CLINICAL STUDY REPORT
CIAO-II

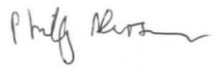
Randomised controlled trial of the short-term effects of OROS-methylphenidate on ADHD symptoms and behavioural outcomes in young male prisoners with attention deficit hyperactivity disorder

Sponsor Protocol Code:	3551
EudraCT Number:	2015-004271-78
ClinicalTrials.gov Identifier:	ISRCTN16827947
REC Number:	16/EE/0117
Investigational Drugs (IMPs):	Concerta XL
Indication:	Attention-Deficit/Hyperactivity Disorder (ADHD)
Development Phase:	Phase IV
Study Begin (FPFV):	17/10/2016
Study End (LPLV):	06/06/2019
Report Version & Issue Date:	v.1.4 26.04.2021
Co-sponsor Name and Address:	King's College London King's Health Partners Clinical Trials Office F16 Tower Wing Guy's Hospital Great Maze Pond London SE19RT
Co-sponsor contact details:	
Chief Investigator:	Professor Philip Asherson

SIGNATURE PAGE

By signing below, I approve the contents of this Clinical Study Report, and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. The clinical trial reported herein was conducted in accordance with the principles contained in the Declaration of Helsinki, Good Clinical Practice (GCP) and all applicable laws and regulations.

Chief Investigator: Philip Asherson

Printed name	**Signature**	**Date**
Professor Philip Asherson		**26th April 2021**

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APPENDICES

1. Ethics

Independent Ethics Committee or Institutional Review Board
The study protocol and amendments were reviewed and approved by a National Research Ethics Service East of England- Essex Research Ethics Committee (ref: 16/EE/0117).

Ethical conduct of the study
The trial was conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki (1996) as amended, the principles of Good Clinical Practice (GCP) and in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, the Research Governance Framework for Health and Social Care, the Data Protection Act 1998 and other regulatory requirements as appropriate. The trial protocol and substantial amendments were reviewed by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA)

Subject information and consent
Participants was recruited from HMP YOI Isis (London) and HM YOI Polmont (Falkirk). Consent was initially obtained for prisoners to be screened for ADHD and if they were screened positive, they would be invited for a diagnostic interview for Adult ADHD. Once the diagnosis of Adult ADHD and the participant was suitable for the trial based on the inclusion eligibility criteria, the participant were asked to consent to be part of the clinical trial. Once consent for the trial had been signed additional checks to confirm all inclusion and exclusion eligibility criteria were done.

2. Data Monitoring

The Data Monitoring Committee (DMC) for the trial were Professor Seena Fazel (chair), University of Oxford, Professor Chris Hollis, University of Nottingham and Adrian Cook, University College London. The committee monitored the safety, efficacy, ethical conduct and quality of data and reported to the Trial Steering Committee prior to their meetings.

The Trial Steering Committee (TSC) for the trial were Professor Jenny Shaw (chair), University of Manchester, Dr Ylva Ginsberg, Dr Peter Mason, Anthony Davis, Dr Ulrich Muller-Sedgwick, Professor Philip Asherson, Professor Lindsay Thomson, Beverley Nolker and user representative. The TSC provided overall supervision of the conduct of the trial.

3. Sponsors, Investigators and Trial Sites

Co-Sponsors	
King's College London ***King's Health Partners Clinical Trials Office*** ***F16, Tower Wing, Guy's Hospital*** ***Great Maze Pond*** ***London SE1 9RT***	

Chief Investigator ***Professor Philip Asherson*** ***Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry Psychology and Neuroscience (IoPPN), King's College London De Crespigny Park, London, SE5 8AF***	
4. Co-Investigator(s), Statistician, Laboratories, Database Management	
Professor Sabine Landau (trial statistician and co-applicant) ***Department of Biostatistics and Health Informatics, Institute of Psychiatry Psychology and Neuroscience (IoPPN), King's College London, De Crespigny Park, London, SE5 8AF***	***Prof John Strang (co-applicant)*** ***Addiction Department, Institute of Psychiatry Psychology and Neuroscience (IoPPN), King's College London, De Crespigny Park, London, SE5 8AF***
Professor Susan Young (co-applicant) ***Psychology Services Limited, PO1735, Croydon, CR0 7WA***	***Prof Lindsay Thomson (co-applicant)*** ***The State Hospital and Forensic Network, Division of Psychiatry, University of Edinburgh, Morningside Park, Edinburgh, EH10 5HF***
Dr Andrew Forrester (co-applicant) ***Greater Manchester Mental Health NHS Foundation Trust, Bury New road, Prestwich, Manchester, M25 3BL*** ***Offender Health Research Network, University of Manchester, Oxford Road, Manchester, M13 9PL***	***Prof Stephen Lawrie (co-applicant)*** ***Division of Psychiatry, University of Edinburgh, Morningside Park, Edinburgh, EH10 5HF***
Prof Thomas Fahy (co-applicant) ***Forensic Department, Institute of Psychiatry Psychology and Neuroscience (IoPPN), King's College London, De Crespigny Park, London, SE5 8A***	***Dr Sheila Howitt (co-applicant)*** ***Division of Psychiatry, University of Edinburgh, Morningside Park, Edinburgh, EH10 5HF***

Ms Rachel Holland (trial statistician) ***Department of Biostatistics and Health Informatics, Institute of Psychiatry Psychology and Neuroscience (IoPPN), King's College London, De Crespigny Park, London, SE5 8AF***	***Ms Lena Johansson (Clinical Trial Manager)*** ***Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry Psychology and Neuroscience (IoPPN), King's College London De Crespigny Park, London, SE5 8AF***

5. Study Synopsis

Title of clinical trial	Randomised controlled trial of the short term effects of OROS-methylphenidate on ADHD symptoms and behavioural outcomes in young male prisoners with attention deficit hyperactivity disorder
Protocol Short Title/Acronym	CIAO-II
Study Phase	Phase IV study
Sponsor name	King's College London
Chief Investigator	Professor Philip Asherson
Eudract number	2015-004271-78
REC number	16/EE/0117
IRAS project ID:	179456
Medical condition or disease under investigation	Attention-Deficit/Hyperactivity Disorder (ADHD)
Purpose of clinical trial	The overall aim of the trial was to investigate the effects of OROS-MPH in young male prisoners (age 16-25) meeting DSM-5 diagnostic criteria for ADHD
Primary objective	To establish the efficacy of OROS-MPH in reducing ADHD symptoms (inattention and hyperactivity-impulsivity) in young male offenders aged 16-25, meeting diagnostic criteria for DSM-5 ADHD.
Secondary objective (s)	To investigate the efficacy of OROS-MPH in young male offenders aged 16-25, meeting DSM-5 diagnostic criteria for ADHD, on reducing secondary outcomes that are indicators of behavioural and functional impairments used in the management of young prisoners in the UK. These include emotional dysregulation, antisocial behaviour in the prison, violent attitudes (a measure linked to aggression) and reports of behaviour from prison staff. To investigate the hypothesis that improvements in secondary behavioural outcomes are mediated by improvements in ADHD symptoms or emotional dysregulation?
Trial Design	An 8-week parallel arm randomised placebo-controlled trial of an extended release formulation of MPH (OROS-MPH), on ADHD

	symptoms, behaviour and functional outcomes in young male offenders aged 16-25, meeting DSM-5 criteria for ADHD.
Endpoints	The primary outcome measure is the level of ADHD symptoms measured at 8 weeks on the investigator rated Connors Adult ADHD rating scale (CAARS-O). This addressed the question of efficacy of OROS-MPH on ADHD symptoms in young prisoners meeting DSM-5 diagnostic criteria for ADHD. Secondary outcomes address important exploratory questions about the effects on comorbid symptoms and behavioural impairments that are commonly seen in offenders with ADHD. There were 13 secondary outcomes including: emotional dysregulation (WRAADDS); the number of adjudications for antisocial behaviour and rule breaking in the previous 8-weeks (critical incidents); ratings of aggressive behaviour by prison staff and educational staff using the prison officer and education staff modified overt aggression scale (MOAS-P and MOAS-E respectively, and classroom behaviour report cards (BRC-P and BRC-E); attitudes towards violence (MVQ); a self-rated scale of subjective well-being, symptoms and life functioning designed to measure psychological distress before and after treatment (CORE-M); a measure of excessive spontaneous mind wandering (MEWS); comorbid mental health symptoms (BSI); a rating scale for irritability (ARI-S); and the clinical global impression (CGI) scale for therapeutic effects.
Planned number of subjects	200 randomised to a 1:1 ratio
Summary of eligibility criteria	Inclusion criteria: Male; aged 16 to 25 years at consent for screening; English speaking; able to provide informed consent; meet DSM-5 ADHD criteria. Exclusion criteria: Lacked capacity to give informed consent; IQ less than 60; serious risk of violence to the researcher; current major depression, psychosis, mania or hypomania; past history of bipolar disorder or schizophrenia; medical contraindications to the use of stimulants; drug seeking behaviour or craving; currently prescribed ADHD medication.

IMP, dosage and route of administration	Over-coated Concerta XL (OROS-methylphenidate) capsules, taken orally, at doses of 18, 36, 54 and 72 mg.
Active comparator product(s)	There is no active comparator.
Maximum duration of treatment of a subject	8 weeks
Version and date of protocol amendments	v.2.0 30.08.18

6. Glossary of terms

ADHD: Attention Deficit Hyperactivity Disorder

AES: Adverse events scale

Audit C: Alcohol Use Disorders Identification Test for consumption

ARI-S: Rating scale for irritability

B-ADHD: Barkley ADHD self-rating scale for DSM-IV ADHD symptoms

BRC: Behaviour report card

BSI: Behavioural symptom inventory

CAARS-O: Connors Adult ADHD Rating Scale Observer

CGI: Clinical Global Impression scale

CI: Chief Investigator

CORE-M: Core outcome measure scale

CTQ: Childhood trauma questionnaire

DMC: Data Monitoring Committee

DIVA: Diagnostic Interview for DSM-IV ADHD

DSM: Diagnostic and Statistical Manual of Mental Disorders

EudraCT: European Clinical Trials Database

HMPPS: Her Majesty's Prison and Probation Service

HRA: Health Research Authority

KCL CTU: King's College London Clinical Trials Unit

KHP CTO: King's Health Partner's Clinical Trials Office

MEWS: Mind Excessively Wandering Scale

MHRA: Medicines and Healthcare products Regulatory Agency

MINI: MINI International Neuropsychiatric interview

MOAS: Modified Overt Aggression Scale

NICE: National Institute for Health and Care Excellence

NIDA National Institute on Drug Abuse Quick Screen: Drug use

MVQ: Maudsley Violence Questionnaire

OROS-MPH: OROS methylphenidate

PI: Principle Investigator

RPAQ: The Reactive-Proactive Aggression Questionnaire

SIGN: Scottish Intercollegiate Guidelines Network

SPS: Scottish Prison Service

TMG: Trial Management Group

TSC: Trial Steering Committee

WASI-II: Wechsler Abbreviated Scale of Intelligence second edition

Weiss-CD: Weiss conduct disorder scale

WRAADDS: Wender-Reimherr Adult Attention Deficit Disorder Scale

ZAN-BPD: Zanarini Rating Scale for Borderline Personality Disorder

7. Publication (reference)

Asherson, P., L. Johansson, R. Holland, T. Fahy, A. Forester, S. Howitt, S. Lawrie, J. Strang, S. Young, S. Landau, and L. Thomson. 2019. 'Randomised controlled trial of the short-term effects of OROS-methylphenidate on ADHD symptoms and behavioural outcomes in young male prisoners with attention-deficit/hyperactivity disorder (CIAO-II)', Trials, 20: 663.

8. Study period (years)

The first patient first visit (FPFV) was on the 17th of October 2016 and the last patient last visit (LPLV) was on the 6th of June 2019. The patient recruitment was complete on the 2nd of April 2019. The end of trial is defined as database lock which was on the 27th of August 2019.

9. Phase of development

Phase IV

10. Objectives

Primary objective: What is the efficacy of OROS-MPH in reducing inattention and hyperactivity-impulsivity in young male prisoners meeting diagnostic criteria for DSM-5 ADHD?

Secondary objective: What is the efficacy of OROS-MPH in reducing secondary outcomes that are key indicators of behavioural and functional impairments used in the management of young male prisoners in the UK? These include emotional dysregulation, antisocial behaviour in the prison, violent attitudes (a measure linked to aggression) and reports of behaviour from prison staff.

Tertiary objective: Are improvements in secondary behavioural outcomes mediated by improvements in ADHD symptoms or emotional dysregulation?

11. Background and Context

It is established that a high proportion of prisoners meet diagnostic criteria for ADHD, with prevalence among prisoners estimated to be between 20 to 30%. It is also established that stimulants such as methylphenidate can reduce the symptoms of ADHD and this is a recommended first line treatment in the UK. However, it is not clear whether prisoners with ADHD will show the same beneficial effects of methylphenidate. Differences may arise because problems with poor attention span, forgetfulness, being overactive and restless or impatient might be better explained by other conditions such as anxiety and depression, personality disorder, post-traumatic stress disorder and drug abuse. This trial follows an open label study investigating the effects of OROS-methylphenidate, an extended release preparation of methylphenidate, showing significant reductions in ADHD symptoms. The trial looks at young male offenders who have undiagnosed or untreated ADHD and investigates the effects of OROS-MPH in this group using a randomised placebo-controlled study design.

12. Methodology

CIAO-II was an 8-week, parallel arm, double blinded, randomised, placebo-controlled trial of an extended release formulation of MPH (OROS-MPH) compared to placebo on ADHD symptoms. The primary outcome was ADHD symptoms after 8 weeks of treatment. Secondary outcome measures included assessments of emotional dysregulation, attitudes towards violence, general psychopathology and reports of behaviour within the prison. Participants in the trial were young male prisoners aged 16-25 who met DSM-5 criteria for ADHD at the time of screening. Participants were randomised to 8-weeks treatment with either OROS-MPH or placebo, titrated over the first 5-weeks to balance ADHD symptom improvement against adverse effects. Medication was then maintained at a stable dose for the final three weeks of the trial.

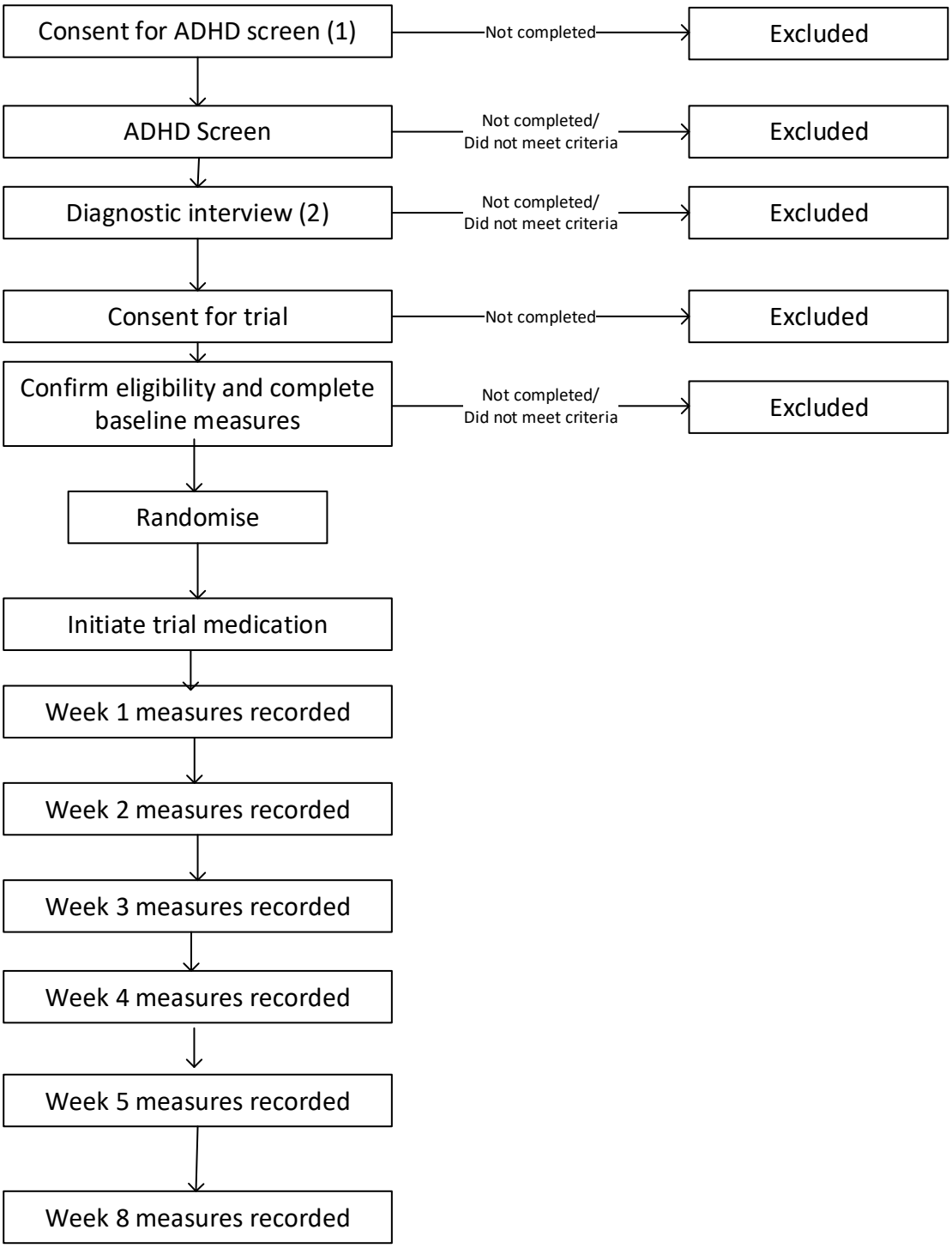
200 participants were randomised and allocated in a 1:1 ratio to either OROS-MPH (n=101) or placebo (n=99). Randomisation was conducted by the King's Clinical Trial Unit (KCTU) with blinding of investigators, pharmacy staff, and participants. The statistical team remained blinded to trial arm allocation until all planned statistical analyses were completed. On completion of the 8-week trial, OROS-MPH or another medication for ADHD was offered to both the OROS-MPH and placebo treated groups as part of their ongoing clinical care.

Following consent to be screened for ADHD (consent I), screening questionnaire data was collected by the research teams using a DSM-IV ADHD symptom rating scale (Barkley and Murphy 1998). Patients who screened positive were invited to complete the Diagnostic Interview for Adult ADHD (DIVA 2.0) (Kooij 2010). This was followed by a clinical assessment by a psychiatrist trained in the diagnostic assessment of ADHD, including collateral information obtained from an informant whenever feasible. Participant's expected release date could change at any time and additional convictions and charges could be added. Hence it was not always possible to predict if a participant

would be transferred, released or deported. For this reason, it is possible that some participants initially excluded due to high risk of release could have taken part in the trial.

Following clinical review, patients who met diagnostic criteria for ADHD and met the other eligibility criteria for the trial, were invited to take part in the clinical trial. Eligibility for the study was further checked and recorded once the consent form for the clinical trial (consent II) had been signed and baseline assessments had been completed, prior to randomisation. Using an algorithm that applies the DSM-5 criteria to the DIVA 2.0 interview data, cases were checked to ensure they met diagnostic criteria for DSM-5 ADHD. A clinical assessment and review by a psychiatrist trained in the diagnostic assessment of ADHD, checked all inclusion and exclusion criteria prior to randomisation.

Figure 1: Flow chart of participants through the pre-trial assessment and trial procedures



Notes

1. Prior to consent to be screened for ADHD, potential participants will be provided with information about the trial. Initial consent (screening and diagnostic step) allows for the use of screening questionnaires (Barkley ADHD self-rating scale for DSM-IV ADHD symptoms3.
2. Where ADHD is suspected a diagnostic interview for ADHD is done which includes the DIVA interview for adult ADHD. Diagnosis of ADHD and suitability for the trial are then confirmed by a medical assessment prior to consent for the trial.

Trial Medication

The trial medication was Concerta XL 18 mg or placebo capsules. These were over-encapsulated and packaged in bottles of 46. Each bottle was assigned a unique randomisation number and the randomisation system allocated the right bottle to each patient.

Dosing Regimen

All trial medication was titrated in the same. Treatment started at an initial dose of 1 capsule of trial medication at the start of week 1. The number of capsules was then increased weekly over the following 4 weeks, in increments of 1 capsule, to a maximum of 4 capsules. This reflected a dose range for the active medication of 18, 36, 54 and 72 mg. Titration upwards was stopped if all 18 ADHD symptoms were scored as negligible or absent (score of 0 or 1 on the CAARS-O), if there were unacceptable adverse effects reported or participants were not willing to increase the dose. The trial medication could also be reduced by 1 capsule if there was a limiting adverse event, in which case there were no further increases in dose for the duration of the trial, or potentially cessation of trial medication. A stable dose was maintained for the final 3 weeks of the trial.

13. Number of patients (planned and analysed)

13.1 Planned

The sample size of 200 young male offenders were recruited within the time frame.

13.2 Analysed

1183 prisoners consented to be screened. Of these, 585 screened negative on the Barkley ADHD self-rating scale and a further 52 were excluded. Of the 546 who were then assessed more fully, 153 did not have ADHD (using the Diagnostic Interview for ADHD in adults – DIVA 2.0), 86 failed to attend, a further 28 were likely to leave the prison during the course of the trial, and 6 failed eligibility checks, leaving 273 who were asked to consent for trial. Of these, 54 refused consent, leaving 219 who consented to the trial, and were formally checked for eligibility. Of the 219, 3 were no longer willing to participate, 2 were assessed after the trial had completed recruitment, and 14 failed eligibility criteria, leaving 200 participants who were randomised.

At the primary outcome timepoint of eight weeks, follow-up rates were good with 90, 94 participants completing final outcome measures in the OROS-MPH and placebo arms respectively. Participants who wished to withdraw were asked if they would allow MOAS-P, critical Incidents and BRC-P to be recorded (one participant in the OROS-MPH arm, wished to withdraw and did not provide study outcomes but allowed prison record data to be used). Overall, this was a follow-up rate of 89% for OROS-MPH, 95% for placebo.

The reasons for patient withdrawal from the study

In this study we distinguished between formal withdrawal from the trial, refusal to take further medication with completion or partial completion of outcomes or transfer out of the prison. 6 participants formally withdrew (4 OROS-MPH and 2 placebo). Of these, 5 no longer wished to take part and one withdrew for reason 'Other – medication didn't work'. 4 participants had withdrawn by week 5, a further 2 withdrew by week 8. In addition, a further 9 participants (6 OROS-MPH and 3 placebo) left the trial because they were released, deported or released to an inaccessible prison. One participant allowed their prison records to be accessed (OROS-MPH) but did not provide primary outcome data. A total 26 of participants (19 OROS-MPH and 7 placebo arm) stopped trial medication but provided 8 week outcome data and out of these two participants moved to an accessible prison

but were not able to receive trial medication.

14. Diagnosis and main criteria for inclusion

Eligibility for the study was checked and recorded once the consent form (consent II) has been signed and baseline assessments had been completed, prior to randomisation. Using an algorithm that applied the DSM-5 criteria to the DIVA 2.0 interview data, cases were checked to ensure they met diagnostic criteria for DSM-5 ADHD. A clinical review by a psychiatrist trained in the diagnostic assessment of Adult ADHD was then completed to check all the inclusion and exclusion criteria.

Inclusion criteria: male; aged 16 to 25 years at consent for screening; English speaking; able to provide informed consent; meet DSM-5 ADHD criteria.

Exclusion criteria: Lacked capacity to give informed consent; IQ less than 60; serious risk of violence to the researcher; current major depression, psychosis, mania or hypomania; past history of bipolar disorder or schizophrenia; medical contraindications to the use of stimulants; drug seeking behaviour or craving; currently prescribed ADHD medication.

15. Test product, dose and mode of administration

IMP

Concerta XL 18mg (OROS-MPH) prolonged release capsules, taken orally, one to twice daily. Dosing was initiated at 18 mg and increased by 18 mg a week to a maximum dose of 72mg.

Treatment with OROS-methylphenidate or placebo started at 1 capsule for 1 week. The number of capsules increased weekly over 5 weeks to a maximum dose of 4 capsules. Titration upwards was stopped if all 18 ADHD symptoms were scored as negligible, there were unacceptable adverse effects, or participants objected to an increase. A stable dose was maintained for the final 3-weeks.

16. Duration of treatment

The duration of treatment is 8 weeks, with an initial titration phase of 5 weeks, and maintenance phase of 3 weeks.

17. Reference therapy, dose and mode of administration

Placebo capsules were titrated in the same way as OROS-MPH. Participants did not usually take medication every day but took the full dose on the day that they took medication. By week 5, participants were taking on average 1.60 and 2.40 capsules, dropping to 1.41 and 1.99 capsules per day by week 8, in the OROS-MPH and placebo arms, respectively. Participants in the OROS-MPH arm were less likely to be titrated to a higher dose and were less likely to take the full dose.

18. Criteria for evaluation: Endpoints

18.1 Efficacy

Primary endpoint

The primary endpoint was the level of ADHD symptoms measured on the investigator rated CAARS-O at 8 weeks post treatment initiation.

Secondary Efficacy Parameters

These addressed questions about the effects of trial treatment on comorbid symptoms and behavioural impairments at 8 weeks. There were 13 secondary outcomes including: emotional dysregulation (WRAADDS), irritability (ARI-S), spontaneous mind wandering (MEWS), attitudes towards violence (MVQ), common psychopathological symptoms (BSI), overall therapeutic effect (CGI), current psychological distress (CORE-M), the number of reported adjudications (critical incidents), prison officer ratings of behaviour (BRC-P) and aggression (MOAS-P), education staff ratings of behaviour (BRC-E and MOAS-E), and engagement with the educational program (proportion scheduled sessions attended).

Moderator analyses: The following baseline variables were tested as possible moderators of treatment effect: Borderline personality disorder (ZAN-BPD), childhood trauma (CTQ), and reactive and proactive aggression (RPAQ-R and RPAQ-P).

Mediation analyses: We investigated individual mediating effect of CAARS-O hyperactivity sub-scores, CAARS-O inattention sub-scores and WRAADDS emotional dysregulation measured at 5 weeks on behavioural outcomes (BRC-P and Critical Incidents) measured at 8 weeks.

18.2 Safety

Safety Parameters

Safety remained the responsibility of the prison mental healthcare team. Adverse events (AE) of any medical or non-medical intervention identified or recorded by the research team at each site, were verified by the clinician who was part of the research team, or an assigned medical colleague at specialist registrar grade or above who was a member of the prison healthcare team, or the clinical lead for the project. The decision to stop treatment following an adverse event remained the responsibility of the clinical team. Minor adverse events that did not come under official reporting procedures were reported to the clinical team, e.g. sleep disturbance, minor levels of anxiety or dysthymia, small increases in HR and BP, reduced appetite and other minor physical symptoms that did not endanger patients or cause more than minor distress. All other adverse events from medication were recorded and reported in line with The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006.

The research team acting on behalf of King's College London as sponsors had delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004) to the King's Health Partners Clinical Trials Office (KHPCTO). Reporting of Serious Adverse Events (SAEs) continued until last patient last dose has been completed. For each participant, Adverse Events (AEs) were recorded from randomisation, and reporting of AEs was for the period from the time of first dose of the trial medication to the end of their involvement in the trial (last dose at the end of 8-weeks). All SAEs, serious adverse reactions (SARs) and serious unexpected serious adverse reaction (SUSARs) and important medical events (IMEs) (excepting those specified in this protocol as not requiring reporting) were reported immediately by the Chief Investigator or designated site investigators to the KHPCTO in accordance with the current Pharmacovigilance Policy. We notified Janssen-Cilag Ltd. at the same time.

Specific Safety Endpoints

The KHP CTO reported SUSARs and other SARs to the regulatory authorities (MHRA), competent authorities of other European Economic Area (EAA) states in which the trial is taking place. The Chief Investigator reported to the relevant ethics committees. There were no SUSAR or SAR and only one SAE identified as an Important Medical Event (IME) was reported in this study.

Reporting timelines were as follows: SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days. SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction. The Chief Investigator and KHP CTO (on behalf of the co-sponsors), submitted a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

19. Statistical Methods

Analysis of Efficacy Variables

A detailed statistical analysis plan (SAP) was developed by the trial statisticians in collaboration with the chief investigator and reviewed by the Data Monitoring Committee (DMC), and reviewed and approved by the Trial Steering Committee (TSC) before the trial database was locked. Here we provide a summary of the statistical analysis approaches employed according to this plan. However, note that some analyses decision could only be finalised after having sight of the data, namely the necessity to employ multiple imputation to handle the missing data generating process and the distributional assumptions for some of the non-questionnaire secondary outcomes.

An intention-to-treat (ITT) approach was used for all primary and secondary week-8 outcomes, that is participants were analysed in the groups to which they were randomised irrespective of adherence with study medication. The primary outcome measure CAARS-O and the secondary outcome measure MEWS, WRAADDS, ARI-S, CORE-M, BSI, MVQ, CGI were continuous variables. Their modelling relied on normal assumptions for error terms and treatment effects were quantified by trial arm differences (and standardised differences). MOAS-E, MOAS-P and Behaviour report cards (BRC-P, BRC-E) had also been expected to follow normal distributions and Critical Incidents had been expected to follow a Poisson distribution. However, on review the residuals or all of MOAS-P, MOAS-E, BRC-P, BRC-E and critical incidents were noticeably positive skewed and possibly over dispersed or zero inflated and could not be modelled by a normal distribution.

The number of education sessions scheduled at 8-weeks was defined as scheduled to attend any of offender training, vocational training or education sessions. We had intended to use logistic regression to analyse education as a binary variable of whether any education sessions were scheduled or not, but at baseline almost all (187 of 200) participants had some form of education session scheduled. At week 8, this increased to 191 of 200 participants. Due to this lack of variability in the binary education outcome we instead analysed the underlying count variable “number of any form of education scheduled between baseline and week 8” using a negative binomial distribution to allow for positive skewness and overdispersion of this variable. The proportion of education sessions attended out of those scheduled was also described by arm.

Education outcomes were only considered for the sub-population of prisoners enrolled in education at baseline. 187 study participants were enrolled in some form of education at baseline. However,

within this sub-population only 83 MOAS-E baseline forms were completed. Similarly, only 67 BRC-E forms were completed. We considered an actual sample size of less than half the intended size at baseline too small to attempt meaningful formal inference. Thus, education outcomes MOAS-E and BRC-E were only summarized descriptively.

BRC-P was approximated by a negative binomial distribution which is appropriate as, although not directly defined as a count of incidents, the questionnaire is a weighted proxy count of incidents of inappropriate behaviour. So BRC-P was modelled in the same way as the number of education session scheduled.
MOAS-P exhibited large zero inflation and too few remaining data points to allow modelling of the distribution (143 of the 200 participants who were included in the study were rated "0" on MOASP at eight weeks). We therefore dichotomised this outcome to give a binary variable (1 = participant had any aggressive event, 0 =no aggression), and analysed it using logistic regression.

For Critical Incidents, which is a count of incidents, the data were positively skewed and zero inflated. However, the residuals were no longer zero inflated after baseline count of incidents was included in the analysis model. A negative binomial model rather than a Poisson distribution was employed to allow for overdispersion. In addition, the time in prison was included in the model as an offset to model the fact that the number of critical incidents reported at week-8 are proportional to the time spend in prison between randomisation and withdrawal or 56 days.
Formal trial arm comparisons were carried out by multiple imputation (MI), more specifically by using the flexible Multivariate Imputation by Chained equations (MICE) approach (Imai, Keele, and Tingley 2010). This was necessary because withdrawal from treatment was found to be predictive of missing primary outcomes (missing CAARS-O at eight weeks). Withdrawal from treatment was defined as withdrawing completely from the trial, either through choice or through release, transfer or deportation, or withdrawing from treatment only. The association between treatment withdrawal during the trial and missing data in the primary outcome at 8-weeks was tested using Fisher's exact test and found to be predictive ($p<0.001$). Thus, an MI approach was pursued to allow for a missing data generating mechanism that was missing at random (MAR), with the observed variables allowed to drive missingness including withdrawal from treatment.

20. Summary – Conclusions

20.1 Demographic data

Tables 1 summarises the baseline (pre-randomisation) demographic variables for each trial arm and overall. Table 2 summarises continuous baseline variables including: age, IQ, height and BMI. Table 3 summarises baseline comorbid symptoms and disorders.

Table 1: Demographic data for all patients (safety population)

Table 1: Summaries of categorical demographic baseline variables by trial arm and overall							
Item name	Category name	OROS-MPH		Placebo		Total sample	
		N	N (%)	N	N (%)	N	N (%)
Site	ISIS	101	58 (57.4)	99	57 (57.6)	200	115 (57.5)
	Polmont		43 (42.6)		42 (42.4)		85 (42.5)
Ethnicity	White (White British, White Irish, White Other)	101	64 (63.4)	99	61 (61.6)	200	125 (62.5)
	Other (Asian, Other mixed, Other, Black African and white, Black Caribbean and white)		19 (18.8)		10 (10.1)		29 (14.5)
	Black (Black African, Black Caribbean, Other Black)		18 (17.8)		28 (28.3)		46 (23.0)
Education	No qualifications	101	42 (41.6)	99	37 (37.4)	200	79 (39.5)
	Any qualifications		59 (58.4)		62 (62.6)		121 (60.5)
Age of leaving school	14 or less	101	26 (25.7)	99	25 (25.3)	200	51 (25.5)
	15		32 (31.7)		22 (22.2)		54 (27.0)
	16 or more		35 (34.7)		43 (43.4)		78 (39.0)
	Unknown		8 (7.9)		9 (9.1)		17 (8.5)
Employed (including in education)	Unemployed	101	67 (66.3)	99	66 (66.7)	200	133 (66.5)
	Employed		34 (33.7)		33 (33.3)		67 (33.5)
Offence category	Serious violence or sexual	101	15 (14.9)	99	14 (14.1)	200	29 (14.5)
	Assault		25 (24.8)		26 (26.3)		51 (25.5)
	Drug related		27 (26.7)		30 (30.3)		57 (28.5)
	Burglary or theft		27 (26.7)		20 (20.2)		47 (23.5)
	Other including possession of weapon, driving and wilful fire raising		7 (6.9)		9 (9.1)		16 (8.0)
Previous ADHD treatment	Yes	101	27 (26.7)	99	20 (20.2)	200	47 (23.5)
	No or unknown[1]		74 (73.3)		79 (79.8)		153 (76.5)
Age when ADHD meds last taken	13 or less	101	9 (8.9)	99	3 (3.0)	200	12 (6.0)
	14 or more		18 (17.8)		12 (12.1)		30 (15.0)
	Unknown		74 (73.3)		84 (84.9)		158 (79.0)
[1] Five or less were unknown							

Table 2: Summaries of baseline continuous variables by trial arm and overall

Baseline Characteristics	OROS-MPH		Placebo		Overall	
	N	Mean (sd)	N	Mean (sd)	N	Mean (sd)
Age, IQ, height and BMI						
age [range is 16-25]	101	20.6 (1.9)	99	20.8 (1.9)	200	20.7 (1.9)
WASI-II	101	89.9 (13.5)	99	88.9 (12.4)	200	89.4 (13.0)
Height in centimetres	101	176.4 (7.2)	99	177.2 (6.6)	200	176.8 (6.9)
Body mass index	101	23.7 (3.4)	99	23.7 (3.7)	200	23.7 (3.5)
Clinical measures						
CAARS-O [range 0-54] [1]	100	36.4 (9.8)	99	37.2 (8.7)	199	36.8 (9.2)
CAARS-O Inattention [range 0-27]	101	17.9 (5.1)	99	18.5 (4.7)	200	18.2 (4.9)
CAARS-O Hyperactivity [range 0-27] [1]	100	18.6 (5.7)	99	18.7 (5.1)	199	18.6 (5.4)
WRAADDS [range 0-30]	101	17.5 (5.7)	99	18.1 (5.6)	200	17.8 (5.7)
WRAADDS - Temper subscale [range 0-9]	101	4.7 (2.5)	99	5.2 (2.3)	200	4.9 (2.4)
WRAADDS - Lability subscale [range 0-12]	101	8.0 (2.3)	99	8.1 (2.2)	200	8.0 (2.2)
WRAADDS - Over-reactivity subscale [range 0-9]	101	4.8 (2.2)	99	4.8 (2.3)	200	4.8 (2.2)
ARI-S [range 0-14]	101	9.3 (3.5)	99	9.3 (3.7)	200	9.3 (3.6)
MEWS [range 0-36]	101	25.7 (6.7)	99	26.8 (6.2)	200	26.3 (6.5)
CGI-severity score [range 1-7]	101	4.0 (1.0)	99	3.9 (1.1)	200	3.9 (1.0)
CORE-M [range 0-136]	101	43.5 (13.9)	99	44.8 (15.3)	200	44.2 (14.6)
MVQ [range 0-75] [2]	101	33.2 (9.4)	99	34.6 (9.9)	200	33.9 (9.6)
Weiss CD [range 0-45]	101	17.9 (7.7)	99	18.7 (7.8)	200	18.3 97.7)
Blood pressure systolic	101	123.6 (11.2)	99	124.1 (11.9)	200	123.9 (11.5)
Blood pressure diastolic	101	68.2 (9.9)	99	68.1 (9.5)	200	68.2 (9.7)
Heart rate - beats per minute	101	70.9 (10.7)	99	70.0 (11.8)	200	70.4 (11.2)
Putative moderator variables						
RPAQ_P [range 0-24] [3]	101	6.8 (5.2)	98	7.6 (5.6)	199	7.2 (5.4)
RPAQ_R [range 0-22] [3]	101	14.1 (4.8)	98	14.6 (5.0)	199	14.4 (4.9)
RPAQ total [range 0-46] [3]	101	20.9 (9.2)	98	22.2 (9.7)	199	21.5 (9.4)
CTQ [range 28-140] [4]	101	48.8 (18.8)	99	48.9 (20.7)	200	48.9 (20.7)
ZAN-BPD [range 0-36]	101	6.9 (5.1)	99	6.3 (4.2)	200	6.6 (4.6)
BSI [range 0-212]	101	52.5 (32.5)	99	52.9 (35.9)	200	52.7 (34.2)

[1] CAARS-O reported for 100 cases in OROS-MPH arm because there were more than 20% missing items (2 out of 9) in the hyperactivity subscale for one individual
[2] MVQ subscale scores were not included in the statistical analysis plan
[3] RPAQ reported for 57 cases in the placebo arm but there were more than 20% missing items for one participant
[4] CTQ subscale scores not included in the statistical analysis plan

10 participants were under 18 years old at the time of randomisation (7 OROS-MHP and 3 placebo arm)

Table 3: Summaries of baseline co-existing disorders and symptoms from the MINI interview assessment

Co-existing disorders	OROS-MPH		Placebo		Overall	
	N	N with disorder (%)	N	N with disorder (%)	N	N with disorder (%)
Antisocial Personality Disorder (ASPD)	101	72 (71.3)	99	77 (77.8)	200	149 (74.5)
Mood disorder (major depression, suicidality, manic, hypomanic)	101	30 (29.7)	99	33 (33.3)	200	63 (31.5)
Anxiety disorder (panic, agoraphobia, social anxiety, obsessive-compulsive disorder, PTSD)	101	19 (18.8)	99	19 (19.2)	200	38 (19.0)
Potential problematic alcohol use[1]	101	78 (77.2)	99	71 (71.7)	200	149 (74.5)
Illicit drug use[2]	101	99 (98.0)	99	95 (96.0)	200	194 (97.0)
MINI checklist symptom scores [range 0-10 for each item]						
	N	min/med/max[3]	N	min/med/max	N	min/med/max
Depression	101	0/1/7	99	0/1/8	200	0/1/8
Anger	101	0/4/9	99	0/5/9	200	0/4/9
Mania	101	0/0/6	99	0/0/3	200	0/0/6
Anxiety	101	0/1/8	99	0/1/8	200	0/1/8
Physical symptoms	101	0/0/6	99	0/0/5	200	0/0/6
Suicidal thoughts	101	0/0/3	99	0/0/3	200	0/0/3
Psychosis	101	0/0/1	99	0/0/3	200	0/0/3
Sleep problems	101	0/4/9	99	0/4/10	200	0/4/10
Memory problems	101	0/3/7	99	0/3/7	200	0/3/7
Repetitive thoughts/behaviours	101	0/0/7	99	0/0/7	200	0/0/7
Dissociation	101	0/0/0	99	0/0/5	200	0/0/5
Personality function	101	0/2/9	99	0/2/8	200	0/2/9

[1] Alcohol use is defined using the AUDIT-C definition of problematic alcohol use, i.e. a score of 5 or more.
[2] Illicit drug use is defined as any reported use (problematic or not) within the year prior to incarceration of cannabis, cocaine, methamphetamine, inhalants, sedatives, sleeping pills, hallucinogens, street or prescription opioids, spice or other misuse.
[3] min=minimum / med=median / max=maximum

20.2 Primary outcome

The estimated score difference between the OROS-MPH and placebo arms for CAARS-O at 8 weeks was a reduction of 0.57 95% CI (-2.41 to 3.56). This was an improvement in the OROS-MPH arm but the effect on CAARS-O when standardised was very small at 0.06. The difference was not statistically significant (see Table 5) and was smaller than the difference that the trial was powered to detect (MCID=5 points, as per our sample size calculation).

Table 4 reports the change in CAARS-O scores relative to baseline within subscale and the responder rate. To investigate the responder rate, we applied the operational definition of a responder applied by NICE (NICE 2018), of a 20% reduction in the baseline CAARS-O score. The percentage of responders was 48.3% for OROS-MPH and 47.9% for the placebo arm.

Table 4: Reduction in CAARS-O as percentage of baseline scores and number of responders defined as a 20% reduction from baseline CAARS-O scores.

		OROS-MPH		**Placebo**		**Overall**
Reduction in CAARS-O as percentage of baseline scores						
Outcome measure	**N**	**Mean (sd)**	**N**	**Mean (sd)**	**N**	**Mean (sd)**
CAARS-O: total scale	89	21.24 (33.8)	94	20.12 (29.7)	183	20.66 (31.7)
CAARS-O: inattention subscale		26.40 (36.9)		22.12 (35.6)		24.22 (36.12)
CAARS-O: hyperactivity/ impulsivity subscale		11.67 (59.3)		16.33 (36.4)		14.08 (48.8)
Responder rate at 8 weeks defined as 20% reduction from baseline CAARS-O score						
	N	**N responders (%)**	**N**	**N responders (%)**	**N**	**N responders (%)**
CAARS-O: total scale	89	43 (48.3)	94	45 (47.9)	183	88 (48.1)
CAARS-O: inattention subscale		50 (55.6)		51 (54.3)		101 (54.9)
CAARS-O: hyperactivity/ impulsivity subscale		39 (44.3)		44 (46.8)		83 (45.6)

Secondary outcome:

Small improvements between the active and placebo arm were seen for WRAADDS, MEWS, MVQ, BSI and CGI (therapeutic effects), but deterioration was seen for ARI-S and CORE-M. However, none of the secondary outcomes showed statistically significant differences between the OROS-MPH and placebo arms (Table 5).

Table 5: Outcome measure	OROS-MPH		Placebo		Overall	
	Number observed	Mean (sd)	Number observed	Mean (sd)	Number observed	Mean (sd)
CAARS-O at baseline	100*	36.4 (9.8)	99	37.2 (8.7)	199	36.8 (9.2)
CAARS-O at week 1	96	32.4 (9.9)	98	31.2 (11.5)	194	31.8 (10.7)
CAARS-O at week 2	92	28.8 (11.2)	97	29.6 (11.3)	189	29.2 (11.3)
CAARS-O at week 3	93	28.3 (11.3)	94	30.3 (12.0)	187	29.3 (11.7)
CAARS-O at week 4	92	26.0 (12.5)	96	29.1 (11.9)	188	27.6 (12.3)
CAARS-O at week 5	92	27.5 (12.7)	95	28.8 (11.5)	187	28.2 (12.1)
CAARS-O at week 8	90	28.0 (11.9)	94	29.3 (11.6)	184	28.7 (11.7)
MEWS at baseline	101	25.7 (6.7)	99	26.8 (6.2)	200	26.3 (6.5)
MEWS at week 5	92	20.5 (9.3)	95	21.4 (9.4)	187	21.0 (9.3)
MEWS at week 8	90	19.8 (10.0)	94	21.9 (9.2)	184	20.9 (9.6)
BSI at baseline	101	52.5 (32.5)	99	52.9 (35.9)	200	52.7 (34.2)
BSI at week 5	92	38.4 (28.6)	95	36.3 (25.3)	187	37.4 (26.9)
BSI at week 8	88	35.0 (25.1)	93	39.0 (34.1)	181	37.1 (30.0)
WRAADDS emotional dysregulation at baseline	101	17.5 (5.7)	99	18.1 (5.6)	200	17.8 (5.7)
WRAADDS emotional dysregulation at week 5	92	13.6 (5.8)	95	14.3 (6.5)	187	14.0 (6.2)
WRAADDS emotional dysregulation at week 8	90	13.4 (6.1)	94	14.5 (7.0)	184	13.9 (6.6)
WCD at baseline	101	17.9 (7.7)	99	18.7 (7.8)	200	18.3 (7.7)
ARI-S at baseline	101	9.3 (3.5)	99	9.3 (3.7)	200	9.3 (3.6)
ARI-S at week 5	92	8.2 (3.7)	95	7.6 (4.2)	187	7.9 (3.9)
ARI-S at week 8	90	8.2 (4.1)	94	8.0 (4.5)	184	8.1 (4.3)
CORE-M at baseline	101	43.5 (13.9)	99	44.8 (15.3)	200	44.2 (14.6)
CORE-M at week 8	89	38.0 (12.3)	94	39.0 (13.4)	183	38.6 (12.8)
MVQ at baseline	101	33.2 (9.4)	99	34.6 (9.9)	200	33.9 (9.6)
MVQ at week 5	92	30.8 (11.2)	94	32.4 (10.9)	186	31.6 (11.0)
MVQ at week 8	90	30.6 (12.5)	94	33.1 (11.7)	184	31.9 (12.1)
CGI severity of illness at baseline	101	4.0 (1.0)	99	3.9 (1.1)	200	3.9 (1.0)
CGI severity of illness at week 5	90	3.6 (1.0)	94	3.6 (1.0)	184	3.6 (1.0)
CGI severity of illness at week 8	89	3.5 (1.1)	94	3.6 (1.0)	183	3.6 (1.1)
CGI therapeutic effects at week 5 (not recorded at baseline) [Range from 1 – Marked effects with no side effects, through 10 – minimal effect with side effects which don't significally interfere with function to 15 – worse with significant side effects]	84	10.0 (4.1)	94	10.9 (3.0)	178	10.5 (3.6)
CGI therapeutic effects at week 8 (not recorded at baseline)	86	10.1 (4.2)	93	10.9 (3.4)	179	10.5 (3.8)

Other non-continuous measures:

Education

At baseline 187 out of 200 people had some form of education scheduled. Only 7 people in the OROS-MPH arm and 6 people in placebo arm were not in any kind of education. The median number of sessions scheduled was 21 in the OROS-MPH arm and 25 in the placebo arm, and the median number of sessions attended was 15 and 19 respectively. The mean proportion of sessions attended in the 8 weeks prior to randomisation was 0.78 (s.d.=0.31) and 0.84 (s.d.=0.26) in the OROS-MPH and placebo arms respectively. However, reports from education staff about behaviour in education sessions were difficult to obtain, with only 83 MOAS-E and 67 BRC-E forms completed at baseline.

At week 8 this measure was not collected or missing for 9 participants (7 in OROS-MPH and 2 in placebo arm). The median number of sessions scheduled across the 8 weeks of the trial was 34 and 32 respectively. Of the sessions scheduled, the median number of sessions attended was 23 in the OROS-MPH Arm and 22 in the placebo arm, giving mean proportions attended of 0.80 (s.d. = 0.28) and 0.82 (s.d. = 0.26) respectively.

Due to the extreme lack of participants without any sessions scheduled, it was not possible to analyse education scheduled using logistic regression. As it was recorded as a count of sessions with noticeable skew, it was analysed as a negative binomial. The estimated incident rate ratio between OROS-MPH and the placebo arm was 0.98 (95% CI 0.84, 1.14, p = 0.78) which is a very small and non-significant decrease in sessions scheduled in the active arm (Table 6).

At baseline, the median Modified Overt Aggression Scale by education staff (MOAS-E) score was 0 in both trial arms with a maximum score of 12 and 10 in the OROS-MPH and placebo arms respectively. At week 8, median MOAS-E score was still 0 in both trial arms with a maximum score of 1 and 2 in OROS-MPH and placebo respectively. The Behaviour Report Card by education staff (BRC-E) median score was 18.6 and 17.5 at baseline and 17.5 and 18.0 in OROS-MPH and placebo arms respectively.

Table 6: Estimated odds ratios (ORs) or incidence rate ratios (IRRs) comparing secondary binary and count outcomes between trial arms at 8 weeks.					
Measure	**Description**	**OROS-MPH vs Placebo (ratios above 1 indicate an improvement under OROS-MPH)**			
		Estimated OR [ln(OR)]	**95% CI for OR [95% CI for ln(OR)]**	**Test (z)**	**p-value***
MOAS-P	Any act of aggression reported in the week prior to the week 8 timepoint (yes/no)	0.57 [-0.56]	0.28, 1.15 [-1.26, 0.14]	-1.56	0.12
Measure	**Description**	**Estimated IRR [ln(IRR)]**	**95% CI for IRR [95% CI ln(IRR)]**	**Test (z)**	**p-value***
BRC-P	Behavioural report score for the week prior to the week 8 timepoint	0.95 [-0.05]	0.85, 1.06 [-0.16, 0.06]	-0.98	0.33
Critical incidents	Number of critical incidents recorded across the 8 weeks of the trial	0.75 [-0.28]	[0.45,1.25] [-0.79, 0.23]	1.09	0.28
Education sessions scheduled	Number of any type of education session scheduled across the 8 weeks of the trial	0.98 [-0.02]	0.84, 1.14 [-0.17, 0.13]	-0.28	0.78

Behavioural reports from prison officers

Behaviour Report Card by prison staff (BRC-P) and Modified Overt Aggression Scale by prison staff (MOAS-P) are prison officer reports of behaviour completed at baseline. 50 out of 200 (25%) participants had the minimum score of 6 for BRC-P at baseline and 143 of 200 (71%) participants had a score of 0 for MOAS-P at baseline. This means that they had zero incidents of aggression reported in the week before baseline).

For BRC-P, the median score at baseline was 8 in both arms. At week 8, the median BRC-P score was 9 for the OROS-MPH arm and 8 for the placebo arm. The BRC-P was formally analysed using a negative binomial model, which estimated the incident rate ratio between the OROS-MPH arm and the placebo arm as 0.95 (95% CI 0.85 to 1.06, p=0.33) (Table 6).

The median MOAS-P score at baseline was 0 in both arms, with 75 (74.3%) of the OROS-MPH and 68 (68.7%) of the placebo arm having zero incidents. At week 8, the median MOAS-P score was still 0 in both arms, with the majority (123 of 179) of participants having a score of 0, with a slightly larger percentage in the placebo arm (68.7%) in the placebo arm compared to the OROS-MPH arm (64.8%). Due to the small size of the subpopulation with recorded numbers of events, this outcome variable was dichotomised (1 = Yes, any aggressive events seen, 0 = No, no aggressive events) and analysed using logistic regression. At 8 weeks the odds ratio between trial arms of any aggressive events as measured using MOAS-P was 0.57 (95% CI 0.28 to 1.15, p=0.12) implying a non-significant improvement in the placebo arm (Table 5). This surprisingly low odds ratio estimate is due to adjusting for the baseline level of events in the analysis model, which appears to be the driver of the aggressive events (MOAS-P) at week 8.)

Critical incidents were prison records of negative behaviours noted in the eight weeks immediately before baseline and before the final time point of 8 weeks. At baseline, this outcome was observed in all 200 participants. 125 (62.5%) of participants had no negative behaviours reported. The number of reports at baseline of negative behaviours ranged from 0 to 10, with a median of 0. Trial arms were very similar at baseline with a median of 0 reported for both the OROS-MPH and placebo. By week 8, the trial arms were still very similar with a median of 0 for both arms. The estimated incident rate ratio in critical incidents between the OROS-MPH arm and placebo at 8 weeks was 0.75 (95% CI -0.45 to 1.25, p=0.28) (Table 6).

20.3 Safety results

The numbers of adverse events (AE) within a category are reported by person and not by number of events. Out of 336 AEs reported, 184 were in the OROS-MPH arm and 152 in the placebo arm Only 1 serious adverse event was reported and categorised as an Important Medical Event (IME) which was not considered related to the trial medication.

The numbers of participants reporting adverse events were broadly similar in the two trial arms with the exception of the High-Level Group term (HLGT) categories for ‘Appetite and general nutritional disorders’ which largely reflected appetite loss, and ‘depression’. For appetite and nutritional disorders 13 individuals in the OROS-MPH arm reported problems compared to 2 in the placebo arm. For depressive symptoms, 12 in the OROS-MPH reported problems compared to 4 in the placebo arm.

Expected adverse effects were also enquired after systematically at each visit using the medication Adverse Event Scale (AES). Each Item on this scale is rated 0=not at all; 2=sometimes; 3=often; 4=all the time. The scale was dichotomised 0 (not at all or sometimes) and 1 (often or all the time) reflecting the absence or presence of the adverse event respectively. The numbers and % of participants with each individual symptom are reported across the entire post-randomisation period, between randomisation and week 8. This shows that the most common adverse effects in the post-randomisation period related to the use of OROS-MPH compared to placebo are headache (17.8% versus 10.1%), dry mouth (19.8% versus 10.1%), sweating (19.8% versus 8.1%), and appetite

reduction (34.7% versus 19.2%) (Table 7).

Finally, blood pressure and heart rate were recorded at baseline, at each titration point during weeks 1 to 5 and at week 8. Body Mass Index (weight/height) was recorded at baseline, week 5 and week 8. The values overall and by trial arm are shown in Table 8. There was no noticeable difference between trial arms at any point in the trial.

Table 7: Adverse Events scale across the trial period: numbers and percentage with the symptom

Adverse Events Scale (AES) items	OROS-MPH (N=101)	Placebo (N=99)	Overall (N=200)
	N (%)	N (%)	N (%)
Headache	18 (17.8)	10 (10.1)	28 (14.0)
Dryness of the skin	14 (13.9)	18 (18.2)	32 (16.0)
Dryness of the eyes	2 (2.0)	4 (4.0)	6 (3.0)
Dryness of the mouth	20 (19.8)	10 (10.1)	30 (15.0)
Thirst	22 (21.8)	18 (18.2)	40 (20.0)
Sore throat	8 (7.9)	6 (6.1)	14 (7.0)
Dizziness	6 (5.9)	3 (3.0)	9 (4.5)
Nausea	8 (7.9)	3 (3.0)	11 (5.5)
Stomach aches	7 (6.9)	3 (3.0)	10 (5.0)
Vomiting	1 (1.0)	1 (1.0)	2 (1.0)
Sweating	20 (19.8)	8 (8.1)	28 (14.0)
Appetite reduction	35 (34.7)	19 (19.2)	54 (27.0)
Diarrhoea	6 (5.9)	1 (1.0)	7 (3.5)
Frequent urination	14 (13.9)	11 (11.1)	25 (12.5)
Tics	3 (3.0)	6 (6.1)	9 (4.5)
Sleep difficulties	56 (55.5)	50 (50.5)	106 (53.0)
Mood instability	40 (39.6)	46 (46.5)	86 (43.0)
Irritability	49 (48.5)	49 (49.5)	98 (49.0)
Agitation/Excitability	42 (41.6)	43 (43.4)	85 (42.5)
Sadness	17 (16.8)	19 (19.2)	36 (18.0)
Heart palpitations	6 (5.9)	3 (3.0)	9 (4.5
Sexual dysfunction	2 (2.0)	0 (0.0)	2 (1.0)

Table 8: Vital signs and BMI							
Vital signs		**OROS-MPH**		**Placebo**		**Overall**	
		N	**Mean (sd)**	**N**	**Mean (sd)**	**N**	**Mean (sd)**
BMI	Baseline	101	23.7 (3.4)	99	23.7 (3.7)	200	23.7 (3.5)
	Week 5	88	23.4 (3.5)	88	24.2 (3.8)	176	23.8 (3.7)
	Week 8	86	23.6 (3.4)	87	24.2 (3.8)	173	23.9 (3.6)
Blood pressure systolic	Baseline	101	123.6 (11.2)	99	124.1 (11.9)	199	123.9 (11.5)
Blood pressure diastolic		101	68.2 (9.9)	99	68.1 (9.5)	199	68.2 (9.7)
Heart rate		101	70.9 (10.7)	99	70.0 (11.8	199	70.4 (11.2)
Blood pressure systolic	Week 1	98	124.1 (10.3)	98	125.2 (11.9)	196	124.7 (11.0)
Blood pressure diastolic		98	71.8 (9.7)	98	70.8 (10.1)	196	71.3 (9.9)
Heart rate		98	76.5 (11.4)	98	72.1 (10.4)	196	74.3 (11.1)
Blood pressure systolic	Week 2	92	124.5 (9.4)	98	124.6 (12.1)	190	124.5 (10.8)
Blood pressure diastolic		92	70.9 (9.1)	98	70.9 (10.0)	190	70.9 (8.5)
Heart rate		92	75.8 (11.7)	98	74.4 (13.6)	190	75.1 (12.7)
Blood pressure systolic	Week 3	93	124.1 (12.3)	95	122.5 (10.2)	188	123.3 (11.3)
Blood pressure diastolic		93	72.0 (10.0)	95	69.8 (9.4)	188	70.9 (9.7)

Table 8: Vital signs and BMI

Vital signs		OROS-MPH		Placebo		Overall	
		N	Mean (sd)	N	Mean (sd)	N	Mean (sd)
Heart rate		93	75.7 (12.1)	95	71.5 (10.8)	188	73.6 (11.6)
Blood pressure systolic	Week 4	92	124.1 (13.3)	96	125.2 (14.6)	188	124.6 (13.9)
Blood pressure diastolic		92	72.5 (11.2)	96	69.6 (9.0)	188	71.0 (10.2)
Heart rate		92	75.9 (12.7)	96	73.5 (11.5)	188	74.7 (12.1)
Blood pressure systolic	Week 5	91	124.4 (11.5)	93	124.7 (12.0)	184	124.6 (11.8)
Blood pressure diastolic		91	70.7 (10.3)	93	69.9 (10.2)	184	70.3 (10.2)
Heart rate		91	75.0 (12.5)	93	72.9 (10.6)	184	73.9 (11.6)
Blood pressure systolic	Week 8	89	125.0 (12.5)	93	125.5 (14.0)	182	125.2 (13.2)
Blood pressure diastolic		89	70.9 (11.6)	93	70.6 (9.3)	182	70.8 (10.4)
Heart rate		89	74.8 (11.2)	93	71.9 (11.4)	182	73.3 (11.3)

Table: Listing of Adverse Events for all patients *(state which version of the MedDRA dictionary or other medical dictionary was used to code the events)*

MedDRA March 2020

Table 9: List of all AEs
(Code clarification: 777- Not applicable, 888- Not done, 999-Unknown)

Trial arm: 1= Concerta XL 18 mg, 2= Placebo	ID	Description	SOC	HLGT	Start date	Ongoing	Stop date	Drug related	Drug acction	Outcome	Intensity
02	17	Hayfever	SOC Immune system disorders	Allergic conditions	16/06/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	18	Hayfever	SOC Immune system disorders	Allergic conditions	11/06/2018	0. No	11/06/2018	0. No	0. None	1. Recovered	1. Mild
02	18	Hayfever	SOC Immune system disorders	Allergic conditions	17/06/2018	0. No	17/06/2018	0. No	0. None	1. Recovered	1. Mild
02	21	Hayfever	SOC Immune system disorders	Allergic conditions	15/05/2017	0. No	15/05/2017	0. No	0. None	1. Recovered	1. Mild
02	21	Hayfever	SOC Immune system disorders	Allergic conditions	28/05/2017	0. No	28/05/2017	0. No	0. None	1. Recovered	1. Mild

02	21	Hayfever	SOC Immune system disorders	Allergic conditions	02/06/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	34	Hayfever	SOC Immune system disorders	Allergic conditions	12/06/2017	0. No	21/07/2017	0. No	0. None	1. Recovered	1. Mild
02	44	Hayfever	SOC Immune system disorders	Allergic conditions	08/07/2017	0. No	13/08/2017	0. No	0. None	1. Recovered	1. Mild
02	75	Hayfever	SOC Immune system disorders	Allergic conditions	23/04/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	76	Hayfever	SOC Immune system disorders	Allergic conditions	20/05/2018	0. No	20/05/2018	0. No	0. None	1. Recovered	1. Mild
02	76	Hayfever	SOC Immune system disorders	Allergic conditions	27/05/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	80	Hayfever	SOC Immune system disorders	Allergic conditions	26/04/2018	0. No	26/05/2018	0. No	0. None	1. Recovered	1. Mild
01	83	Hayfever	SOC Immune system disorders	Allergic conditions	10/06/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	84	Hayfever	SOC Immune system disorders	Allergic conditions	08/08/2018	0. No	08/08/2018	0. No	0. None	3. Continuing	1. Mild

01	93	Hayfever	SOC Immune system disorders	Allergic conditions	05/06/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	118	Hayfever	SOC Immune system disorders	Allergic conditions	15/02/2017	0. No	17/02/2017	0. No	0. None	1. Recovered	1. Mild
02	169	Hayfever	SOC Immune system disorders	Allergic conditions	02/07/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	176	Hayfever	SOC Immune system disorders	Allergic conditions	06/07/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	999.
01	1	Loss of appetite	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	03/11/2016	0. No	24/11/2016	1. Yes	0. None	1. Recovered	1. Mild
01	10	Weight Loss	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	31/10/2016	1. Yes (at end of study)		1. Yes	0. None	3. Continuing	1. Mild
02	11	Minor loss of appetite	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	10/01/2017	0. No	18/01/2017	999.	0. None	1. Recovered	1. Mild
01	27	Weight Loss	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	14/03/2017	1. Yes (at end of study)		1. Yes	0. None	3. Continuing	1. Mild

01	28	Loss of appetite	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	18/04/2017	1. Yes (at end of study)		1. Yes	0. None	3. Continuing	1. Mild
01	30	Reduced Appetite	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	03/05/2017	1. Yes (at end of study)		1. Yes	0. None	3. Continuing	1. Mild
01	43	Weight Loss	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	23/08/2017	1. Yes (at end of study)		999.	0. None	3. Continuing	1. Mild
01	48	Appetite/Weight Loss	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	09/10/2017	1. Yes (at end of study)		1. Yes	0. None	3. Continuing	1. Mild
02	52	Weight gain	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	24/10/2017	1. Yes (at end of study)		999.	0. None	3. Continuing	1. Mild
01	53	Weight loss	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	17/09/2017	1. Yes (at end of study)		999.	0. None	3. Continuing	1. Mild
01	57	Appetite reduction	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	13/12/2017	1. Yes (at end of study)		999.	0. None	3. Continuing	1. Mild
01	59	Appetite loss	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	28/12/2017	1. Yes (at end of study)		999.	0. None	3. Continuing	1. Mild

01	89	Appetite Reduction	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	10/09/2018	0. No	10/09/2018	1. Yes	0. None	1. Recovered	1. Mild
01	89	Weight Loss	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	10/09/2018	0. No	10/09/2018	1. Yes	0. None	1. Recovered	1. Mild
01	103	Appetite Loss	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	05/12/2018	0. No	01/01/1900	1. Yes	1. Dose reduced	1. Recovered	2. Moderate
01	111	Poor appetite	SOC Metabolism and nutrition disorder	Appetite and general nutritional disorders	28/01/2019	0. No	03/02/2019	1. Yes	1. Dose reduced	1. Recovered	2. Moderate
02	71	Lump in right testicle	SOC Neoplasms benign, malignant and unspecified	Benign neoplasm	13/04/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	102	Lump on back of head	SOC Neoplasms benign, malignant and unspecified	Benign neoplasm	13/12/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	111	Testicular lump	SOC Neoplasms benign, malignant and unspecified	Benign neoplasm	29/11/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	10	Abnormal PLT and Hb	SOC Blood and lymphatic system disorders	Blood and lymphatic system disorders	31/10/2016	0. No	31/10/2016	0. No	0. None	1. Recovered	1. Mild

02	13	Head Bruising	SOC Injury, poisoning and procedural complications	Bone and joint injuries	08/06/2017	0. No	08/06/2017	0. No	0. None	1. Recovered	1. Mild
02	13	Wound on knuckles	SOC Injury, poisoning and procedural complications	Bone and joint injuries	08/06/2017	0. No	08/06/2017	0. No	0. None	1. Recovered	1. Mild
02	55	Pain in arm (due to broken arm)	SOC Injury, poisoning and procedural complications	Bone and joint injuries	05/12/2017	0. No	06/12/2017	0. No	0. None	1. Recovered	1. Mild
02	55	Pain in arm (due to broken arm)	SOC Injury, poisoning and procedural complications	Bone and joint injuries	15/12/2017	0. No	15/12/2017	0. No	0. None	1. Recovered	1. Mild
02	55	Pain in arm (due to broken arm)	SOC Injury, poisoning and procedural complications	Bone and joint injuries	14/01/2018	0. No	14/01/2018	0. No	0. None	1. Recovered	1. Mild
02	55	Pain in elbow (due to broken arm)	SOC Injury, poisoning and procedural complications	Bone and joint injuries	25/12/2017	0. No	25/12/2017	0. No	0. None	1. Recovered	1. Mild
02	71	Painful ankle, fell down stairs	SOC Injury, poisoning and procedural complications	Bone and joint injuries	10/03/2018	0. No	10/03/2018	0. No	0. None	1. Recovered	1. Mild
01	137	Bruised foot	SOC Injury, poisoning and procedural complications	Bone and joint injuries	23/09/2017	1. Yes (at end of study)		0. No	0. None	1. Recovered	1. Mild

02	153	Sore big toe (hurt playing football)	SOC Injury, poisoning and procedural complications	Bone and joint injuries	21/12/2017	0. No	28/12/2017	0. No	0. None	1. Recovered	1. Mild
02	159	Sore Ankle(Previous injury)	SOC Injury, poisoning and procedural complications	Bone and joint injuries	08/02/2018	0. No	08/02/2018	0. No	0. None	1. Recovered	1. Mild
01	28	Heart palpitations	SOC Cardiac disorders	Cardiac signs and symptoms	18/04/2017	1. Yes (at end of study)		999.	0. None	3. Continuing	1. Mild
01	62	Racing heart	SOC Cardiac disorders	Cardiac signs and symptoms	23/01/2018	0. No	05/02/2018	999.	1. Dose reduced	1. Recovered	2. Moderate
02	106	Episode of heart palpitations	SOC Cardiac disorders	Cardiac signs and symptoms	03/12/2018	0. No	03/12/2018	999.	0. None	1. Recovered	1. Mild
01	157	Heart Palpitations	SOC Cardiac disorders	Cardiac signs and symptoms	20/02/2018	0. No	20/02/2018	999.	0. None	1. Recovered	1. Mild
01	176	Heart Palpitations, ECG normal	SOC Cardiac disorders	Cardiac signs and symptoms	01/08/2018	0. No	07/08/2018	999.	0. None	1. Recovered	999.
01	10	Sickness due to drug use	SOC Psychiatric disorder	Conditions associated with drug abuse	25/12/2016	0. No	25/12/2016	0. No	0. None	1. Recovered	1. Mild
01	10	Under the influence of legal high	SOC Psychiatric disorder	Conditions associated with drug abuse	25/12/2016	0. No	25/12/2016	0. No	0. None	1. Recovered	1. Mild

02	45	Suspected spice intake, nurses reported slurred speech and appeared tipsy	SOC Psychiatric disorder	Conditions associated with drug abuse	23/08/2017	0. No	23/08/2017	0. No	0. None	1. Recovered	1. Mild
01	87	Suspected spice use	SOC Psychiatric disorder	Conditions associated with drug abuse	25/06/2018	0. No	26/06/2018	0. No	2. Temporarily interrupted	1. Recovered	1. Mild
02	131	Cannabis use	SOC Psychiatric disorder	Conditions associated with drug abuse	05/2017	999.		777.	0. None	777.	777.
02	136	Regular cannabis use prior to and throughout trial see file note 8	SOC Psychiatric disorder	Conditions associated with drug abuse	01/01/1900	1. Yes (at end of study)		777.	0. None	777.	777.
02	161	Withdrawals from Methadone	SOC Psychiatric disorder	Conditions associated with drug abuse	01/04/2018	0. No	06/04/2018	0. No	0. None	1. Recovered	1. Mild
02	180	Spice use throughout trial reported week 8	SOC Psychiatric disorder	Conditions associated with drug abuse	01/01/1900	1. Yes (at end of study)		0. No	0. None	777.	777.
02	182	Reported spice use at week 8 appointment, placed on substance misuse observations	SOC Psychiatric disorder	Conditions associated with drug abuse	02/04/2019	0. No	03/04/2019	0. No	0. None	1. Recovered	999.

02	182	Reported spice use at weekly appointment, reviewed and restarted 15.2.19	SOC Psychiatric disorder	Conditions associated with drug abuse	12/02/2019	0. No	15/02/2019	0. No	2. Temporarily interrupted	1. Recovered	999.
02	186	Placed on substance misuse observations, spice use	SOC Psychiatric disorder	Conditions associated with drug abuse	17/12/2018	0. No	18/12/2018	0. No	777.	1. Recovered	2. Moderate
01	191	Put on substance misuse observations, spice use	SOC Psychiatric disorder	Conditions associated with drug abuse	12/02/2019	0. No	13/02/2019	0. No	2. Temporarily interrupted	1. Recovered	999.
02	193	Dihydrocodeine and Co-Codamol use reported at week 8	SOC Psychiatric disorder	Conditions associated with drug abuse	10/04/2019	0. No	24/04/2019	0. No	0. None	1. Recovered	777.
02	193	Spice Use	SOC Psychiatric disorder	Conditions associated with drug abuse	05/04/2019	0. No	06/04/2019	0. No	0. None	1. Recovered	777.
02	195	Cannabis use	SOC Psychiatric disorder	Conditions associated with drug abuse	21/12/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	777.
02	195	Spice use, placed on substance misuse observations	SOC Psychiatric disorder	Conditions associated with drug abuse	05/03/2019	0. No	06/03/2019	0. No	3. Permanently interrupted	1. Recovered	999.

02	195	Spice use, placed on substance misuse observations	SOC Psychiatric disorder	Conditions associated with drug abuse	19/03/2019	0. No	20/03/2019	0. No	3. Permanently interrupted	1. Recovered	999.
01	199	Cannabis Use	SOC Psychiatric disorder	Conditions associated with drug abuse	03/05/2019	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	199	Spice use	SOC Psychiatric disorder	Conditions associated with drug abuse	15/05/2019	0. No	17/05/2019	0. No	3. Permanently interrupted	1. Recovered	1. Mild
01	199	Spice Use	SOC Psychiatric disorder	Conditions associated with drug abuse	31/05/2019	0. No	02/06/2019	0. No	777.	1. Recovered	1. Mild
01	1	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	05/12/2016	0. No	05/12/2016	0. No	0. None	1. Recovered	1. Mild
02	2	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	07/11/2016	0. No	07/11/2016	0. No	0. None	1. Recovered	1. Mild
01	5	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	07/11/2016	0. No	07/11/2016	0. No	0. None	1. Recovered	1. Mild
01	7	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	22/11/2016	0. No	22/11/2016	0. No	0. None	1. Recovered	1. Mild
02	9	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	01/11/2016	0. No	01/11/2016	0. No	0. None	1. Recovered	1. Mild

01	10	C/O Tooth Pain	SOC Gastrointestinal disorders	Dental and gum disorders	21/12/2016	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	10	Swollen Gums	SOC Gastrointestinal disorders	Dental and gum disorders	21/11/2016	0. No	21/11/2016	0. No	0. None	1. Recovered	1. Mild
01	10	Tooth Abscess	SOC Gastrointestinal disorders	Dental and gum disorders	23/11/2016	0. No	30/11/2016	0. No	0. None	1. Recovered	2. Moderate
01	10	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	22/11/2016	0. No	22/11/2016	0. No	0. None	1. Recovered	1. Mild
01	10	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	09/12/2016	0. No	09/12/2016	0. No	0. None	1. Recovered	1. Mild
01	10	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	13/12/2016	0. No	13/12/2016	0. No	0. None	1. Recovered	1. Mild
02	16	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	20/02/2017	0. No	20/02/2017	0. No	0. None	1. Recovered	1. Mild
02	16	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	20/03/2017	0. No	20/03/2017	0. No	0. None	1. Recovered	1. Mild
02	17	Bleeding Gums	SOC Gastrointestinal disorders	Dental and gum disorders	19/05/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	18	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	01/06/2018	0. No	01/06/2018	0. No	0. None	1. Recovered	1. Mild

02	21	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	27/04/2016	0. No	27/04/2017	0. No	0. None	1. Recovered	1. Mild
01	22	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	01/03/2017	0. No	01/03/2017	0. No	0. None	1. Recovered	1. Mild
01	22	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	05/03/2017	0. No	05/03/2017	0. No	0. None	1. Recovered	1. Mild
01	22	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	17/03/2017	0. No	17/03/2017	0. No	0. None	1. Recovered	1. Mild
01	22	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	22/03/2017	0. No	25/04/2017	0. No	0. None	1. Recovered	1. Mild
02	26	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	17/01/2017	0. No	17/01/2017	0. No	0. None	1. Recovered	1. Mild
02	26	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	13/02/2017	0. No	13/02/2017	0. No	0. None	1. Recovered	1. Mild
02	26	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	19/03/2017	0. No	19/03/2017	0. No	0. None	1. Recovered	1. Mild
01	27	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	05/02/2017	0. No	05/02/2017	0. No	0. None	1. Recovered	1. Mild
01	30	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	19/04/2017	0. No	19/04/2017	0. No	0. None	1. Recovered	1. Mild
01	30	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	22/05/2017	0. No	22/05/2017	0. No	0. None	1. Recovered	1. Mild

02	33	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	21/08/2017	0. No	21/08/2017	0. No	0. None	1. Recovered	1. Mild
01	34	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	10/07/2017	0. No	10/07/2017	0. No	0. None	1. Recovered	1. Mild
01	36	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	13/06/2017	0. No	13/06/2017	0. No	0. None	1. Recovered	1. Mild
01	36	Tooth Pain	SOC Gastrointestinal disorders	Dental and gum disorders	19/06/2017	0. No	19/06/2017	0. No	0. None	1. Recovered	1. Mild
01	43	Tooth Pain	SOC Gastrointestinal disorders	Dental and gum disorders	14/08/2017	0. No	14/08/2017	0. No	0. None	1. Recovered	1. Mild
01	43	Tooth Pain	SOC Gastrointestinal disorders	Dental and gum disorders	26/08/2017	0. No	29/08/2017	0. No	0. None	1. Recovered	1. Mild
01	64	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	06/04/2018	0. No	06/04/2018	0. No	0. None	1. Recovered	1. Mild
01	65	Tooth Pain	SOC Gastrointestinal disorders	Dental and gum disorders	22/01/2018	0. No	22/01/2018	0. No	0. None	1. Recovered	1. Mild
02	73	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	04/04/2018	0. No	12/04/2018	0. No	0. None	1. Recovered	1. Mild
01	74	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	12/02/2018	0. No	12/02/2018	0. No	0. None	1. Recovered	1. Mild
02	81	Tooth decay	SOC Gastrointestinal disorders	Dental and gum disorders	01/01/1900	1. Yes (at end		0. No	0. None	3. Continuing	1. Mild

						of study)					
02	81	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	20/05/2018	0. No	21/05/2018	0. No	0. None	1. Recovered	1. Mild
01	83	Hole in tooth	SOC Gastrointestinal disorders	Dental and gum disorders	01/01/1900	0. No	18/06/2018	0. No	0. None	1. Recovered	1. Mild
01	84	Dental Treatment	SOC Gastrointestinal disorders	Dental and gum disorders	10/09/2018	0. No	10/09/2018	0. No	0. None	1. Recovered	1. Mild
01	84	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	22/07/2018	0. No	22/07/2018	0. No	0. None	1. Recovered	1. Mild
01	85	Tooth Pain	SOC Gastrointestinal disorders	Dental and gum disorders	04/09/2018	0. No	04/09/2018	0. No	0. None	1. Recovered	1. Mild
01	86	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	08/08/2018	0. No	08/08/2018	0. No	0. None	1. Recovered	1. Mild
02	88	Dental treatment for lost filling	SOC Gastrointestinal disorders	Dental and gum disorders	03/07/2018	0. No	03/07/2018	0. No	0. None	1. Recovered	1. Mild
01	96	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	17/10/2018	0. No	17/10/2018	0. No	0. None	1. Recovered	1. Mild
02	98	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	10/11/2018	0. No	12/11/2018	0. No	0. None	1. Recovered	1. Mild
01	104	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	12/11/2018	0. No	12/11/2018	0. No	0. None	1. Recovered	1. Mild

01	111	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	09/01/2019	0. No	22/01/2019	0. No	0. None	1. Recovered	1. Mild
01	111	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	02/02/2019	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	112	Tooth pain	SOC Gastrointestinal disorders	Dental and gum disorders	22/01/2019	0. No	22/01/2019	0. No	0. None	1. Recovered	1. Mild
02	114	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	28/02/2019	0. No	28/02/2019	0. No	0. None	1. Recovered	1. Mild
02	114	Toothache	SOC Gastrointestinal disorders	Dental and gum disorders	07/03/2019	0. No	07/03/2019	0. No	0. None	1. Recovered	1. Mild
01	120	Gum Abcess	SOC Gastrointestinal disorders	Dental and gum disorders	20/01/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	2. Moderate
01	133	Dental Pain	SOC Gastrointestinal disorders	Dental and gum disorders	16/05/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	999.
02	184	Dental Pain	SOC Gastrointestinal disorders	Dental and gum disorders	06/02/2019	0. No	11/02/2019	0. No	0. None	1. Recovered	2. Moderate
01	1	Mood instability	SOC Psychiatric disorder	Depressed mood disorders and disturbances	14/11/2016	0. No	23/11/2016	1. Yes	3. Permanently interrupted	1. Recovered	3. Severe

01	6	Suicide Attempt	SOC Psychiatric disorder	Depressed mood disorders and disturbances	01/03/2017	0. No	01/03/2017	0. No	0. None	1. Recovered	1. Mild
01	19	Feeling low and depressed	SOC Psychiatric disorder	Depressed mood disorders and disturbances	07/02/2017	0. No	07/02/2017	1. Yes	1. Dose reduced	1. Recovered	1. Mild
01	27	Self Harm	SOC Psychiatric disorder	Depressed mood disorders and disturbances	24/02/2017	0. No	24/02/2017	0. No	0. None	1. Recovered	1. Mild
01	68	Mood instability (initiated a fight)	SOC Psychiatric disorder	Depressed mood disorders and disturbances	31/01/2018	0. No	31/01/2018	999.	0. None	3. Continuing	1. Mild
01	74	Low mood	SOC Psychiatric disorder	Depressed mood disorders and disturbances	19/02/2018	0. No	01/01/1900	999.	0. None	1. Recovered	1. Mild
01	87	Self harm to left wrist	SOC Psychiatric disorder	Depressed mood disorders and disturbances	09/07/2018	0. No	09/07/2018	0. No	0. None	1. Recovered	1. Mild
01	109	Low mood	SOC Psychiatric disorder	Depressed mood disorders and disturbances	10/12/2018	0. No	24/12/2018	1. Yes	3. Permanently interrupted	1. Recovered	1. Mild
02	112	Low Mood	SOC Psychiatric disorder	Depressed mood disorders and disturbances	28/01/2019	0. No	11/02/2019	1. Yes	2. Temporarily	1. Recovered	2. Moderate

									interrupted		
02	112	Mood Instability	SOC Psychiatric disorder	Depressed mood disorders and disturbances	28/01/2019	0. No	19/02/2019	1. Yes	2. Temporarily interrupted	1. Recovered	2. Moderate
01	115	Low mood	SOC Psychiatric disorder	Depressed mood disorders and disturbances	25/02/2019	0. No	01/04/2019	999.	0. None	1. Recovered	1. Mild
01	121	Hypomania	SOC Psychiatric disorder	Depressed mood disorders and disturbances	09/02/2017	2. Yes (but not at study end yet)		1. Yes	3. Permanently interrupted	3. Continuing	1. Mild
02	148	Placed on Talk to Me observations	SOC Psychiatric disorder	Depressed mood disorders and disturbances	09/11/2017	0. No	21/11/2017	0. No	0. None	1. Recovered	1. Mild
02	148	Puncture wound in arm, self harmed with pen	SOC Psychiatric disorder	Depressed mood disorders and disturbances	10/11/2017	0. No	11/11/2017	0. No	0. None	1. Recovered	1. Mild
02	158	Poor sleep and low mood	SOC Psychiatric disorder	Depressed mood disorders and disturbances	19/03/2018	0. No	19/03/2018	0. No	0. None	1. Recovered	1. Mild
02	161	Poor sleep and low mood	SOC Psychiatric disorder	Depressed mood disorders and disturbances	16/03/2018	1. Yes (at end of study)		999.	0. None	3. Continuing	1. Mild

01	183	Placed on talk to me observations	SOC Psychiatric disorder	Depressed mood disorders and disturbances	10/09/2018	0. No	11/09/2018	0. No	0. None	1. Recovered	999.
01	183	Self-harm, superficial cuts	SOC Psychiatric disorder	Depressed mood disorders and disturbances	12/09/2018	0. No	19/09/2018	0. No	0. None	1. Recovered	999.
01	192	Placed on talk to me observations	SOC Psychiatric disorder	Depressed mood disorders and disturbances	30/11/2018	0. No	06/12/2018	0. No	0. None	1. Recovered	1. Mild
01	12	Dizziness	SOC Nervous system disorders	Dizziness	21/11/2016	0. No	21/11/2016	1. Yes	3. Permanently interrupted	1. Recovered	1. Mild
01	28	Dizziness	SOC Nervous system disorders	Dizziness	18/04/2017	1. Yes (at end of study)		999.	0. None	3. Continuing	1. Mild
01	109	Dizzy	SOC Nervous system disorders	Dizziness	10/12/2018	0. No	24/12/2018	1. Yes	3. Permanently interrupted	1. Recovered	1. Mild
01	117	Dizziness	SOC Nervous system disorders	Dizziness	04/01/2017	0. No	04/01/2017	1. Yes	0. None	1. Recovered	1. Mild
01	120	Dizziness	SOC Nervous system disorders	Dizziness	18/01/2017	0. No	20/01/2017	1. Yes	3. Permanently	1. Recovered	2. Moderate

									interrupted		
01	121	Chest pain, dizziness, blurred vision in one eye	SOC Nervous system disorders	Dizziness	01/01/1900	0. No	01/01/1900	0. No	0. None	1. Recovered	1. Mild
02	13	Raised T4	SOC Endocrine	Endocrine	27/06/2017	0. No	27/06/2017	0. No	0. None	1. Recovered	1. Mild
02	15	Skin Rash/Spots	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	22/03/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	17	Dry Scalp	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	19/05/2017	0. No	16/06/2017	0. No	0. None	1. Recovered	1. Mild
02	17	Itchy Skin	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	19/05/2017	0. No	16/06/2017	0. No	0. None	1. Recovered	1. Mild
02	20	Excessively sweating feet	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	01/10/2018	0. No	01/10/2018	0. No	0. None	1. Recovered	1. Mild
02	20	Genital Warts	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	13/09/2018	0. No	20/09/2018	0. No	0. None	1. Recovered	1. Mild
02	29	Rash on biceps	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	19/07/2017	0. No	19/07/2017	0. No	0. None	1. Recovered	1. Mild
02	33	Dandruff/Facial Spots	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	25/08/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild

02	33	Dry Skin/Scalp	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	16/08/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	36	Dry Palms	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	23/06/2017	0. No	23/06/2017	999.	0. None	1. Recovered	1. Mild
02	56	Skin lesions	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	01/01/1900	0. No	01/11/2017	0. No	0. None	1. Recovered	2. Moderate
01	58	Warts on palms of hands	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	01/01/1900	0. No	08/12/2017	0. No	0. None	1. Recovered	1. Mild
02	63	Athletes foot/veruca	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	26/01/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	73	Ringworm in groin	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	15/03/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	83	Itchy skin after shower/red rash	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	19/06/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	94	Ingrown toenail on right foot	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	02/09/2018	0. No	02/09/2018	0. No	0. None	3. Continuing	1. Mild
02	110	Spots on head	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	14/12/2018	0. No	16/01/2019	0. No	0. None	1. Recovered	1. Mild

01	111	Dry Skin	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	28/01/2019	0. No	03/02/2019	1. Yes	1. Dose reduced	1. Recovered	1. Mild
02	114	Spots on penis	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	19/02/2019	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	118	Facial Acne	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	03/02/2017	999.		0. No	0. None	999.	999.
01	121	Rash	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	01/01/1900	999.		999.	0. None	999.	999.
01	122	Athlete's foot	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	24/02/2017	0. No	11/03/2017	0. No	0. None	1. Recovered	1. Mild
01	122	Eczematous rash L ankle	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	01/01/1900	0. No	11/03/2017	0. No	0. None	1. Recovered	1. Mild
01	122	Oedema L ankle	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	01/01/1900	0. No	11/03/2017	0. No	0. None	1. Recovered	1. Mild
02	123	Psoriasis	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	01/01/1900	1. Yes (at end of study)		0. No	0. None	3. Continuing	999.
02	124	Acne	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	01/01/1900	1. Yes (at end of study)		0. No	0. None	3. Continuing	999.
02	124	Rash on hands (pompholyx)	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	22/05/2017	999.		0. No	0. None	999.	999.

02	125	Dry skin on face	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	28/03/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	130	Spots on arm	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	07/06/2017	1. Yes (at end of study)		0. No	0. None	1. Recovered	1. Mild
02	131	Acne	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	20/04/2017	999.		0. No	0. None	999.	1. Mild
02	132	Psoriasis	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	01/01/1900	1. Yes (at end of study)		0. No	0. None	3. Continuing	2. Moderate
01	135	Dry Skin	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	22/06/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	135	Foot pain / Athlete's foot	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	04/07/2017	999.		0. No	0. None	1. Recovered	1. Mild
01	138	Acne on back	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	07/06/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	138	Dry skin on hands	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	07/06/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	139	Dry Skin (face/neck)	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	26/07/2017	0. No	09/08/2017	0. No	3. Permanently	1. Recovered	1. Mild

									interrupted		
02	140	Acne	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	02/08/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	2. Moderate
02	153	Dry skin on upper arms, upper back	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	10/12/2017	0. No	23/01/2018	999.	1. Dose reduced	1. Recovered	1. Mild
02	158	Spot on side of nose (saw nurse)	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	16/01/2018	0. No	16/01/2018	0. No	0. None	1. Recovered	1. Mild
02	161	dry skin + spots on shins	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	14/03/2018	0. No	16/03/2018	999.	0. None	1. Recovered	1. Mild
01	164	Psoriasis/eczema on back of head	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	12/03/2018	1. Yes (at end of study)		0. No	0. None	999.	1. Mild
02	168	Small area of red skin, size of 5p	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	27/07/2018	0. No	31/07/2018	999.	0. None	1. Recovered	1. Mild
01	171	Dry Skin on face	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	26/06/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	176	Ingrown toenails	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	999.
01	192	Urticaria type rash to trunk	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	02/11/2018	0. No	15/11/2018	0. No	0. None	1. Recovered	999.

01	197	Eczema	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	15/03/2019	1. Yes (at end of study)		0. No	0. None	3. Continuing	999.
01	200	Acne	SOC Skin and subcutaneaous disorder	Epidermal and dermal conditions	2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	154	Ear bleeding (wake up with dried blood in ear)	SOC Ear and labyrinth disorders	External ear disorder	24/01/2018	0. No	24/01/2018	999.	0. None	1. Recovered	1. Mild
01	162	Ear Wax/Dullness of hearing	SOC Ear and labyrinth disorders	External ear disorder	13/04/2018	1. Yes (at end of study)		999.	0. None	3. Continuing	1. Mild
01	197	Sore ear, excessive wax	SOC Ear and labyrinth disorders	External ear disorder	01/03/2019	1. Yes (at end of study)		0. No	0. None	3. Continuing	999.
01	41	Eye Pain	SOC Eye disorders	Eye disorder NOS	24/08/2017	0. No	24/08/2017	0. No	0. None	1. Recovered	1. Mild
02	2	C/O bloating and indegestion	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	21/10/2016	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	27	Nausea and vomitting	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	27/03/2017	0. No	27/03/2017	999.	0. None	1. Recovered	1. Mild

02	45	Heartburn	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	31/07/2017	0. No	31/07/2017	0. No	0. None	1. Recovered	1. Mild
02	45	Heartburn	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	19/08/2017	0. No	19/08/2017	0. No	0. None	1. Recovered	1. Mild
01	46	Nausea	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	02/10/2017	0. No	09/10/2017	999.	3. Permanently interrupted	1. Recovered	1. Mild
02	54	Vomiting	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	28/12/2017	0. No	28/12/2017	999.	0. None	1. Recovered	1. Mild
02	55	Stomach pain	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	17/01/2018	0. No	17/01/2018	999.	0. None	1. Recovered	1. Mild
01	59	Stomach ache	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	28/12/2017	0. No	28/12/2017	999.	0. None	1. Recovered	1. Mild
01	68	Constipation	SOC Gastrointestinal disorders	Gastrointestinal motility and	09/03/2018	0. No	09/03/2018	0. No	0. None	1. Recovered	1. Mild

				defaecation disorders							
01	78	Stomach ache	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	22/05/2018	1. Yes (at end of study)		999.	1. Dose reduced	3. Continuing	1. Mild
02	92	C/O feeling ill/diarrhoea	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	02/08/2018	0. No	02/08/2018	999.	0. None	1. Recovered	1. Mild
01	96	Nausea	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	22/10/2018	0. No	12/11/2018	1. Yes	1. Dose reduced	1. Recovered	1. Mild
02	102	Upset Stomach	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	05/11/2018	0. No	05/11/2018	0. No	0. None	1. Recovered	1. Mild
01	103	Nausea	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	05/12/2018	0. No	01/01/1900	1. Yes	1. Dose reduced	1. Recovered	2. Moderate
02	119	Loose stools	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	03/02/2017	0. No	13/02/2017	999.	0. None	1. Recovered	1. Mild

02	132	Vomiting bug	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	23/06/2017	0. No	24/06/2017	999.	0. None	1. Recovered	999.
01	137	Vomiting	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	01/09/2017	0. No	11/09/2017	1. Yes	3. Permanently interrupted	1. Recovered	2. Moderate
01	139	Diarrhea	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	02/08/2017	0. No	09/08/2017	1. Yes	3. Permanently interrupted	1. Recovered	1. Mild
01	152	Nausea/Vomiting	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	30/11/2017	0. No	14/12/2017	999.	3. Permanently interrupted	1. Recovered	1. Mild
02	153	stomach cramps	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	28/12/2017	0. No	05/01/2018	999.	1. Dose reduced	1. Recovered	1. Mild
02	156	Vomiting (potential food-poisoning)	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	17/01/2018	0. No	17/01/2018	999.	0. None	1. Recovered	1. Mild
02	158	Constipation	SOC Gastrointestinal disorders	Gastrointestinal motility and	02/02/2018	0. No	06/02/2018	0. No	0. None	1. Recovered	1. Mild

				defaecation disorders							
01	162	Heartburn	SOC Gastrointestinal disorders	Gastrointestinal motility and defaecation disorders	27/03/2018	0. No	27/03/2018	0. No	0. None	1. Recovered	1. Mild
02	42	Bleeding from anus when opening bowels	SOC Gastrointestinal disorders	Gastrointestinal NOS	21/02/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	182	Blood in sputum/vomit, torn minor capillary no treatment required	SOC Gastrointestinal disorders	Gastrointestinal NOS	28/02/2019	0. No	01/01/1900	999.	0. None	1. Recovered	999.
01	10	C/O Pain	SOC General disorders and administration site consitions	General disorders NOS	14/11/2016	0. No	14/11/2016	999.	0. None	1. Recovered	1. Mild
01	10	C/O Pain	SOC General disorders and administration site consitions	General disorders NOS	18/11/2016	0. No	18/11/2016	999.	0. None	1. Recovered	1. Mild
02	11	Burning sensation in palms	SOC General disorders and administration site conditions	General disorders NOS	28/12/2016	0. No	28/12/2016	0. No	0. None	1. Recovered	1. Mild
02	13	Breast Swelling	SOC General disorders and admswallowingistration sisw consitions	General disorders NOS	05/06/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	2. Moderate

01	22	General Pain	SOC General disorders and administration site conditions	General disorders NOS	03/04/2017	0. No	03/04/2017	0. No	0. None	1. Recovered	1. Mild
01	34	Nasal Pain	SOC General disorders and administration site conditions	General disorders NOS	08/07/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	54	Chest pain	SOC General disorders and administration site conditions	General disorders NOS	29/12/2017	0. No	29/12/2017	0. No	0. None	1. Recovered	1. Mild
02	76	Difficulties swallowing tablets	SOC General disorders and admswallowingistration sisw consitions	General disorders NOS	23/04/2018	1. Yes (at end of study)		0. No	1. Dose reduced	3. Continuing	1. Mild
01	117	Participant does not like the way the increased dose makes him feel, requested lowering of dose	SOC General disorders and administration site conditions	General disorders NOS	17/01/2017	1. Yes (at end of study)		1. Yes	1. Dose reduced	777.	1. Mild
02	125	Chest pain (middle of chest)	SOC General disorders and administration site conditions	General disorders NOS	05/04/2017	0. No	05/04/2017	0. No	1. Dose reduced	1. Recovered	1. Mild
01	135	Nose blocked	SOC General disorders and administration site conditions	General disorders NOS	01/01/1900	999.		0. No	0. None	999.	2. Moderate
01	141	Nasal Congestion	SOC General disorders and	General disorders NOS	10/07/2017	0. No	13/07/2017	0. No	0. None	1. Recovered	1. Mild

			administration site conditions								
02	156	Dose reduced at participant reqest, see file note 71	SOC General disorders and administration site conditions	General disorders NOS	15/02/2018	1. Yes (at end of study)		777.	1. Dose reduced	777.	777.
01	179	Chest pain	SOC General disorders and administration site conditions	General disorders NOS	20/09/2018	0. No	23/09/2018	999.	0. None	1. Recovered	1. Mild
02	181	Felt unwell	SOC General disorders and administration site consitions	General disorders NOS	29/08/2018	0. No	29/08/2018	0. No	0. None	1. Recovered	1. Mild
01	185	Chest pain	SOC General disorders and administration site conditions	General disorders NOS	11/10/2018	0. No	11/10/2018	0. No	0. None	1. Recovered	1. Mild
01	191	Feeling of lump in throat, predates medication advised to use Gaviscon	SOC General disorders and administration site consitions	General disorders NOS	01/2019	0. No	20/02/2019	0. No	0. None	1. Recovered	1. Mild
01	194	Chest pain, seen by nurse, no observed issues	SOC General disorders and administration site conditions	General disorders NOS	12/02/2019	0. No	13/02/2019	0. No	0. None	1. Recovered	2. Moderate
01	196	Bleeding nose, difficulty breathing, historical issue. Referred to ENT	SOC General disorders and administration site conditions	General disorders NOS	07/02/2019	1. Yes (at end of study)		0. No	0. None	3. Continuing	999.

01	19 9	Swelling on nose/spot on septum	SOC General disorders and administration site conditions	General disorders NOS	18/04/20 19	0. No	25/04/20 19	0. No	0. None	1. Recovere d	1. Mild
02	3	Headache	SOC Nervous system disorders	Headache	09/12/20 16	0. No	09/12/20 16	999.	0. None	1. Recovere d	1. Mild
02	4	Headache	SOC Nervous system disorders	Headache	05/03/20 17	0. No	05/03/20 17	999.	0. None	1. Recovere d	1. Mild
02	4	Headache	SOC Nervous system disorders	Headache	09/03/20 17	0. No	09/03/20 17	999.	0. None	1. Recovere d	1. Mild
02	11	Headaches	SOC Nervous system disorders	Headache	28/12/20 16	0. No	03/01/20 17	999.	0. None	1. Recovere d	1. Mild
01	12	Headaches	SOC Nervous system disorders	Headache	21/11/20 16	0. No	21/11/20 16	1. Yes	3. Permanen tly interrupte d	1. Recovere d	2. Modera te
02	13	Headache	SOC Nervous system disorders	Headache	09/06/20 17	0. No	09/06/20 17	0. No	0. None	1. Recovere d	1. Mild
02	14	Headache	SOC Nervous system disorders	Headache	31/12/20 16	0. No	31/12/20 16	999.	0. None	1. Recovere d	1. Mild
02	14	Headache	SOC Nervous system disorders	Headache	28/11/20 16	0. No	28/11/20 16	0. No	0. None	1. Recovere d	1. Mild
02	16	Headache	SOC Nervous system disorders	Headache	17/01/20 17	0. No	17/01/20 17	999.	0. None	1. Recovere d	1. Mild

02	16	Headache	SOC Nervous system disorders	Headache	14/02/2017	0. No	14/02/2017	999.	0. None	1. Recovered	1. Mild
02	16	Headache	SOC Nervous system disorders	Headache	21/02/2017	0. No	21/02/2017	999.	0. None	1. Recovered	1. Mild
02	18	Headache	SOC Nervous system disorders	Headache	07/05/2018	0. No	07/05/2018	999.	0. None	1. Recovered	1. Mild
02	18	Headache	SOC Nervous system disorders	Headache	30/05/2018	0. No	30/05/2018	999.	0. None	1. Recovered	1. Mild
02	18	Headache	SOC Nervous system disorders	Headache	04/06/2018	0. No	04/06/2018	999.	0. None	1. Recovered	1. Mild
02	18	Headache	SOC Nervous system disorders	Headache	11/05/2018	0. No	11/05/2018	999.	0. None	1. Recovered	1. Mild
02	18	Headache	SOC Nervous system disorders	Headache	01/06/2018	0. No	01/06/2018	999.	0. None	1. Recovered	1. Mild
01	22	Headache	SOC Nervous system disorders	Headache	07/03/2017	0. No	07/03/2017	999.	0. None	1. Recovered	1. Mild
01	22	Headache	SOC Nervous system disorders	Headache	12/03/2017	0. No	12/03/2017	999.	0. None	1. Recovered	1. Mild
01	22	Headache	SOC Nervous system disorders	Headache	14/03/2017	0. No	14/03/2017	999.	0. None	1. Recovered	1. Mild
01	22	Headache	SOC Nervous system disorders	Headache	26/03/2017	0. No	04/04/2017	999.	0. None	1. Recovered	1. Mild

02	24	Headache	SOC Nervous system disorders	Headache	17/01/2017	0. No	17/01/2017	999.	0. None	1. Recovered	1. Mild
02	24	Headache	SOC Nervous system disorders	Headache	19/01/2017	0. No	19/01/2017	999.	0. None	1. Recovered	1. Mild
02	24	Headache	SOC Nervous system disorders	Headache	16/01/2017	0. No	16/01/2017	999.	0. None	1. Recovered	1. Mild
01	25	Headache	SOC Nervous system disorders	Headache	20/02/2017	0. No	21/02/2017	999.	0. None	1. Recovered	1. Mild
01	25	Headache	SOC Nervous system disorders	Headache	16/03/2017	0. No	16/03/2017	999.	0. None	1. Recovered	1. Mild
01	25	Headache	SOC Nervous system disorders	Headache	21/03/2017	0. No	21/03/2017	999.	0. None	1. Recovered	1. Mild
01	27	Headache	SOC Nervous system disorders	Headache	11/02/2017	0. No	11/02/2017	999.	0. None	1. Recovered	1. Mild
01	28	Headache	SOC Nervous system disorders	Headache	18/04/2017	1. Yes (at end of study)		999.	0. None	3. Continuing	2. Moderate
01	30	Headache	SOC Nervous system disorders	Headache	30/04/2017	0. No	30/04/2017	999.	0. None	1. Recovered	1. Mild
01	46	Headache	SOC Nervous system disorders	Headache	02/10/2017	0. No	09/10/2017	999.	3. Permanently interrupted	1. Recovered	1. Mild

02	49	Headache	SOC Nervous system disorders	Headache	14/11/2017	0. No	16/11/2017	999.	0. None	1. Recovered	1. Mild
02	54	Headache	SOC Nervous system disorders	Headache	13/12/2017	1. Yes (at end of study)		999.	0. None	3. Continuing	1. Mild
02	54	Headache	SOC Nervous system disorders	Headache	25/12/2017	0. No	25/12/2017	999.	0. None	1. Recovered	1. Mild
02	54	Headache	SOC Nervous system disorders	Headache	10/01/2018	1. Yes (at end of study)		999.	0. None	3. Continuing	1. Mild
02	55	Headache	SOC Nervous system disorders	Headache	09/12/2017	0. No	09/12/2017	999.	0. None	1. Recovered	1. Mild
01	57	Headache	SOC Nervous system disorders	Headache	13/12/2017	0. No	13/12/2017	999.	0. None	1. Recovered	1. Mild
02	63	Mild headaches	SOC Nervous system disorders	Headache	28/12/2017	0. No	22/01/2018	999.	0. None	1. Recovered	1. Mild
01	74	Headache	SOC Nervous system disorders	Headache	24/03/2018	0. No	24/03/2018	999.	0. None	1. Recovered	1. Mild
01	74	Migraine	SOC Nervous system disorders	Headache	12/02/2018	0. No	12/02/2018	999.	0. None	1. Recovered	1. Mild
01	84	c/o headaches and sweating	SOC Nervous system disorders	Headache	23/07/2018	0. No	24/07/2018	999.	0. None	1. Recovered	1. Mild

01	84	Headache	SOC Nervous system disorders	Headache	17/07/2018	0. No	17/07/2018	999.	0. None	1. Recovered	1. Mild
01	84	Headache	SOC Nervous system disorders	Headache	24/07/2018	0. No	24/07/2018	999.	0. None	1. Recovered	1. Mild
01	85	Headache	SOC Nervous system disorders	Headache	01/09/2018	0. No	01/09/2018	999.	0. None	1. Recovered	1. Mild
01	86	Headache	SOC Nervous system disorders	Headache	12/08/2018	0. No	12/08/2018	999.	0. None	1. Recovered	1. Mild
01	87	Headache	SOC Nervous system disorders	Headache	30/06/2018	0. No	30/06/2018	999.	0. None	1. Recovered	1. Mild
01	87	Headache	SOC Nervous system disorders	Headache	21/07/2018	0. No	21/07/2018	999.	0. None	1. Recovered	1. Mild
01	91	Headache	SOC Nervous system disorders	Headache	06/07/2018	0. No	06/07/2018	999.	0. None	1. Recovered	1. Mild
01	91	Headache	SOC Nervous system disorders	Headache	17/07/2018	0. No	17/07/2018	999.	0. None	1. Recovered	1. Mild
02	92	Headache	SOC Nervous system disorders	Headache	06/07/2018	0. No	06/07/2018	999.	0. None	1. Recovered	1. Mild
01	111	Headache	SOC Nervous system disorders	Headache	16/01/2019	0. No	16/01/2019	999.	0. None	1. Recovered	1. Mild
01	128	Headache and blurred vision	SOC Nervous system disorders	Headache	17/03/2017	0. No	18/03/2017	0. No	0. None	1. Recovered	999.

02	134	Headache/Migraine	SOC Nervous system disorders	Headache	07/07/2017	0. No	07/07/2017	0. No	0. None	1. Recovered	1. Mild
01	147	Headache	SOC Nervous system disorders	Headache	03/12/2017	0. No	06/12/2017	999.	0. None	1. Recovered	999.
01	12	C/O Sore throat	SOC Infections and infestations	Infections and infestations	02/01/2017	0. No	02/01/2017	0. No	0. None	1. Recovered	1. Mild
02	24	C/O Cold	SOC Infections and infestations	Infections and infestations	28/01/2017	0. No	28/01/2017	0. No	0. None	1. Recovered	1. Mild
02	29	Balanitis	SOC Infections and infestations	Infections and infestations	08/08/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	45	C/O Cold	SOC Infections and infestations	Infections and infestations	05/09/2017	0. No	05/09/2017	0. No	0. None	1. Recovered	1. Mild
02	54	Cold and flu	SOC Infections and infestations	Infections and infestations	28/12/2017	0. No	29/12/2017	0. No	0. None	1. Recovered	1. Mild
02	54	Infection of the upper respiratory tract	SOC Infections and infestations	Infections and infestations	29/12/2017	0. No	05/01/2018	0. No	0. None	1. Recovered	1. Mild
01	65	Trichomoniasis	SOC Infections and infestations	Infections and infestations	04/01/2018	0. No	13/01/2018	0. No	0. None	1. Recovered	1. Mild
02	71	Cold	SOC Infections and infestations	Infections and infestations	26/03/2018	0. No	01/01/1900	0. No	0. None	1. Recovered	1. Mild

02	79	c/o sore throat	SOC Infections and infestations	Infections and infestations	03/09/2018	0. No	03/09/2018	0. No	0. None	1. Recovered	1. Mild
01	82	Chlamydia	SOC Infections and infestations	Infections and infestations	31/05/2018	0. No	14/06/2018	0. No	0. None	1. Recovered	1. Mild
01	82	Urethritis	SOC Infections and infestations	Infections and infestations	31/05/2018	0. No	04/06/2018	0. No	0. None	1. Recovered	1. Mild
01	85	Throat Pain	SOC Infections and infestations	Infections and infestations	11/09/2018	0. No	13/09/2018	0. No	0. None	1. Recovered	1. Mild
02	101	Chlamydial Infection	SOC Infections and infestations	Infections and infestations	08/11/2018	0. No	15/11/2018	0. No	0. None	1. Recovered	1. Mild
02	106	c/o flu	SOC Infections and infestations	Infections and infestations	06/12/2018	0. No	06/12/2018	0. No	0. None	1. Recovered	1. Mild
01	129	Cold symptoms	SOC Infections and infestations	Infections and infestations	23/05/2017	0. No	31/05/2017	0. No	0. None	1. Recovered	1. Mild
01	157	Minor herpes simplex (lip)	SOC Infections and infestations	Infections and infestations	23/01/2018	0. No	30/01/2018	999.	0. None	1. Recovered	1. Mild
02	159	Chest Infection	SOC Infections and infestations	Infections and infestations	20/02/2018	0. No	14/03/2018	0. No	0. None	1. Recovered	1. Mild
02	159	Common Cold	SOC Infections and infestations	Infections and infestations	30/01/2018	0. No	05/02/2018	0. No	0. None	1. Recovered	1. Mild
02	168	Cold sore	SOC Infections and infestations	Infections and infestations	28/06/2018	0. No	03/07/2018	0. No	0. None	1. Recovered	1. Mild

02	170	Cold symptoms	SOC Infections and infestations	Infections and infestations	20/08/2018	0. No	24/08/2018	0. No	0. None	1. Recovered	1. Mild
02	189	Cold symptoms, nasal congestion and cough, viral infection	SOC Infections and infestations	Infections and infestations	30/11/2018	0. No	04/12/2018	0. No	0. None	1. Recovered	1. Mild
02	13	Lower Back Pain	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	26/04/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	2. Moderate
02	20	Swollen wrist	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	19/08/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	22	back pain	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	05/04/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	29	Back Pain	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	19/07/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	41	Arm/Back Pain	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	25/08/2017	0. No	01/01/1900	0. No	0. None	1. Recovered	1. Mild
01	43	Foot Pain	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	25/07/2017	0. No	25/07/2017	0. No	0. None	1. Recovered	1. Mild

01	47	Ligament tear	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	25/10/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	74	Joint pain in left leg	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	20/03/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	74	Leg pain	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	17/02/2018	0. No	17/02/2018	0. No	0. None	1. Recovered	1. Mild
01	77	Joint disorder	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	01/01/1900	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	77	Joint pain in wrist	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	11/04/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	78	Painful finger	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	02/2017	0. No	25/04/2018	0. No	0. None	1. Recovered	1. Mild
01	84	Pain in right hand when flexed	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	03/09/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	86	Swollen ankle	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	18/08/2018	0. No	18/08/2018	0. No	0. None	1. Recovered	1. Mild

02	94	Neck pain	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	12/08/2018	0. No	12/08/2018	0. No	0. None	1. Recovered	1. Mild
02	94	Painful xiphoid process (located outwards instead of inwards)	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	13/08/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	94	Swollen painful chest	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	23/07/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	99	Small swelling on cheekbone	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	30/11/2018	0. No	30/11/2018	0. No	0. None	1. Recovered	1. Mild
02	99	Swollen right hand	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	19/10/2018	0. No	26/10/2018	0. No	0. None	1. Recovered	1. Mild
01	103	Shoulder Pain	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	08/12/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	113	Painful dark red little finger	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	02/02/2019	0. No	03/02/2019	0. No	0. None	1. Recovered	1. Mild
02	116	Left arm soft tissue damage	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	02/02/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild

02	123	Left knee pain	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	24/03/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	999.
01	129	Elbow pain	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	24/04/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	145	Muscular Pain R Arm	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	06/10/2017	0. No	07/10/2017	0. No	0. None	1. Recovered	1. Mild
02	148	Pain in finger (R hand)	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	30/10/2017	0. No	31/10/2017	0. No	0. None	1. Recovered	1. Mild
02	153	back pain	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	11/12/2017	0. No	19/12/2017	0. No	0. None	1. Recovered	1. Mild
01	157	Pain in left arm, ongoing numbness and pins & needles	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	05/01/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	168	Lower lumbar discomfort	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	08/08/2018	0. No	20/08/2018	0. No	0. None	1. Recovered	1. Mild
02	169	Musculoskeletal chest pain	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	22/06/2018	0. No	22/06/2018	0. No	0. None	1. Recovered	2. Moderate

02	178	Knee Discomfort	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	25/09/2018	0. No	25/09/2018	0. No	0. None	1. Recovered	1. Mild
01	188	Growing pains	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	06/11/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	190	Sore head	SOC Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	16/11/2018	0. No	28/11/2018	0. No	0. None	1. Recovered	1. Mild
02	102	Infected eye/cyst	SOC Eye disorders	Ocular infection infestation, irritations and inflammation	12/11/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	132	Eye marginally inflamed	SOC Eye disorders	Ocular infection infestation, irritations and inflammation	30/05/2017	0. No	31/05/2017	0. No	0. None	1. Recovered	1. Mild
02	16	Panic Episodes	SOC Psychiatric disorder	Psychiatric and behavioural symptoms	06/02/2017	0. No	13/02/2017	0. No	0. None	1. Recovered	1. Mild
02	72	Swollen knuckles after punching a wall following flashbacks (PTSD)	SOC Psychiatric disorder	Psychiatric and behavioural symptoms	12/07/2018	0. No	01/01/1900	0. No	0. None	1. Recovered	1. Mild

02	80	Behavioural change- was hostile towards psychiatrist	SOC Psychiatric disorder	Psychiatric and behavioural symptoms	29/05/2018	0. No	29/05/2018	0. No	0. None	1. Recovered	1. Mild
02	92	Behavioural Change	SOC Psychiatric disorder	Psychiatric and behavioural symptoms	28/07/2018	0. No	28/07/2018	0. No	0. None	1. Recovered	2. Moderate
01	111	Temper Outbursts	SOC Psychiatric disorder	Psychiatric and behavioural symptoms	28/01/2019	0. No	03/02/2019	1. Yes	1. Dose reduced	1. Recovered	1. Mild
01	115	Anxiety	SOC Psychiatric disorder	Psychiatric and behavioural symptoms	05/03/2019	0. No	01/04/2019	999.	0. None	1. Recovered	1. Mild
02	132	Hypnopompic hallucination	SOC Psychiatric disorder	Psychiatric and behavioural symptoms	18/05/2017	0. No	18/05/2017	999.	0. None	1. Recovered	999.
01	137	Agitation/excitability	SOC Psychiatric disorder	Psychiatric and behavioural symptoms	07/09/2017	0. No	11/09/2017	1. Yes	3. Permanently interrupted	1. Recovered	2. Moderate
01	164	Behaviour Change	SOC Psychiatric disorder	Psychiatric and behavioural symptoms	17/04/2018	1. Yes (at end of study)		777.	3. Permanently interrupted	777.	777.
01	200	Anxiety	SOC Psychiatric disorder	Psychiatric and	26/03/2019	1. Yes (at end		0. No	0. None	3. Continuing	1. Mild

				behavioural symptoms		of study)					
01	34	Breathing impairment	SOC Respiratory, thoracic and mediastinal disorders	Respiratory, thoracic and mediastinal disorders	08/07/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	162	Blackouts (?Epilepsy related)	SOC Nervous system disorders	Seizures	14/03/2018	1. Yes (at end of study)		999.	0. None	3. Continuing	1. Mild
01	7	Sleep problems	SOC Psychiatric disorder	Sleep disorders and disturbances	07/11/2016	1. Yes (at end of study)		1. Yes	0. None	3. Continuing	1. Mild
01	10	Sleep Loss	SOC Psychiatric disorder	Sleep disorders and disturbances	23/11/2016	1. Yes (at end of study)		0. No	0. None	3. Continuing	3. Severe
02	14	Sleep Loss	SOC Psychiatric disorder	Sleep disorders and disturbances	10/01/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	2. Moderate
02	16	Insomnia	SOC Psychiatric disorder	Sleep disorders and disturbances	06/02/2017	0. No	13/02/2017	999.	0. None	1. Recovered	1. Mild
02	18	Sleep Loss	SOC Psychiatric disorder	Sleep disorders and disturbances	31/05/2018	1. Yes (at end of study)		1. Yes	0. None	3. Continuing	1. Mild
01	25	Sleeplessness	SOC Psychiatric disorder	Sleep disorders and disturbances	20/02/2017	1. Yes (at end of study)		999.	0. None	2. Recovered with sequelae	1. Mild

01	30	Sleep Loss	SOC Psychiatric disorder	Sleep disorders and disturbances	03/05/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	44	Sleep Problems	SOC Psychiatric disorder	Sleep disorders and disturbances	04/07/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	57	Sleep difficulties	SOC Psychiatric disorder	Sleep disorders and disturbances	13/12/2017	0. No	13/12/2017	999.	0. None	1. Recovered	1. Mild
01	68	Sleep difficulties	SOC Psychiatric disorder	Sleep disorders and disturbances	12/02/2018	1. Yes (at end of study)		999.	1. Dose reduced	3. Continuing	1. Mild
01	84	c/o insomnia	SOC Psychiatric disorder	Sleep disorders and disturbances	02/08/2018	1. Yes (at end of study)		999.	0. None	3. Continuing	1. Mild
02	102	C/O Sleep problems	SOC Psychiatric disorder	Sleep disorders and disturbances	20/11/2018	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
01	111	Sleep problems	SOC Psychiatric disorder	Sleep disorders and disturbances	28/01/2019	0. No	03/02/2019	1. Yes	1. Dose reduced	1. Recovered	2. Moderate
02	112	Sleep Problems	SOC Psychiatric disorder	Sleep disorders and disturbances	28/01/2019	0. No	19/02/2019	1. Yes	2. Temporarily interrupted	1. Recovered	2. Moderate

01	115	Sleep distruption	SOC Psychiatric disorder	Sleep disorders and disturbances	25/02/2019	1. Yes (at end of study)		999.	0. None	3. Continuing	1. Mild
02	143	Poor sleep	SOC Psychiatric disorder	Sleep disorders and disturbances	25/09/2017	0. No	28/09/2017	999.	0. None	1. Recovered	999.
01	160	Poor sleep	SOC Psychiatric disorder	Sleep disorders and disturbances	12/03/2018	1. Yes (at end of study)		999.	0. None	3. Continuing	999.
01	200	Poor Sleep	SOC Psychiatric disorder	Sleep disorders and disturbances	09/05/2019	1. Yes (at end of study)		0. No	1. Dose reduced	3. Continuing	1. Mild
02	4	Cuts (head and hand)	SOC Injury, poisoning and procedural complications	Soft tissue injury	28/03/2017	0. No	28/03/2017	0. No	0. None	1. Recovered	1. Mild
01	22	minor cuts and swelling	SOC Injury, poisoning and procedural complications	Soft tissue injury	26/03/2017	0. No	26/03/2017	0. No	0. None	1. Recovered	1. Mild
01	34	Bruising on nose	SOC Injury, poisoning and procedural complications	Soft tissue injury	22/07/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild
02	38	Ankle Soreness/Soft Tissue Injury	SOC Injury, poisoning and procedural complications	Soft tissue injury	12/06/2017	0. No	13/06/2017	0. No	0. None	1. Recovered	1. Mild

01	41	Blurry Vision (due to an assault)	SOC Injury, poisoning and procedural complications	Soft tissue injury	24/08/2017	0. No	24/08/2017	0. No	0. None	1. Recovered	1. Mild
01	41	Eye injury during restraint	SOC Injury, poisoning and procedural complications	Soft tissue injury	23/08/2017	0. No	23/08/2017	0. No	0. None	1. Recovered	1. Mild
01	58	Cut on left ear	SOC Injury, poisoning and procedural complications	Soft tissue injury	23/12/2017	0. No	01/01/1900	0. No	0. None	1. Recovered	1. Mild
01	58	Cut on occipital region	SOC Injury, poisoning and procedural complications	Soft tissue injury	23/12/2017	0. No	01/01/1900	0. No	0. None	1. Recovered	1. Mild
01	62	Assaulted with boiling water, sustained severe burns to chest and face	SOC Injury, poisoning and procedural complications	Soft tissue injury	03/01/2018	0. No	14/01/2018	0. No	0. None	1. Recovered	2. Moderate
01	77	Cut finger	SOC Injury, poisoning and procedural complications	Soft tissue injury	03/04/2018	0. No	04/04/2018	0. No	0. None	1. Recovered	1. Mild
01	85	Discoloured and striated toenails due to micro trauma	SOC Injury, poisoning and procedural complications	Soft tissue injury	03/09/2018	0. No	03/09/2018	0. No	0. None	1. Recovered	1. Mild
01	87	Cut thumb on tin of tuna	SOC Injury, poisoning and procedural complications	Soft tissue injury	23/06/2018	0. No	23/06/2018	0. No	0. None	1. Recovered	1. Mild

02	127	Abrasion to left knee	SOC Injury, poisoning and procedural complications	Soft tissue injury	16/05/2017	0. No	16/05/2017	0. No	0. None	1. Recovered	1. Mild
01	145	Nose pain & black eye from altercation	SOC Injury, poisoning and procedural complications	Soft tissue injury	29/10/2017	0. No	09/11/2017	0. No	0. None	1. Recovered	1. Mild
01	145	Sore Head, lump behind ear after altercation	SOC Injury, poisoning and procedural complications	Soft tissue injury	10/10/2017	0. No	11/10/2017	0. No	0. None	1. Recovered	1. Mild
02	158	Bruising and swelling to L eye (after assault)	SOC Injury, poisoning and procedural complications	Soft tissue injury	16/02/2018	0. No	20/02/2018	0. No	0. None	1. Recovered	1. Mild
02	159	Swollen Face after altercation	SOC Injury, poisoning and procedural complications	Soft tissue injury	23/01/2018	0. No	25/01/2018	0. No	0. None	1. Recovered	1. Mild
01	174	Graze to upper arm and swollen knuckle following altercation, no pain	SOC Injury, poisoning and procedural complications	Soft tissue injury	03/07/2018	0. No	03/07/2018	0. No	0. None	1. Recovered	999.
02	182	1 inch deep cut to finger from saw. Steristrips applied	SOC Injury, poisoning and procedural complications	Soft tissue injury	07/02/2019	0. No	01/01/1900	0. No	0. None	1. Recovered	999.
01	185	Sore wrists and scratch under eye after restraint	SOC Injury, poisoning and procedural complications	Soft tissue injury	12/11/2018	0. No	12/11/2018	0. No	0. None	1. Recovered	1. Mild

02	186	Received slash wound to face, required hospital day treatment, 5 interrupted sutures, removed 26/11	SOC Injury, poisoning and procedural complications	Soft tissue injury	16/11/2018	0. No	26/11/2018	0. No	0. None	1. Recovered	999.
02	193	Superficial cuts to fingers	SOC Injury, poisoning and procedural complications	Soft tissue injury	20/03/2019	0. No	20/03/2019	0. No	0. None	1. Recovered	777.
01	35	Loss of energy	SOC Psychiatric disorder	Somatic symptom and related disorders	08/05/2017	0. No	08/05/2017	1. Yes	3. Permanently interrupted	1. Recovered	2. Moderate
01	84	Slow and drowsy feeling	SOC Psychiatric disorder	Somatic symptom and related disorders	07/09/2018	1. Yes (at end of study)		1. Yes	1. Dose reduced	3. Continuing	1. Mild
01	152	Drowsy / lethargic	SOC Psychiatric disorder	Somatic symptom and related disorders	06/12/2017	0. No	07/12/2017	999.	0. None	1. Recovered	1. Mild
01	200	Problems urinating and erectile dysfunction	SOC Renal and urinary disorder	Urinary problem NOS	2018	0. No	22/04/2019	0. No	0. None	1. Recovered	1. Mild
01	10	Vitamin Deficiency	SOC Metabolism and nutrition disorder	Vitamin related disorders	02/12/2016	0. No	29/12/2016	0. No	0. None	1. Recovered	1. Mild

02	15	vitamin d deficiency	SOC Metabolism and nutrition disorder	Vitamin related disorders	20/03/2017	1. Yes (at end of study)		0. No	0. None	3. Continuing	1. Mild

Table: Listing of Serious Adverse Events for all patients

Only 1 serious adverse event was reported and categorised as an Important Medical Event (IME) which was not considered related to the trial medication.

Within the per protocol population (n= 200), a total of 336 AEs, including one SAE (classified as an IME), were identified as treatment-emergent and included in the safety analysis. Summary tables for AEs and SAEs are presented in the appendix of this synopsis.

Overall, 160 patients (80%) patients reported at least one AE (82 OROS-MPH and 78 placebo). The proportion that experienced at least one SAE was 1 (0.5%)

Incidence of adverse drug reactions (ADRs): 34 AEs in OROS-MPH and 12 AEs in placebo (13.7 %) were assessed as related to at least one study drug and 0 (0.0%) patients experienced a ADR.

There were no Serious Adverse Reactions (SARs), no unexpected SARs and no SUSARs.

20.4 Conclusion

The trial targeted a sample that could be generalised to other prison populations of young males aged 16-25, meeting ADHD diagnostic criteria for ADHD, in the United Kingdom. To increase generalisability a screening approach was taken to ensure that as many prisoners as possible who met diagnostic criteria were identified and invited to take part in the trial. Exclusion criteria were kept to a minimum and focused on excluding the minority of participants who were high risk to researchers, or who had co-existing disorders for which medical treatment of ADHD was a strong caution or contraindicated.

The primary and secondary outcomes from this study failed to show statistically significant differences between the OROS-MPH and placebo treatment groups from baseline to the outcome assessment at 8 weeks, or at the earlier assessment at 5 weeks. Any differences between the mean or median scores for the two arms were negligible for any of the outcome measures and are unlikely to be clinically meaningful even if found to be significant in a larger study sample. To check for the possibility of a hidden effect in the trial data for any reason, we conducted a further analysis to look for two distinct clusters of outcomes in the data. We would expect to see a bimodal distribution if there were any drug effects, reflecting the existence of two response groups. We checked the distribution in the change of CAARS-O scores from baseline to week 8 by plotting the distribution of change scores but found only a single smooth function that gave no hint of two distinct responder groups within the data.

Additional post-hoc analyses were conducted (after the planned analyses had been completed) to try and identify any potential reasons for these results but none were identified. In conclusion the study was robustly neutral and does not support the routine treatment of young adult offenders with methylphenidate.

21. Date of Report

This is version 1.4 of the Clinical Study Report synopsis, dated 26th of April 2021

APPENDICES

i) Summary of treatment-emergent AEs in the per protocol population

Table 10: Adverse events by body system code by trial arm - number and percentage of participants reporting adverse effects

SOC category	HLGT category	OROS-MPH (N=101)	OROS-MPH number of events	Placebo (N=99)	Placebo number of events	Total sample (N=200)
		N (%)		N (%)		N (%)
Blood and lymphatic system disorders	Blood and lymphatic system disorders	1 (1.0)	1	0 (0.0)	0	1 (1.0)
Cardiac disorders	Cardiac signs and symptoms	4 (4.0)	4	1 (1.0)	1	5 (2.5)
Ear and labyrinth disorders	External ear disorder	3 (3.0)	3	0 (0.0)	0	3 (2.0)
Endocrine	Endocrine (raised T4)	0 (0.0)	0	1 (1.0)	1	0 (0.0)
Eye disorders	Eye disorders NOS	1 (1.0)	1	0 (0.0)	0	1 (1.0)
	Ocular infection infestation, irritations and inflammation	0 (0.0)	0	2 (2.0)	2	2 (1.0)
Gastrointestinal disorders	Dental and gum disorders	22 (22.0)	35	15 (14.7)	37	37 (18.5)
	Gastrointestinal motility and defaecation disorders	11 (11.0)	11	11 (11.0)	12	22 (11.0)
	Gastrointestinal NOS	0 (0.0)	0	2 (2.0)	2	2 (1.0)
General disorders	General disorders NOS	12 (12.0)	13	7 (6.9)	7	19 (9.5)
Immune system disorders	Allergic conditions	5 (5.0)	5	9 (8.8)	13	14 (7.0)
Infections and infestations	Infections and infestations	6 (6.0)	6	12 (11.8)	14	18 (9.0)
Injury, poisoning and procedural complications	Bone and joint injuries	1 (1.0)	1	5 (4.9)	9	6 (3.0)
	Soft tissue injury	11 (11.0)	14	8 (7.8)	8	19 (9.5)
Metabolism and nutrition disorder	Appetite and general nutritional disorders	13 (13.0)	14	2 (2.0)	2	15 (7.5)
	Vitamin related disorders	1 (1.0)	1	1 (1.0)	1	2 (1.0)
Musculoskeletal and connective tissue disorders	Musculoskeletal disorders	15 (15.0)	17	13 (12.7)	16	28 (14.0)
Neoplasms benign, malignant and unspecified	Benign neoplasm	1 (1.0)	1	2 (2.0)	2	3 (1.5)
Nervous system disorders	Dizziness	6 (6.0)	6	0 (0.0)	0	6 (3.0)
	Headache	17 (17.0)	27	14 (13.7)	26	31 (15.5)
	Seizures	1 (1.0)	1	0 (0.0)	0	1 (0.5)
Psychiatric disorder	Conditions associated with drug abuse	4 (4.0)	7	9 (8.8)	13	13 (6.5)
	Depressed mood disorders and disturbances	12 (12.0)	13	4 (3.9)	6	16 (8.0)

	Psychiatric and behavioural symptoms	5 (5.0)	5	5 (4.9)	5	10 (2.5)
	Sleep disorders and disturbances	11 (11.0)	11	7 (6.9)	7	18 (9.0)
	Somatic symptom and related disorders	3 (3.0)	3	0 (0.0)	0	3 (1.5)
Renal and urinary disorder	Urinary problem NOS	1 (1.0)	1	0 (0.0)	0	1 (0.5)
Respiratory, thoracic and mediastinal disorders	Respiratory, thoracic and mediastinal disorders	1 (1.0)	1	0 (0.0)	0	0 (0.0)
Skin and subcutaneous disorder	Epidermal and dermal conditions	16 (16.0)	20	22 (21.6)	26	38 (19.0)

ii) Summary of treatment-emergent ARs in the per protocol population

N/A

iii) Summary of treatment‐emergent SAEs in the study population

N/A

iv) Summary of treatment-emergent SARs in the study population

N/A