Pearson correlation

analysis will be employed. All tests will be two-sided with an alpha level of 0.05. The 95% CI and the p-value will also be presented.

Safety
AEs will be listed and reviewed. Only treatment emergent AEs (i.e., those occurring after first use of the study treatment) will be tabulated. AEs occurring prior to randomization will be included in the AE listing. AE tables will be presented using the safety population.

1. INTRODUCTION

Pain is a multidimensional, subjective experience, which can have an effect both physically and psychologically. While there is very little known about the cognitive and mobility deficit experienced by individuals with everyday pain (pain treatable with OTC medicine) – the purpose of this study - there is, however, a vast amount of research on individuals with chronic or disease specific pain. Therefore, this introduction will review and reference the previous work on individuals with chronic pain as a background to the study proposed.

Individuals with chronic pain often report deficits in their mobility and movement. For example, patients with chronic neck pain have significantly decreased range of movement in all anatomical values during repeated cervical spine movements compared to age-matched, healthy control subjects (Vogt et al., 2007). Furthermore, individuals with hip or knee pain, due to osteoarthritis, have reported limitations in physical activities and this has been shown to be associated with the level of pain and range of motion of hip flexion (van Dijk et al., 2009). This study also showed that the level of pain was associated with performance-based limitations (timed walking test) and range of motion.

Mobility and movement are not the only deficits experienced by individuals with chronic pain, but cognition is also thought to be affected. Clinical data supporting this includes observed deficit in attention, executive and general cognitive functioning in individuals suffering chronic pain (reviewed in Moriaty and Finn, 2011). Furthermore, recent research has investigated the effect of pain on cognitive function and showed that generalized and neuropathic pain, in comparison to localized pain, has a greater effect on cognition (Landrø et al., 2013).

The effect of pain on cognitive attention has been well studied in chronic pain patients and it is hypothesized that pain competes for cognitive resources against daily tasks which act as attention demanding stimuli (Eccelston, 1994). In one study,

those with chronic pain had significantly higher error rates in an attention capacity probe task compared to healthy individuals (Veldhuijzen et al., 2006). The authors of this study concluded that allocation of attention resources was impaired in chronic pain sufferers rather than their capacity. Chronic pain patients, compared to matched controls also seem to have slower reaction times in a variety of cognitive tests (reviewed in Moriaty and Finn, 2011).

Memory studies in chronic pain patients have predominantly tested explicit/working memory. For example, fibromyalgia (FM) patients had a significant cognitive deficit compared to age matched healthy controls and control subjects who were 20 years older than each of the FM patient. The cognitive performance of the FM patients was similar to the older control group, which in turn performed poorly compared to the younger control group. In particular, memory and vocabulary deficits were most prevalent (Park et al, 2001). A recent systematic review further supports this evidence by suggesting that people with chronic pain perform worse on working memory tests in comparison to healthy control subjects (Berryman et al., 2013).

Chronic pain has also been shown to affect executive function, which includes higher order tasks such as planning, organization and control of conflicting thoughts. Chronic pain patients perform poorly on executive function tests, including interference or attention switching tasks, for example, one study showed that those experiencing intense pain had performance decrements in an attention demanding numerical interference task, but only at the most complex level (Eccelston, 1994). This study is interesting as it sheds light on the correlation between intensity of pain and cognitive deficit which is infrequently explored.

Although previous research has advanced our knowledge in the interaction between individuals with chronic pain, cognition and mobility, very little is known about the effects of everyday pain on cognition and mobility. Therefore further work is needed to fully understand the effects of everyday pain (i.e., individuals with pain suitable for OTC medication) on cognition and mobility. Furthermore, a better understanding of the effects of analgesic medications on cognition is required in individuals with everyday pain. While some have investigated the effects of Ibuprofen (Allen et al., 2003), little is known about the effects of paracetamol on cognition in individuals with everyday pain. Caffeine has been demonstrated to increase the absorption and efficacy in formulation with paracetamol (Renner et al., 2007). Therefore the effects of paracetamol with and without caffeine will be investigated.

This study will investigate the effects of everyday pain on cognition and mobility in otherwise healthy individuals. The effects of one dose of paracetamol with and

without caffeine on cognitive function and mobility will also be investigated. This study will also explore the relationship between type and intensity of everyday pain with cognitive function and mobility.

2. OBJECTIVES AND ENDPOINTS

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 change of muscle score to post-treatment assessment period.

3. STUDY PLAN

3.1. 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 **4. ADVERSE EVENTS** - **TO BE COLLECTED FROM THE TIME OF SIGNATURE OF THE CONSENT FORM FOR ALL SUBJECTS WHO ARE ELIGIBLE AT ASSESSMENT FAMILIARIZATION STAGE**

(AFTER CONFIRMED SUBJECT ELIGIBILITY BUT PRIOR TO FAMILIARIZATION TASKS).

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

3.2. Subject Restrictions

Lifestyle/ Dietary
Assessment visits (visits 2 and 3): • Subjects will be requested to refrain from excessive alcohol consumption for 24 hours prior to assessment visits 2 and 3. Excessive alcohol consumption is an amount that would result in a positive alcohol breath test at the start of each assessment visit. If, the subject has a positive alcohol breath test at visit 2 or 3 then the visit may be rescheduled. • Subjects should abstain from any caffeine products for 4 hours prior to the visit on assessment days. • While on site subjects are asked to adhere to the following restrictions; no smoking, food, fluids or medication other than study medication and water provided. • Subjects should stay at the site until all assessments are completed on assessment days and during their time on site will be required not to work during any breaks.
Medications and Treatments
No analgesics, other pain/inflammation therapy, **OR VITAMIN SUPPLEMENTS** are allowed to be taken 48 hours prior to the day of the pain-state and pain-free state assessment days (visit 2 and 3). No other medication or product which could

counteract paracetamol and/or caffeine is permitted on assessment days. No anti-depressants may be taken for the study duration.

3.3. Type and Planned Number of Subjects

A sufficient number of subjects will be screened to randomize approximately 65 subjects to ensure approximately 60 evaluable subjects complete the entire study. This will ensure approximately 20 evaluable subjects per treatment arm.

Subjects will be recruited from GSK employees or a local Clinical Research Organization via advertisement. Subjects may also be recruited from a panel of pain sufferers held by the HPL.

3.4. Study Design and Dose Justification

The Brief Pain Inventory (BPI) (Cleeland CS., 2009; Appendix 2) is a common measurement tool for assessing clinical pain. The BPI allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. It has been validated in studies in cancer patients and fibromyalgia sufferers (Klepsted et al, 2002; Arnold LM et al, 2007) and these studies have shown subjects to indicate a baseline pain level of 4-6 to question 4. A score of ≥5 to Q6 has been chosen for the current study of subjects with everyday pain as they will be subjects with everyday pain as they will be primarily be recruited from the general population experiencing a transient pain episode; cognitive impairment has been correlated with pain intensity.

A recovery period of up to 30 days ensures participants are pain free (0 in response to Question 6 on Brief Pain Inventory – Short Form) upon their return for pain-free measurement. This is a simpler design than a prospective study and prevents habituation effects in cognitive and mobility assessments.

Two independent batteries of cognitive tests will be used to assess cognition. CANTAB and Axon Sports are validated and widely used tests of cognition. Three mobility measures (Gait, Time to Standing, Grip Force [Roberts HC et al, 2011]) have been selected as a range of movements that may be affected by pain.

Subjects will take two tablets of their allocated treatment once. This dosage is based on the recommended dosing as per the product label.

In line with ICH guidelines, for a study to be classed as truly double blind, not only does the subject and the assessor (and any appropriate member of staff who may be involved in treatment dispensing, analysis of data etc.) need to be blinded as to the

treatment the subject receives, but the treatments under investigation must be identical in every way (e.g. colour, flavour, appearance, packaging). The products tested in this study will differ in visual appearance (colours/packaging). This study will therefore be described as assessor blind. Every effort will be made to ensure that subjects (wearing eye masks) and other staff members remain blind to the treatment received by the subject. Dispensing and supervised product usage will be performed in a separate area. Subjects will be instructed not to discuss their treatment with team members supervising the assessments.

4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Summary of Product Characteristics for Panadol® Extra Advance and Panadol® Advance, and the Investigator Brochure for the Placebo.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. CONSENT
Demonstrates understanding of the study procedures, restrictions and willingness to participate as evidenced by voluntary written informed consent and has received a signed and dated copy of the informed consent form.

2. AGE
Aged between 18-65 years.

3. GENDER
Subject is male or female. If female of childbearing potential, the subject is practicing a reliable method of contraception in the opinion of the investigator. For the purposes of this study, reliable contraception is defined as abstinence, oral contraceptive, either combined or progestogen alone OR injectable progestogen OR implants of levonorgestrel OR estrogenic vaginal ring OR percutaneous contraceptive patches OR intrauterine device or intrauterine system OR double barrier method (condom or occlusive cap [diaphragm or cervical vault caps] plus spermicidal agent [foam, gel, film, cream, suppository]) OR male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject

4. COMPLIANCE
Understands and is willing, able and likely to comply with all study procedures and restrictions.

5. COMPLETION OF FAMILIARISATION TASKS
Adequately completes cognition and mobility familiarisation tasks in the opinion of the investigator.

6. GENERAL HEALTH
Good general and mental health with, in the opinion of the investigator or medically qualified designee: A. No clinically significant and relevant abnormalities in medical history or upon physical examination. B. Absence of any condition that might impact on the subject's safety or wellbeing or affect the individual's ability to understand and follow study procedures and requirements. C. BMI $\geq$18.5 and $\leq$30 kg/m^2

7. PAIN TYPE AND INTENSITY
A. VISIT 1 ONLY – Has experienced a minimum of two recurrent, acute pain episodes within the past 3 months OR is currently suffering from a flare up episode of recurrent, acute pain (see appendix 3). B. VISIT 2 ONLY – A score $\geq$5 to question 6 (rated on scale 0-10) on the Brief Pain Inventory – Short Form. C. Subjects presenting with only one of the following pain types: Joint (Knee, Hip); Back; Headache; Period; (see appendix 4).

4.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. PREGNANCY
A. Women who are pregnant (Visit 1) B. Women of child bearing potential who test positive on a urine pregnancy test (Visit 1 or Visit 2) 1. Females of non-child bearing potential will not be required to complete urinary pregnancy test. Post-menopausal females not requiring a pregnancy test will be defined as: • Age ≥ 50 years with spontaneous cessation of menses for 12 or more months • Age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic

2. BREAST-FEEDING
Women who are currently breast-feeding

3. GENERAL HEALTH
In the opinion of the medical designee, subject suffers from medical condition(s) that may be aggravated due to testing procedures or may impact the interpretation or integrity of data. Conditions related to renal, hepatic, respiratory, blood, immune systems or heart dysfunction will be considered.

4. COLOUR BLIND
Subject is colour blind.

5. CONCURRENT MEDICATION/ MEDICAL HISTORY
A. Current (within 14 days of the start of the study) or regular use of any prescription, over-the-counter (OTC), herbal medicine unless the medication has been approved by the study physician. **FOR STUDY VISITS 2 and 3,** ~~OTC~~ analgesics for pain relief and vitamin supplements are permitted only until 48 hours prior to **START OF** study visits. B. Current or in the 30 days prior to dosing use of any drug, food, herbal product, or dietary supplement known to induce or inhibit hepatic drug metabolism (e.g. barbiturates, theophylline, cimetidine, or erythromycin). C. Use of analgesics and anti-inflammatory drugs 48 hours prior to dosing at Visit 2 **AND VISIT 3**. D. Known to be taking any other medication which could counteract with paracetamol and/or caffeine.

E. Current or past use of anti-depressants or psychoactive drugs within the previous 2-years.

6. ALLERGY/ INTOLERANCE

A. Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.

7. SUBSTANCE ABUSE

A. Positive breath alcohol test at Visit 2.
B. Positive urine drugs of abuse test at Visit 2.

8. CLINICAL STUDY/ EXPERMENTAL PRODUCT

A. Participation in another clinical study (including cosmetic studies) or receipt of an investigational product within 7 days of the screening visit.
B. Previous participation and randomization in this study.

9. LIFESTYLE

A. Subject has excessive frequent caffeine intake equivalent to 6 cups of brewed coffee or 12 cups of tea per day.
B. Unwilling to abstain from any caffeine products from 4 hours prior to the visit on assessment days (Visit 2 and 3).
C. Current Smoker (or regular nicotine consumption): Subject smokes more than 3 cigarettes per day (or equivalent for e-cigarettes, chewing tobacco or pipes). Investigator to ensure there is no impact of withdrawal effect from those with nicotine dependence.
D. Current Alcohol Consumer: Subject consumes greater than 21 units of alcohol per week (male) and 14 units per week (female) (e.g. Spirit 25ml = 1 unit / AlcoPop 275ml = 1.5 unit / Bottle of beer 330 ml = 1.7 unit / Glass of wine 175ml = 2.1 unit / Pint of beer 568 ml = 3 unit).

10. PERSONNEL

Members of the study site staff or members of their immediate family.

11. INVESTIGATOR'S OPINION

Any subject who in the opinion of the investigator should not take part in this study.

4.3. Screening/ Baseline Failures

Screen failures are defined as subjects who consent to participate in the study but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events. Re-screening and re-evaluation of subjects will be allowed in this study per the following rules:

1. It is allowable for subjects to be re-scheduled for Visit 2 if they do not meet the inclusion criteria related to pain intensity (Score of ≥5 on BPI question 6), as long as the re-scheduled date falls within the period of 7-28 days post Visit 1.
2. If the subject fails alcohol breath test at Visit 2 or 3, re-scheduling is permitted as long as the re-scheduled date falls within the period of 7-28 days post-Visit 1 [for Visit 2] or 2-30 days post-Visit 2 [for Visit 3].
3. If the subject fulfills one of the aforementioned criteria and a subsequent date cannot be scheduled within allowable time frames detailed, subjects may be re-screened, effectively rendering them as a 'new subject'.
4. Rescheduling and re-screening rules may be applied to other inclusion/exclusion criteria where the timing of the assessment affects evaluation of the subject. It may not be applied to criteria that in the opinion of the medical designee will impact the integrity and interpretation of study data or subject safety. All such instances not explicitly detailed in the protocol must be checked with the sponsor.

4.4 Women of Childbearing Potential Definition

Female subjects of non-childbearing potential must meet at least one of the following criteria:

1. Have undergone a documented hysterectomy and/or bilateral oophorectomy.
2. Have medically confirmed ovarian failure.

All other female subjects (including females with tubal ligations and females that do NOT have a documented hysterectomy, bilateral oophorectomy and/or ovarian failure) will be considered to be of childbearing potential.

4.5. Withdrawal/ Stopping Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons.

If the reason for removal of a subject from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded on the electronic case report form (CRF). If a subject is withdrawn from the study because of a product limiting AE, thorough efforts should be clearly made to document the outcome. Any AEs ongoing at the final visit will be followed up until resolved, the condition stabilizes, is otherwise explained, or the subject is lost to follow-up.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, at least 2 telephone calls). The contact attempt should be documented in the subject's record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

4.6. Subject Replacement

Subjects who withdraw from the study post-randomization will not be replaced.

4.7. Subject and Study Completion

A completed subject is one who has completed all study visits (Visits 1, 2 and 3). There will be no follow-up post Visit-3 with the exception of subjects with ongoing AEs which will be followed until resolved, the condition stabilizes, is otherwise explained, or the subject is lost to follow-up.

The end of the study is defined as the date of the last subject's last visit.

5. PRODUCT INFORMATION

5.1. Study Product

The following study products will be supplied by the Clinical Supplies Department, GSKCH:

Product Name	Panadol® Extra Advance (500mg paracetamol +65mg caffeine) tablets	Panadol® Advance (500mg paracetamol) tablets	Placebo to match Paracetamol 665mg Sustained Release Tablets Panadol Extend Placebo Tablets
Product Formulation Code (MFC)	UK Marketed Product	UK Marketed Product	PPD Placebo Extend Tablet
Dose	2 tablets taken once	2 tablets taken once	2 tablets taken once
Route of Administration	Oral	Oral	Oral
Dosing Instructions	Take medication with 200 mL of water. Eye mask worn by subject.	Take medication with 200 mL of water. Eye mask worn by subject.	Take medication with 200 mL of water. Eye mask worn by subject.

Other items to be supplied by the Clinical Supplies Department, GSKCH and the GSK HPL:

Name of Item	**Purpose**
Pregnancy tests	Pregnancy
Urine drug test	Drug abuse
Breathalyser	Alcohol abuse
Dosing Cups	Dosing
Eye Masks	Dosing (GSK HPL)

5.2. Dose Schedule

At Visit 2 each subject will receive 2 tablets of the product that they have been randomized to within each stratum

5.3. Dose Modification

No dose modification is permitted in this study.

5.4. Product Compliance

A record of the administration of study products will be kept using the Dosing Accountability Log and the CRF - Any comments on the performance of this procedure should be recorded on the CRF. Any violation of compliance will require evaluation by the investigator and sponsor to determine if the subject will continue in the study.

5.5. Precautions

No special precautions are necessary provided the study is carried out in accordance with this protocol.

5.6. Overdose

An overdose is a deliberate or inadvertent administration of a product at a dose higher than specified in the protocol.

Overdose is not likely to occur in this study. Limited quantities of the product will be supplied, and closely monitored by the site for each subject.

Overdose per se is not an AE. However, any clinical sequelae of an overdose should be reported as an AE (and serious adverse event (SAE), if appropriate). For reporting, follow the AE and SAE reporting instructions.

5.7. Rescue Therapy

No rescue therapy is required in this study.

5.8. Product Assignment

Subjects will be assigned to study product in accordance with the randomization schedule generated by the Biostatistics Department, GSKCH, prior to the start of the study, using validated internal software.

5.8.1 Randomization

A unique screening number will identify each subject screened for study participation. Screening numbers will be assigned in ascending numerical order as each subject signs their consent form. Subjects who meet all inclusion and exclusion criteria will be stratified and randomized according to the randomization schedule. Within each stratum, randomization numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible and completes the pre-treatment cognitive function and mobility assessments.

Subject will be stratified according to the Pain Type (I.e. Joint, Back, Headache and Period). Recruitment into each of the 4 stratum will be controlled as follows:

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

Study site team will ensure that there are minimum 8 subjects in each stratum (≥8) using the recruitment tracking log (see appendix 5).

The randomization schedule will be provided by the Biostatistics Department, GSKCH.

5.8.2 Blinding

The study statistician and other employees of the Sponsor who may influence study outcomes are blinded to the product allocation of subjects.

The assessor will be blinded to the treatment received. The assessor is not permitted in the room where and when the product is dispensed. In order to maintain the blind as much as possible the dispensing staff will not be involved in any cognitive/mobility assessments during the study.

Subjects will wear eye masks at dosing to ensure those familiar with the appearance of Panadol® Advance and Panadol® Extra Advance tablets are not unblinded.

5.8.3 Code Breaks

The blind must only be broken in an emergency where it is essential to know which product a subject received in order to give the appropriate medical care. Wherever possible the Investigator (or designee) must contact the Sponsor prior to breaking the blind. The investigator must document the reason for breaking the code and sign and date the appropriate document.

The study site will receive two versions of the randomization schedule, each in a sealed envelope and clearly marked as either “For Dispensing” or “Emergency Use Only”. The dispensing schedule will be used by the site for subject randomization purposes and will not identify the treatments by name (treatments will be identified as A, B etc corresponding to the labelled study supplies). The other randomization

schedule will only be removed from the sealed envelope in an emergency situation. This schedule will be footnoted with a key identifying the content of treatments A, B etc. However, to maintain the blinding of the study as far as possible, all treatment allocations for all randomization numbers (and the key) on this randomization schedule will be masked with scratch-off panels. Only the panels required for the subject unblinding should be removed.

The study blind must be returned to GSKCH at the end of the study.

5.9. Packaging and Labelling

The contents of the label will be in accordance with all applicable regulatory requirements and will be the responsibility of the Clinical Supplies Department, GSKCH.

Each study label will contain, but not be limited to, protocol number, product code letter, directions for storage, emergency contact telephone number and the statements "For Clinical Trial Use Only" and "Keep out of the reach and sight of children".

The Panadol® Advance and Panadol® Extra Advance tablets will be sourced from the UK market place and supplied in commercial packaging with a study label applied to each sample.

The Placebo to match Paracetamol 665mg Sustained Release Tablets (Panadol Extend Placebo Tablets) will be supplied in cartons containing blister cards. Both the carton and blister card will have a study label affixed.

All sundry items will be provided in their commercial packaging.

Care should be taken with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study. Subjects should be instructed to not remove or deface any part of the study label.

5.9.1. Accountability of Product

All products supplied are for use only in this clinical study and should not be used for any other purpose.

The investigator or designee will maintain a full record of study product accountability. A Product Dispensing Log must be kept current and will contain the following information:

- The identification of the subject to whom the study product was dispensed.

- The date(s) and quantity of the study product dispensed to the subject.
- The date(s) and quantity of the study product returned by the subject (if applicable).

The inventory must be available for inspection by the study monitor during the study. At the end of the study, study product supplies will be verified by the monitor. Study product supplies will then be either collected by the study monitor or returned by the investigator or designee to the GSKCH Clinical Supplies Department or designated vendor.

5.9.2. Storage of Product

Study product supplies must be stored in compliance with the label requirements in a secure place with limited or controlled access.

6. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Schedule of Events section.

Adherence to the study design requirements, including all assessments and procedures are essential and required for study conduct.

6.1. Visit 1 - Screening Visit

6.1.1 Email/Telephone Screening

Prior to the screening visit, email/telephone screening will be conducted for individuals who have responded to advertisement using a standard email/telephone script. This will be conducted by the site recruitment staff or designee.

6.1.2. Informed Consent

The investigator, or designee, must obtain written (signed and dated by the subject) informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The consent form will include a statement of consent permitting the investigator, or designee, to notify the subject's general practitioner of their participation in the study. If no response is received from the general practitioner in relation to the subject's participation before the subject returns for visit 2 then the subject will be considered eligible to proceed providing all other inclusion/exclusion criteria are met.

The investigator, or designee, must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a written consent will be provided by the investigator or by GSKCH. The investigator, or designee, should sign and date the consent form to confirm that the consent process was completed correctly. The subject, will be provided with a copy of their signed and dated consent form and any other written information which they should be instructed to retain.

If, during a subject's participation in the study, any new information becomes available that may affect the subject's willingness to participate in the study, each ongoing subject should receive a copy of this new information and be re-consented into the study. Subjects should be provided with a copy of the signed and dated amended consent form. The date of consent will be recorded on the CRF.

6.1.3. Demographics

The following demographic parameters will be captured by the Investigator or designee and recorded on the CRF: year of birth, gender and race.

6.1.4. Medical History and Concomitant Medication

Medical history for each subject will be assessed as related to the inclusion/exclusion criteria by the Investigator or medically qualified designee. Details of any relevant medical or surgical history, including allergies or drug sensitivity, will be recorded on the CRF. Any concomitant therapy taken in the 30 days prior to the Screening Visit and throughout the study will also be recorded.

6.1.5. Brief Pain Inventory – Short Form Questionnaire

The BPI-Short Form questionnaire (Cleeland CS, 2009) allows the user to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. Initially developed to assess pain related to cancer (Cleeland et al., 1994), the BPI has been shown to be an appropriate measure for pain caused by a wide range of clinical conditions. See Appendix 2.

6.1.6. Pain Recurrence Questionnaire And Pain State Question

The Pain Recurrence Questionnaire (see Appendix 3) will be administered to confirm the eligibility for the study per Inclusion 7A.

The pain state question (See Appendix 4) will be administered to confirm eligibility for the study as per Inclusion 7C.

6.1.7. Physical Exam/Vital Signs

The investigator or designee will perform a physical exam that includes central nervous system, neck, head, ears, eyes, nose and throat, respiratory, cardiovascular, gastrointestinal, abdomen, musculoskeletal, neurological, endocrine/metabolic, hematopoietic/lymphatic and dermatological assessments.

The investigator or designee will measure vital signs while the subject is seated (Blood Pressure measured after 5 minutes seated at rest). The following normal ranges are given as a guide:

- Systolic Blood Pressure $\geq$100 and $\leq$140 mm Hg
- Diastolic Blood Pressure $\geq$60 and $\leq$90 mm Hg
- Heart Rate $\geq$50 and $\leq$100 beats per minute
- Respiratory Rate $\geq$8 and $\leq$20 respirations per minute
- Tympanic Body Temperature $\geq$35.5ºC and $\leq$37.8ºC (95.9-100 ºF)

The outcome of these assessments will be documented in the CRF, including details of any abnormalities. A subject with vital signs marginally outside the normal range

may be included in the study if (in the investigator's opinion) they are not clinically significant.

6.1.8. Anthropometric Measurements

Height will be measured using a wall mounted stadio-meter, with the subject standing without shoes, to the nearest 0.1 cm. Weight will be measured in standard clothing on calibrated weighing scale to the nearest 0.1 kg. BMI will then be calculated as follows:

$$BMI = Weight\ (kg) / [Height]^2\ (m^2)$$

6.1.9. Pregnancy Test

Urine pregnancy testing will be performed on females of child bearing potential according to the test kit manufacturer's instructions. Any urine collected will be disposed of as soon as the test is complete and will be tracked as detailed in section 6.2.1.

6.2. Visit 2 (Pain State) and Visit 3 (Pain-free)

Subjects advised to eat before dosing with no food less than 1 hour before dosing. All pre-treatment assessments will be performed prior to randomization.

6.2.1. Drug and Alcohol Assessment

A urine sample will be collected and analyzed for cannabinoids, amphetamine, cocaine, ecstasy, methamphetamine and morphine before the subject undergoes assessment at Visit 2 and Visit 3 to check eligibility. The urine will be labeled with the subject's number and date to ensure traceability and will be disposed of as soon as the test is complete by flushing down the toilet at the HPL. A tracking log will be used to document collection and destruction of the urine samples. The subject will also breathe into an alcohol breathalyzer at Visit 2 and Visit 3. The results of this analysis must be negative for all such substances in order for the subject to continue in the study.

6.2.2. Pregnancy Test

Urine pregnancy testing will be performed on females of child bearing potential (only Visit 2) according to the test kit manufacturer's instructions. Any urine collected will be disposed of as soon as the test is complete and will be tracked as detailed in section 6.2.1.

6.2.3. Cognitive Function Assessments

Familiarization cognitive function assessments will have been performed at Visit 1. A member of the site team will instruct the subjects to complete the cognitive assessments in the following order:
For the Axon Sports Priming Application the site team will follow administration instructions as outlined in WA-525.

1. Axon Sports Priming Application (approximately 5 minutes)

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).

For the CANTAB tasks (2-6 listed below) the site team will supervise testing which is delivered automatically via tablet devices as provided by Cambridge Cognition.

2. Reaction Time, RTI (approximately 5 minutes)

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). This task takes approximately 5 minutes to complete.

3. One Touch Stockings of Cambridge, OTS (approximately 10 minutes)

This task is a measure of executive function and takes approximately 10 minutes to complete. The participant is shown two displays containing three coloured balls. The displays are presented in such a way that they can easily be perceived as stacks of coloured 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.

4. Attention Switching Task, AST (approximately 8 minutes)

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.

5. Spatial Working Memory, SWM (approximately 6-7 minutes)

This task is a measure of working memory and takes approximately 6-7 minutes to complete. The task involves a number of coloured 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 colour 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 trials of four, six and eight tokens.

6. Rapid Visual information Processing, RVP (approximately 7 minutes)

This task measures attention and takes approximately 7 minutes to complete. A white box appears in the centre 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' (A prime) 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.

6.2.4. Mobility Assessments

Familiarisation mobility assessments will have been performed at Visit 1. A member of the site team will instruct the subjects how to complete the mobility assessments using the following work aids - Gait - WA-532 (optojump), Time to standing - WA-530 (force plate) and grip force - WA-531 (Grip force). These work aids outline procedures for completing the following mobility assessments will be conducted:

1. 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 utilised. Differences in contact phase (m/s), stride length (cm) and walking speed over 5-10m (metres/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 analysed. 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 Optojump 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.

2. 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 measured using a stopwatch 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

continuously as a practice effort and 5-times continuously as a test effort at each visit. There will be a 1-minute rest between the practice and test effort. Differences in average time to standing and average peak GRF output between baseline (pain-state), post-intervention and pain free follow-up assessments will be analysed for the test effort.

3. 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 result from 3 test efforts will be recorded, with the average grip strength being used for data analysis.

6.2.5 Physical Exam / Vital Signs (Visit 2 only pre- and post-treatment)

The investigator or designee will perform a brief physical exam that will be focused on general appearance, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.

The investigator or designee will measure vital signs while the subject is seated (Blood Pressure measured after 5 minutes seated at rest). The following normal ranges are given as a guide:

- Systolic Blood Pressure $\geq$100 and $\leq$140 mm Hg
- Diastolic Blood Pressure $\geq$60 and $\leq$90 mm Hg
- Heart Rate $\geq$50 and $\leq$100 beats per minute
- Respiratory Rate $\geq$8 and $\leq$20 respirations per minute
- Tympanic Body Temperature $\geq$35.5ºC and $\leq$37.8ºC (95.9-100 ºF)

The outcome of these assessments will be documented in the CRF, including details of any abnormalities. A subject with vital signs marginally outside the normal range may be included in the study if ,in the investigator's opinion, they are not clinically significant.

6.2.6. Medical History and Concomitant Medication

Medical history for each subject will be assessed as related to the inclusion/exclusion criteria by the Investigator or medically qualified designee. Details of any relevant medical or surgical history, including allergies or drug sensitivity, will be recorded on the CRF. Any concomitant therapy taken in the 30 days prior to the Screening Visit and throughout the study will also be recorded.

6.2.7. Brief Pain Inventory – Short Form Questionnaire

The BPI-Short Form questionnaire (Cleeland CS, 2009) allows the user to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. Initially developed to assess pain related to cancer (Cleeland et al., 1994), the BPI has been shown to be an appropriate measure for pain caused by a wide range of clinical conditions. See Appendix 2.

6.2.8. Pain State Question

The pain state question (See Appendix 4) will be administered on Visit 2 to confirm eligibility for the study as per Inclusion 7C.

6.3. Study Conclusion

Subjects will be evaluated to determine if they completed all study procedures or if they were discontinued from the study early. If the subject discontinued at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page of the CRF by selecting one of the options below.

1. Subject did not meet study criteria
2. Adverse Event
3. Lost to Follow Up
4. Protocol Violation
5. Withdrawal of Consent
6. Other

7. SAFETY ASSESSMENTS

7.1. Definitions of an Adverse Event and Serious Adverse Event

7.1.1. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

Adverse Event Definition:

- An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of an investigational or washout product, whether or not considered related to the investigational or washout product.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational or washout product.

Events meeting AE definition include:

- Any abnormal laboratory test results (if applicable) or other safety assessments, including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition(s) detected or diagnosed after study product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events NOT meeting definition of an AE include:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder/ condition being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition..
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

7.1.2. Serious Adverse Events

Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:

A. Results in death

B. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

C. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

D. Results in disability/incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

E. Is a congenital anomaly/birth defect

F. Other Situations

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm,

blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse or reports of spontaneous abortion.

7.2. Recording Adverse Events and Serious Adverse Events

Recording of adverse events and serious adverse events:

- The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.
- The investigator or site staff will then record all relevant information regarding an AE/SAE in the CRF.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. Clinical AEs will be described by diagnosis and not by symptoms when possible (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).
- AEs will be collected from the time of signature of the consent form - for all subjects who are eligible at assessment familiarisation stage until Visit 3 or 5 days following last administration of the study product (whichever is the latter).
- SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as **related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of the subject's medical history.

7.3. Evaluating Adverse Events and Serious Adverse Events

Assessment of Intensity:

The investigator or designee will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities

- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Note: An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality:

- The investigator is obligated to assess the relationship between study product and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes (source document) or CRF that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. **However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

7.4. Reporting Adverse Events and Serious Adverse Events

AE Reporting to GSKCH:

- AEs will be recorded in the AE section of the CRF.
- Medical conditions recorded by the subject on a diary card or similar document that meet the definition of an AE must also be recorded in the AE section of the CRF, if not previously well-characterized by the investigator in the subject's medical history.
- AEs elicited by the investigator in a standard manner at the study visits should also be recorded in the AE section of the CRF. The investigator or designee

must ask the subject the following question during each visit including any follow-up visits: ***"Have you felt unwell, experienced any symptoms or taken any medication (since your last visit) (today) (since your last dose) (since the last session)?"***

- The medically qualified investigator should review adverse events in a timely manner; this review should be documented in writing in the source document or in the CRF.
- After the study is completed at a given site, and the site has received their study data on Compact Discs (CDs), the electronic data collection tool will be removed from the internet to prevent the entry of new data or changes to existing data.

SAE Reporting to GSKCH:

A paper copy of the SAE form provided in the investigator study master file should be completed as fully as possible.
It is essential to enter the following information:

- Protocol and subject identifiers
- Subject's demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (see section 8.3)
- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator and GSKCH assessment of the SAE report:

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken on study product
- Outcome if known

The SAE form, completed as fully as possible, and SAE fax cover sheet must be faxed or e-mailed to the appropriate GSKCH Study Manager as soon as possible, **but not later than 24 hours** after study site personnel learn of the event. The GSKCH Study Manager should be notified of the situation by telephone or email.

Fax Serious Adverse Events to:
UK: PPD

The GSKCH Study Manager will be responsible for forwarding the SAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance, the Medical Director responsible for the study and other GSKCH personnel as appropriate via email.

The initial report will be followed up with more information as relevant, or as requested by the GSKCH study manager.

7.5. Follow-up of Adverse Events and Serious Adverse Events

Follow-up of AEs and SAEs:

- After the initial report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition.
- All AEs/SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- Investigators are not obliged to actively seek AEs or SAEs in former subjects. However, if the investigator learns of any SAE, including the death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the investigational product or study participation, the investigator will promptly notify GSKCH.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

Regulatory and ethics reporting requirements for SAEs:

- The investigator will promptly report all SAEs to GSKCH within the designated reporting timeframes (within 24 hours of learning of the event). GSKCH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSKCH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.
- GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IEC and investigators.
- Investigator safety reports are prepared according to GSKCH policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation.
- An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary of listing of SAEs) from GSKCH will file it with the Investigator Brochure (or safety statement) and will notify the IEC, if appropriate according to local requirements.

7.6. Collection of Pregnancy Information

7.6.1. Time Period for Collecting of Pregnancy Information

Collection of Pregnancy Information:

- Pregnancy information will be collected on all pregnancies reported following administration of any investigational product. Information on pregnancy identified during the screening phase and prior to investigational product administration does not need to be collected.

7.6.2. Action to be Taken if Pregnancy Occurs

Action to be Taken:

- The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the investigational product. The investigator will record pregnancy information on the appropriate form and submit it to GSKCH within 2 weeks of learning of the subject becoming pregnant. The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded to GSKCH. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.
- While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination for medical reasons will be recorded as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such. An SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject completed the study and considered by the investigator as possibly related to the investigational product, must be promptly forwarded to GSK.
- While the investigator is not obliged to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- There is no requirement for the subject to be withdrawn from the study as a result of the pregnancy. However if they are withdrawn, this should be recorded in the appropriate section of the CRF.

8. DATA MANAGEMENT

For this study subject data will be entered into an electronic case report form, using a GSKCH validated data system.

8.1. Source Documents/ Data

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified in the Source Document Designation Form. In some cases the CRF can be used as a source document.

Each subject will be assigned and identified by a unique Screening Number. Any reference made to an individual subject within the study must be done using the unique Screening Number.

8.2. Case Report Form

A CRF is a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

For each subject who has given informed consent/assent and has been screened, CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct.

Management of clinical data will be performed in accordance with applicable GSKCH standards and data cleaning procedures to ensure the integrity of the data e.g. removing errors and inconsistencies in the data.

In order to protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded in the CRF or as part of the query text.

Adverse events and concomitant medications terms (if applicable) will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.

Subject data will be entered into GSKCH defined CRFs and transmitted electronically to GSKCH in a validated (21 CFR Part 11 compliant) web-based electronic data capture system PPD .

All CRF pages should be completed during a subject assessment when the CRF has been designated as the source. Data that is sourced elsewhere should be entered into the CRF in an agreed upon timeframe between the Investigator and Sponsor.

The CRFs (including queries, query responses and audit trails) will be retained by GSKCH. Site data archived compact discs (CD(s)) prepared by a third party will be sent to the investigator to maintain as the investigator copy following the decommissioning of the study.

8.3. Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance. Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

8.3.1. Data Queries

Programmed edit checks will be generated automatically, as the data is being entered into the system. Data Management will also run reports and listings on the CRF data, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (Adverse Events and Drugs) are reported appropriately.

The study monitor at the study site will review the CRFs in accordance with the monitoring plan, and any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. Monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction.

8.4. Processing Patient Reported Outcomes

Patient reported outcome (PRO) data are collected directly from the subject PRO measures e.g. diary cards, questionnaires etc, and entered into the sponsor's clinical data management system (DMS) by the study site representative. In instances where the PRO data is entered into the DMS by GSKCH, the PROs will be anonymised, and forwarded to GSKCH for entry, as agreed and documented ahead of the study starting. PROs that are source will be retained by the investigator and certified copies will be sent to GSKCH.

In order to protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded on all PRO's that will be forwarded to GSKCH.

8.5. External Data

External Data are subject data obtained externally to the CRF. These data are generated from laboratory instruments, computers or other sources and then transcribed into a file and format agreed upon by GSKCH to identify the subject and time point referenced in the CRF and/or protocol.

An agreed upon quality control process is performed against the transcribed data to the source to ensure the accuracy of the transcription. The transcribed data is transmitted in an agreed upon format to GSKCH via secured web portal or CD/DVD via mail carrier with tracking capabilities.

Proper reconciliation will be performed between the transcribed data and the clinical database to ensure subject and time point referenced in the Clinical Database match before Clinical Database Freeze (locking of the database) can occur.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1 Sample Size Determination

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

9.2. General Considerations

9.2.1. Definition of Analysis Populations

Safety population: All randomized subjects who receive at least one treatment during study period will be considered as the safety population.

ITT population: All randomized subjects who receive study treatment and have at least one post-baseline efficacy measurement.

PP population: Since this is an exploratory study, no per protocol (PP) population will be defined.

9.2.2. Exclusion of Data from Analysis

There is no intention to exclude any data from the planned analysis.

9.2.3. Criteria for Evaluation

See the following two sub-sections for details.

9.2.4. Criteria for Assessing Efficacy

- Statistically significant deficit in 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) observed between an individual in pain vs. their pain-free performance.
- Statistically significant deficit in mobility (as measured by individual scores from gait, time to standing and grip force assessments) observed between an individual in pain vs. their pain-free performance.

9.2.5. Criteria for Assessing Tolerability

Adverse events (AEs) will be used to evaluate the tolerability for this study.

9.2.6. Criteria for Assessing Bioequivalence

NA.

9.2.7. Handling of Dropouts and Missing Data

Subjects who meet the definition for inclusion in the ITT population and who withdraw from the study early will be included in the statistical analysis up to the point of when they withdraw. There will be no imputation for missing data (i.e., analysis will be conducted on an observed case basis).

9.2.8. Other Issues

Since this is an exploratory study, the multiplicity issue for multiple comparisons in primary efficacy endpoints will not be considered. No p-value adjustments will be done and all p-values will be reported as is.

9.3. Statistical Methods and Analytical Plan

Additional details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following finalization of the protocol and prior to study unblinding / analysis (as appropriate).

9.3.1. Demographic and Baseline Characteristics

Descriptive statistics of demographic and baseline characteristics data will be tabulated. Continuous variables will be presented using summary statistics: number of observation, arithmetic mean, SD, median, minimum and maximum values. Categorical variables will be presented using summary statistics: number of observations, counts, and percentages.

9.3.2. Primary Analysis

The primary efficacy variables are:

- Subject level change from pain-free state in cognition as measured by cognitive function assessment (CANTAB and Axon Sports) in the pain state.

The cognitive function assessment contains the following measurements:

1. Reaction Time (RTI)
2. Rapid Visual information Processing (RVP)
3. Attention Switching Task (AST)
4. Spatial Working Memory (SWM)
5. One Touch Stockings of Cambridge (OTS)
6. Axon Sports Priming Application

Detailed descriptions for each assessment are presented in Section 6.2.
A two-sided paired t-test will be used to analyze the primary efficacy endpoints that are not 'time-related'. For the 'time-related' variables, the non-parametric method using Wilcoxon Sign Rank test will be employed at visit 2 Pre (Baseline) and visit Post (Baseline). All tests will be two-sided with an alpha level of 0.05. The 95% CI and the p-value will also be presented.

9.3.3. Secondary and Exploratory Analysis

The secondary variables are:

- Subject level change from pain-free state in mobility as measured by gait, time to standing and grip force score in the pain state.

The exploratory variables are:

- Correlation between pain type and intensity to cognitive assessments.
- Correlation between pain type and intensity to mobility assessments
- 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 percent change of muscle score to post-treatment assessment period.

The mobility assessment contains the following assessments:

1. Gait score, which consists of three measurements: (1) Contact phase, (2) Stride length, (3) Within test variability.
2. Time to Standing, which consists of two measurements: (1) Time to standing, (2) Ground reaction force (GRF).
3. Grip Force

All the detailed descriptions for these assessments can be found in Section 6.2.3.

A two-sided paired t-test will be used to analyze the secondary efficacy endpoints for subject level change from pain free-state in mobility measurements that are not 'time-

related'. For the 'time-related' mobility variables, the non-parametric method using Wilcoxon Sign Rank test will be employed at visit 2 Pre (Baseline) and visit 2 Post (Baseline). For the between treatment comparisons, the mixed effect model with treatment and pain type as the fixed effect and the baseline value as a covariate will be employed for the change from baseline type of analysis at Visit 2, 1 hour post-treatment and at visit 3 (follow-up visit) for variables other than 'time' related type. For the 'time' related variables, the non-parametric method using Van Elteren's test with stratification factor pain type will be employed. The 95% CI and the p-value will also be presented.

9.3.4. Safety Analysis

AEs will be listed and reviewed. Only treatment emergent AEs (i.e., those occurring after first use of the study treatment) will be tabulated, AEs occurring prior to randomization will be included in the AE listing. AE tables will be presented using the safety population.

9.3.5. Other Analysis

To investigate the relationship between pain type and intensity to cognitive and mobility assessments will be considered as an exploratory analysis and the Pearson correlation analysis method will be used for this purpose.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trials Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IEC/Competent Authority for the trial protocol (including amendments), written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), investigator brochure/ safety statement (including any updates) and any other written information to be provided to subjects. A letter or certificate of approval will be sent by the investigator to the sponsor prior to initiation of the study, and also when subsequent amendments to the protocol are made.
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and GSK procedures, GSK or designee (i.e. third party vendor) monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK or designee will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The extent and nature of monitoring will be described in a written monitoring plan on file at GSKCH. The investigator (or designee) agrees to allow the monitor direct access to all relevant documents and agrees to co-operate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

The sponsor will be available to help investigators prepare for an inspection.

10.5. Conditions for Terminating the Study

Upon completion or premature discontinuation of the study, the GSKCH monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSKCH Standard Operating Procedures.

Both GSKCH and the Investigator reserve the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance.

If the trial is prematurely terminated or suspended for any reason, the investigator site should promptly inform the trial subjects and should assure appropriate therapy/

follow-up for the subjects. Where required by the applicable regulatory requirements, GSKCH should inform the regulatory authority (ies).
In addition:

- If the investigator terminates or suspends a trial without prior agreement of GSKCH, the investigator site should promptly inform the sponsor and the IEC, and should provide the sponsor and the IEC a detailed written explanation of the termination or suspension.
- If the GSKCH terminates or suspends a trial, the investigator should promptly inform the IEC and provide the IEC a detailed written explanation of the termination or suspension.
- If the IEC terminates or suspends its approval/favorable opinion of a trial, the investigator should promptly notify the GSKCH and provide GSKCH with a detailed written explanation of the termination or suspension.

10.6. Records Retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The investigator must assure that the subject's anonymity will be maintained. On CRFs or other documents submitted to GSKCH, subjects should not be identified by their names or initials, but by an identification code. The investigator should keep a separate log of subjects' codes, names and addresses. Documents not for submission to GSKCH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements (GSKCH recommends that documents be kept for 10 years). The investigator is also required to keep subject identification codes on file for at least 15 years after completion or discontinuation of the study. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSKCH and the investigator. The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11. 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.

Berryman, C, Stanton T, Bowering, J, Tabor, A, McFarlane, A, Moseley, L. Evidence for working memory deficits in chronic pain: A systematic review and meta-analysis. *Pain*, 2013; **154**: 1181-1196.

Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, Pandya KJ. Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med*, 1994; **330**(9): 592-596.

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

Eccleston, C. Chronic pain and attention: A cognitive approach. British Journal of Clinical Psychology, 1994; **33**: 535–547.

ICH Topic 6 Guideline for Good Clinical Practice CPMP/ICH/135/95; 1996.

Klepsted P, Loge JH, Borchgrevink PC, Mendoza TR, Cleeland CS, Kaasa S. The Norwegian Brief Pain Inventory Questionnaire: Translation and Validation in Cancer Pain Patients. *Journal of Pain and Symptom Management,* 2002; **24**(5): 517–525.

Landrø NI, Fors EA, Våpenstad LL, Holthe Ø, Stiles TC, Borchgrevink PC. The extent of neurocognitive dysfunction in a multidisciplinary pain centre population. Is there a relation between reported and tested neuropsychological functioning? *Pain*, 2013; **154**(7): 972-7.

Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: A review of clinical and preclinical research. *Prog Neurobiol*, 2011; **93**(3): 385-404.

Park DC, Glass JM, Minear M, Crofford LJ. Cognitive function in fibromyalgia patients. *Arthritis Rheum*, 2001; **44**(9): 2125-33.

Renner B, Clarke G, Grattan T, Beisel A, Mueller C, Werner U, Kobal G, Brune K. Caffeine accelerates absorption and enhances the analgesic effect of acetaminophen. *J Clin Pharmacol*, 2007; **47**(6): 715-26.

Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C and Sayer AA, A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing*, 2011; **40**(4): 423-429.

van Dijk GM1, Veenhof C, Lankhorst GJ, Dekker J. Limitations in activities in patients with osteoarthritis of the hip or knee: the relationship with body functions, comorbidity and cognitive functioning. *Disabil Rehabil,* 2009; **31**(20): 1685-91.

Veldhuijzen DS, Kenemans JL, van Wijck AJ, Olivier B, Kalkman CJ, Volkerts ER. Processing capacity in chronic pain patients: a visual event-related potentials study. *Pain*, 2006; **121**(1-2): 60-8.

Vogt L, Segieth C, Banzer W, Himmelreich H. Movement behaviour in patients with chronic neck pain. *Physiother Res Int*, 2007; **12**(4): 206-12.

WA-525 – *Site staff instructions for conduct of Axon Sports Priming Application*, 2016.

WA-530 - *Site staff instructions for conduct of the time to standing (force plate) assessment*, 2015.

WA-531 - *Site staff instructions for conduct of the Grip force assessment*, 2015.

WA-532 - *Site staff instructions for conduct of the Gait assessment (OptoJump)*, 2015.

World Medical Association Declaration of Helsinki, 59th General Assembly, Seoul 2008.

12. APPENDICES

12.1. Appendix 1 - Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
AMTI	Advanced Mechanical Technology, Inc
AST	Attention Switching Task
BMI	Body Mass Index
BPI	Brief Pain Inventory
CANTAB	Cambridge Cognition Cognitive Assessments
CD	Compact Disc
CRF	Case Report Form
DVD	Digital Versatile Disc
EDC	Electronic Data Capture
FM	Fibromyalgia
GCP	Good Clinical Practice
GP	General Practitioner
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
OTC	Over-the-Counter
OTS	One Touch Stockings of Cambridge
PII	Personally Identifiable Information
PP	Per Protocol
RTI	Reaction time
SAE	Serious Adverse Event
SWM	Spatial Working Memory
SRT	Simple Reaction Time
RVP	Rapid Visual information Processing
RVPA	Rapid Visual information Processing A prime
PRO	Patient Reported Outcome

Trademark Information

Trademarks of the GlaxoSmithKline group of companies:
Panadol

12.2. Appendix 2 - Brief Pain Inventory - Short Form

Visit number: Subject ID:

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form)

Date: ___/___/____ Time: _____

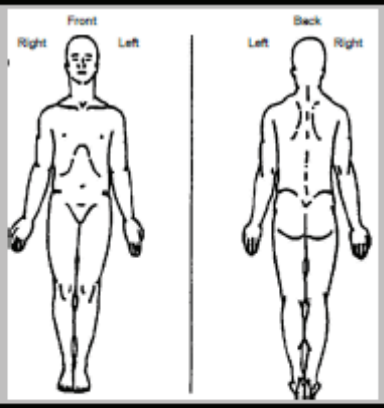
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

Page 1 of 2

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date: ___/____/____ Time:_____

Name:_____ _____ _____

Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% No Relief 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

B. Mood

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

C. Walking Ability

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

E. Relations with other people

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

F. Sleep

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

G. Enjoyment of life

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

Page 2 of 2

12.3. Appendix 3 – Pain Recurrence Questionnaire

Visit number: Subject ID: Date:

Including today, how many episodes of acute (< 3 months in duration), re-current pain have you suffered from in the past 3 months? Please indicate number in relevant box:

Pain Recurrence		
Joint	Knee	
	Hip	
Muscle	Upper Back	
	Lower Back	
Headache		
Period		
Other, please provide details below:		

If currently within an acute pain episode, please indicate where you are currently suffering from pain.

Current Pain		
Not currently suffering from acute pain		
Joint	Knee	
	Hip	
Muscle	Upper Back	
	Lower Back	
Headache		
Period		
Other, please provide details below:		

12.4. Appendix 4 – Pain State Question

Visit number: Subject ID: Date:

Please mark an X to indicate where you are currently suffering pain:

Pain State		
Joint	Knee	
	Hip	
Muscle	Upper Back	
	Lower Back	
Headache		
Period		
Other, please provide details below:		

12.5. Appendix 5 – Recruitment Tracking Log

When a subject is randomised the subject number must be tracked in the below log to ensure that a minimum of 8 subjects per pain type are included in the study:

Minimum subjects per pain type:

	Pain type			
count	**Joint** (Knee or Hip)	**Muscle** (Upper or Lower back)	**Headache**	**Period**
1				
2				
3				
4				
5				
6				
7				
8				

Additional subjects per pain type:

Once 8 subjects are recruited for a pain type please complete the rows below as per the

e.g			000109	

1				
2				
3				

4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				
29				

30				
31				
32				
33*				

*Once the bottom row of the log is populated only pain types to which fewer than 8 subjects have been randomised may be recruited to.

SIGNATURE PAGE

204503 Clinical Protocol

Date	Signed By
07-Dec-2016 11:30:35	PPD
Justification	Clinical Operations Approval

Date	Signed By
07-Dec-2016 11:32:11	PPD
Justification	Biostatistics Approval

Date	Signed By
07-Dec-2016 15:56:24	PPD
Justification	Approved

Date	Signed By
Justification	

Date	Signed By
Justification	

Date	Signed By
Justification	