Simvastatin improves neutrophil function and clinical outcomes in pneumonia: a pilot randomised controlled trial.

INVESTIGATIONAL MEDICAL PRODUCT (IMP)

Active Drug: Simvastatin

Trade name: Accord
Authorisation number MA - PL0075/0017
Composition: The IMP is an over encapsulated Simvastatin 80mg tablet (Accord brand) flush filled with Microcrystalline cellulose in a flush filled with Microcrystalline cellulose in a Size DBAAe1 capsule. Dose regimen: a single daily dose PO or per NG for 7 days.
Manufacturer: Sharp Clinical Services, Waller House Elvicta Business Park Crickhowell NP8 1DF (MIA(IMP) Number: 10284) at MHRA site number 28707.

Placebo:

DBAAe capsule shells filled with Microcrystalline cellulose.
Composition: Size DBAAe1 capsule shells filled with Microcrystalline cellulose.
Dose regimen: a single daily dose PO or per NG for 7 days.
Manufacturer: Sharp Clinical Services Waller House Elvicta Business Park Crickhowell NP8 1DF (MIA(IMP) Number: 10284) at MHRA site number 28707.
Authorisation number: MA10284
Authorisation holder: Sharp Clinical Services, Waller House, Elvicta Business Park, Crickhowell NP8 1DF

Prescription, preparation and administration of IMP

Trial delegation logs will specify the names of physicians authorised to prescribe IMP for this study.

IMP will be prepared by Sharp Clinical Services, and shipped to QEHB / HEFT pharmacy.
The first dose of study drug will be administered as soon as possible, ideally within 4 hours of randomisation and subsequent doses will be given each morning starting on the following calendar day. If for any reason a dose is not administered at the intended time, it may be administered subsequently but not more than 12 hours after the intended time of administration. Administration of the first dose of IMP may be directly observed by a research nurse or research assistant. Trial drug will be stored in the locked drug trolley for the ward where the patient is based and administered on a daily basis.

No dose modification is proposed as this is a daily dose of a single 80mg tablet of simvastatin.

IMP will be labelled and packaged by Sharp Clinical Services Ltd. according to principles of GMP.

This is a double-blind trial: neither subject nor investigator will be aware of a subject's allocation while he / she is participating in the trial. Active and placebo batches of IMP will have identical packaging, labelling and appearance.

The trust pharmacy will inform the Chief Investigator on receipt of IMP deliveries. IMP will be stored in the pharmacy according to GCP principles.

Research nurses or research assistants will withdraw IMP from trust pharmacy on behalf of study participants on production of a signed trial prescription.

Return and destruction of IMP

Research nurses or research assistants will return unused or expired IMP to the appropriate hospital pharmacy, where it will be destroyed according to local standard operating procedures.

Procedures for emergency unblinding

As a placebo controlled, double-blind trial, patients, clinicians and PI will be blinded to each patient's allocation. All trial drugs, whether simvastatin or placebo, will be packaged identically and identified only by a unique trial identifier. Any clinician involved in the care of patients in the study may request emergency unblinding on grounds of safety. Emergency unblinding will be performed by telephone contact with the trial team. This option will be used only if the patient's future treatment requires knowledge of the treatment assignment. The trial coordinator maintains a copy of the treatment allocation log in the respiratory trials office. Out of hours contact is maintained by a mobile phone carried by members of the trial team in rotation who have access to the treatment allocation log in the trials office.

Rationale for choice and dose of simvastatin and 7-day treatment

The diverse effects of statins appear to represent a class effect. As outlined above, in both in vitro and animal experiments statins show consistent effects regardless of the choice of statin. In addition retrospective and prospective human studies have included multiple statins and shown beneficial effects. However, our preliminary *in vitro* studies (as outlined above) utilized simvastatin, and therefore Simvastatin will be investigated in this study.

The decision to examine treatment for 7 days is based on data supporting the average neutrophil lifespan as being 5.4 days, therefore, by 7 days all circulating neutrophils will have been matured in the presence of simvastatin(8).

Only a single animal study has compared 2 doses of simvastatin (5 or 20 mg/kg given intraperitoneal 24 hours before and concomitantly with LPS to induce lung injury) and only the higher dose was effective in attenuating inflammation and subsequent lung injury(9). Importantly, a recent retrospective observational study of statin usage in patients with sepsis found a greater mortality benefit in patients who were receiving a higher dose of statin(10).

Our preliminary *in vitro* data suggests that neutrophil function is optimized at plasma concentrations that reflect an 80mg daily dose, and this has also been found in vivo studies of inflammation(11) . Although it is acknowledged that the risk of adverse side effects is dose related, on the basis of available evidence, simvastatin 80mg is safe, particularly given the duration of treatment is only 7 days and these patients will be monitored. Our preliminary data strongly suggests that Simvastatin positively affects neutrophil responses in the elderly. If the proposed study confirms this finding, we would then perform a clinical trial of Simvastatin as an adjuvant therapy in older patients with pneumonia with clinical endpoints. The volunteers involved in this proposed study may generate data that will change treatment strategies in pneumonia. This may prove to be directly beneficial to their own treatment at some point in the future. However, this is a speculative benefit.

We have assessed the risk to benefit ratio carefully when designing this study and believe risks have been minimized as much as possible. The side effect profile for Simvastatin is well known and the volunteers will be carefully selected to exclude those at higher risk of adverse events. Subjects will be closely monitored and they will be exposed to Simvastatin for a very short duration of treatment.

Justification for Co-prescription with macrolide antibiotics.
Severely ill pneumonia patients are usually treated with a combination of intravenous penicillin and a macrolide antibiotic – typically clarithromycin 500 mg BD in our trust. If we were to exclude patients who were taking clarithromycin therefore the trial would only be able to enrol patients with mild disease (who wouldn't meet the criteria for sepsis) or those known to be intolerant of macrolides (a small proportion of cases). This would clearly be a significant barrier to recruitment. In addition if we excluded such a large proportion of patients with septic pneumonia who receive clarithromycin or erthyromycin, then it limits the generalisability of any findings from this clinical study to the overall population of patients with pneumonia. We therefore propose that we do not exclude patients who are receiving concomitant clarithromycin or erthyromycin from receiving simvastatin. This is the current clinical practice of the applicants who do not stop statin therapy in patients who are admitted with pneumonia.

There are several points to highlight which are important in considering that this would be appropriate. In this study patients are treated within the medical admissions unit, or critical care unit as in-patients and will be closely monitored for adverse events, and specifically creatine kinase and liver transaminases is measured on days 1, 4, and 7 - the duration of study drug administration. The hospital / critical care environment is unique in that it allows the opportunity for rigorous safety monitoring. It should be emphasized that in this study the maximum duration of treatment is only 7 days and treatment will be stopped if a study termination criterion is reached, which include a study drug related AE and hospital discharge. In contrast, in other clinical trials with simvastatin, treatment was long term and was given as an out-patient with follow-up typically only at months 1, 4, and 8 and every 4 months thereafter. Finally, the Data Monitoring and Ethics Committee (DMEC) will closely monitor and review the safety data.

Rationale for selecting patients on low – moderate dose statins.

As stated, changes to neutrophil function have only been noted using doses of simvastatin equivalent to 80mg. Cell studies conducted in our laboratories suggest that this higher dose is the only one that positively affects neutrophil function with lower concentrations not having a similar effect. We have studied the in vitro effects of 80mg Simvastatin on neutrophils isolated from participants on low or moderate doses of Simvastatin and there continues to be a positive effect on migration when the cells are in the presence of higher concentrations of statins. This strongly suggests that low doses of statins are insufficient to cause the positive changes to neutrophils functions that may be beneficial during episodes of pneumonia. In light of this, we propose to include subjects on doses of statins that are lower than or equivalent to 40mg Simvastatin (Atorvastatin 40mg, Simvastatin 10, 20 40mg, Fluvastatin 80mg, Rosuvastatin 10mg) as evidence suggests this will not negatively impact on the potential effect of Simvastatin 80mg in this study. Patients currently receiving statins at the concentrations above would have there usual statin therapy paused during the trial, but this will be reinstated once the 7 days of the study medications were completed.

Safety

The safety and toxicity profile of simvastatin is well known. Simvastatin has been associated with:
Headache (3%)
Abdominal pain (3.2%)
Asthenia (weakness) (1.6%)
Constipation (2.3%)
Diarrhoea (1.9%)
Myalgia (1.2%)
Rhabdomyositis (<0.1%)
Transient rise in liver function tests (1%)
Jaundice (0.1%)
Cirrhosis (0.01%)

In the clinical trial, subjects will be monitored to reduce risks. Simvastatin is a widely prescribed and well-tolerated treatment. To maximise patient safety, liver function tests and cholesterol will be measured before enrolment, 1 and 4 and 7 days of treatment (with either Simvastatin or the placebo).

Pharmacokinetics and Pharmacodynamics:

During the clinical trial, cholesterol levels will be checked to ensure drug compliance and efficacy.

Interactions with other medication:

We seek to minimize the risk of harm arising from administration of simvastatin to study participants by the following measures:

1. Baseline exclusion of patients at increased risk of simvastatin hypersensitivity as outlined in the exclusion criteria.
2. Ensuring that all participants are monitored with appropriate biochemical testing of liver and creatinine kinase levels.
3. Instituting standard therapy for complications for any study participant developing complications: usually liver dysfunction and altered creatinine kinase levels are effectively managed by drug cessation and supportive care.

INVESTIGATIONAL PLAN.

We will undertake a phase II study of simvastatin versus placebo in patients with septic pneumonia testing whether we can detect effects on neutrophil function. These studies will therefore provide a proof of concept for a mechanism of action for statins to facilitate a larger study looking at modulating clinically relevant outcomes in this patient group.

Overall design

This is a randomised double blind placebo controlled study to test the safety and efficacy of simvastatin therapy on neutrophil function in older patients with septic pneumonia. Patients will be randomised to simvastatin 80mg PO OD or placebo for 7 days in a double- blind fashion. An outline of assessments is shown in table 1. Screening and Day 0 should occur on the same day.

Table 1. Study procedures

	Screening	Post consent	Post consent.	Post-consent	Post-consent	Post-consent	Post-consent	Post consent
		Day 0	Day 1	4 days of IMP	7 days of IMP	30 days	180 days	365 days
Informed consent	X							
Check eligibility criteria	X							
Record baseline demographic and clinical data	X							
Review concomitant medications	X							
Blood samples for liver function tests*	X			X	X			
Blood sample for creatinine*	x		x	x	x			

Blood sample for creatinine kinase *	X		X	X	X			
Blood sample for cholesterol		X		X	X			
Blood sample for neutrophil studies and elastase footprint**		x		x				
Optional BAL sample ***			X					
Patient meets inclusion criteria	x	x	x	x	x			
Withdraw IMP from pharmacy		X						
Scheduled first dose of IMP (directly observed)****		X						
Adverse event recording		X	X	X	X			
Clinical outcome data	x	x	x	x	x	x	x	x

*CPK and LFT values will be used from the previous 48 hours if available.
** Blood sampling will also occur again if the patient develops acute lung injury or is reintubated if at a different timepoint to above.
***Bronchoalveolar lavage fluid will be obtained if the patient is ventilated as a result of clinical deterioration.
**** simvastatin or placebo will be administered daily for up to 7 days.

Overview of study population

Patients with community acquired pneumonia aged 55 or over, admitted to hospital**.**

Target Accrual

60 ± 3 patients will be recruited over approximately 18 months. Following randomisation patients will participate in this clinical trial for up to 1 week and clinical data will be followed for up to 1 year.

Subject Selection

Patients will be identified on the daily consultant ward rounds that take place on the 90 bedded clinical decision unit and 80 bedded intensive care unit at the QEHB (approx 60-70 daily admissions). Patients will be eligible to participate in the study if they fulfil the following inclusion and exclusion criteria.

Inclusion criteria:

- Patients at or over 55 years old.
- Meet the BTS criteria for a diagnosis of community acquired pneumonia (CAP) namely symptoms and signs consistent with an acute lower respiratory tract infection associated with new radiographic shadowing for which there is no other explanation(12). We will regard symptoms and signs as having 3 or more of the following: cough, sputum production, breathlessness, pleuritic chest pain, haemoptysis, fever, headache, signs consistent with pneumonia on chest auscultation.
- CAP patients will also need to meet the criteria for sepsis based on the standard definitions as published in Surviving Sepsis Campaign Guidelines and illustrated in the table below

- All sepsis and pneumonia criteria must occur within the same 24 hour period.
- Patients must be enrolled within 48 hours of admission to hospital.

Sepsis is defined as evidence of infection plus Systemic Inflammatory Response Syndrome (SIRS) (Table 2). The Surviving Campaign Guideline definition of sepsis are summarised in Table 3.

Table 2: Systemic Inflammatory Response Syndrome Diagnostic Criteria (1)

2 or more of the following criteria
Fever of more than 38°C or less than 36°C
Heart rate of more than 90 beats per minute
Respiratory rate of more than 20 breaths per minute or a PaCO2 level of less than 32 mm Hg
Abnormal white blood cell count (>12,000/µL or <4,000/µL or >10% bands)

Table 3: Surviving Sepsis Campaign Guideline Definitions of Sepsis (2)

Sepsis	SIRS + new/suspected infection
Severe Sepsis	Sepsis + sepsis-induced organ dysfunction
Organ Dysfunction	Sepsis-induced hypotension Lactate > normal laboratory results Urine output <0.5 mL/kg hr for >2 hrs, despite adequate fluid resuscitation ALI with PaO2/FIO2 <250 in the absence of pneumonia as infection source ALI with PaO2/FIO2 <200 in the presence of pneumonia as infection source Creatinine >176.8 mmol/L) Bilirubin >34.2 mmol/L) Platelet count >100,000/mm^3 Coagulopathy (INR>1.5)
Septic Shock	Severe sepsis + hypotension not revered by fluid resuscitation

Exclusion criteria:

- More than 48 hours from admission at time of consent.
- Current or recent treatment with >40mg Simvastatin, > 40mg Atorvastatin or > 80mg Fluvastatin, > 10mg Rosuvastatin daily within 1 month.
- known prior myositis.
- creatinine kinase >10 times upper limit normal range*
- transaminases (ALT/AST) >8 times upper limit of normal range*
- severe renal impairment (creatinine clearance <30ml/min) not receiving renal replacement therapy

- patients currently receiving ongoing and sustained treatment with any of the following: itraconazole, ketoconazole, HIV protease inhibitors, nefazodone, ciclosporine, amiodarone, verapamil or diltiazem. Fibric acid derivatives (except fenofibrate), danazol.
- A family history of muscular disorders.
- Known HIV or hepatitis B/C infection.
- Contraindication to enteral drug administration (either PO or Per NG) e.g. patients with mechanical bowel obstruction.
- Known participation in other investigational medicinal product (IMP trials within 30 days).
- Consent / relative or advocate assent declined.
- Treatment withdrawal imminent within 24 hours.
- Patients or those who do not adequately understand verbal or written information even with an interpreter.
- Immunosuppression due to corticosteroid or other immunosuppressant use.

*If CK, ALT or AST values are not available as part of routine care, a blood sample will be obtained after informed consent but before randomisation. CK, ALT and AST values may be obtained up to 48 hours prior to randomisation.

Primary outcome measure:

Change in neutrophil NETosis production at day 4 treatment with the drug or placebo.

Secondary outcomes:

1. Change in neutrophil migratory accuracy at Day 4 hours compared to Day 0
2. Safety and tolerability of simvastatin in this patient group.
3. Change in extracellular matrix degradation at Day 4 hours compared to Day 0.
4. Mortality and re-admissions at 30, 180 and 365 days
5. Sequential Organ Failure Assessment (SOFA) scores
6. Intensive Care Unit (ITU) admissions
7. ITU and hospital length of stay

Safety and clinical assessments will be made at baseline, day 4 and day 7. Neutrophil studies will be conducted at baseline and Day 4. Note. Data for Day 4 assessment will take place within a 5 hour window of the provision of the Day 4 CTIMP (simvastatin or placebo).

Stopping criteria

Patients may be discontinued from the study and assessments at any time, at the discretion of the investigator(s).
Specific reasons for discontinuing a patient from this study are:
1. Voluntary discontinuation by the patient, who is free at any time to discontinue participation in the study without prejudice to further treatment.
2. Safety reasons as judged by the investigator.
3. An intolerable adverse event, considered a drug-related (see section 4.6). reaction to Simvastatin therapy. Simvastatin is a well-tolerated medication that is used in millions of people globally to reduce cholesterol levels on the blood. Adverse events on therapy are uncommon. Subjects would be discontinued from the study if they experienced any intolerable adverse events which were considered drug related or if there were a significant change in baseline blood tests on therapy (an increase in liver function tests

(Bilirubin, AST or ALP) to >8 times upper limit normal or CK levels that were elevated >10 times the upper limit).

Patients who discontinue from the study should always be asked about the reason(s) for their discontinuation and about the presence of any adverse events. Adverse events will be followed up and the patients General Practitioner will be informed.

STUDY PROCEDURES

INFORMED CONSENT PROCEDURE

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Eligible patients may only be included in the trial after obtaining written informed consent. Informed consent must be obtained prior to conducting any trial specific procedures and the process for obtaining informed consent must be documented in the patient's medical records. Similar consent mechanisms have been used successfully in other trials in similar populations(13).

Personal Legal Representative (PerLR) Consent

Informed consent will be sought from the patient's PerLR who may be a relative, partner or close friend. The PerLR will be informed about the trial by the responsible clinician or a member of the research team and they will be provided with a copy of the Covering Statement for the PerLR with an attached Participant Information Sheet (PIS) and asked to give an opinion as to whether the patient would object to taking part in such medical research. If the PerLR decides that the patient would have no objection to participating in the trial they will be asked to sign two copies of the PerLR Consent Form, which will then be countersigned by the person taking consent. A copy of the signed informed consent form will be placed in the patients" medical records, whilst the originals will be retained by the PerLR and by the PI in the Investigator Site File (ISF).

Professional Legal Representative (ProfLR) Consent

If the patient is unable to give informed consent and no PerLR is immediately available, a senior doctor (consultant or registrar) who is not connected with the conduct of the trial may act as a ProfLR. Due to the rapidly evolving nature of the sepsis syndrome and in recognition of the need for early preventative treatments, we aim to start the trial drug as soon as possible after hospital admission. If patient's relatives are not present or unlikely to be available within 1 hour to discuss consent following successful screening, ProfLR consent will be obtained. The doctor will be informed about the trial by the responsible clinician or a member of the research team and given a copy of the PIS. If the doctor decides that the patient is suitable for entry into the trial they will be asked to sign two copies of the ProfLR Consent Form. A copy of the signed informed consent form will be placed in the patients" medical records, whilst the originals will be retained by the doctor ProfLR and by the PI in the ISF.

Retrospective Patient Consent

Patients will be informed of their participation in the trial by the responsible clinician or a member of the research team once they regain capacity to understand the details of the trial. The responsible clinician or a member of the research team will discuss the study with the patient and the patient will be given a copy of the PIS to keep. The patient will be asked for consent to participate in the trial and to sign two copies of the Consent to Continue Form, which will then be countersigned by the person taking consent. A copy of the signed Consent Form will be placed in the patient's medical records whilst the originals will be retained by the patient and by the PI in the ISF. Where consent to continue is not obtained, consent from the legal representative will remain valid. If the patient refuses consent, data collected about the patient will not be entered into the analysis.

Withdrawal of Consent

Patients may withdraw or be withdrawn (by PerLR or ProfLR) from the trial at any time without prejudice. Data recorded up to the point of withdrawal will be included in the trial analysis, unless consent to use their data has also been withdrawn. If a patient or legal representative requests termination of the trial drug during the treatment period, the drug will be stopped but the patient will continue to be followed-up as part of the trial. If a patient or a PerLR withdraws consent during trial treatment, the trial drug will be stopped but permission will be sought to access medical records for data related to the trial. If a patient or PerLR wishes to withdraw from the trial after completion of trial treatment, permission to access medical records for trial data will be sought.

DATA MANAGEMENT

Data will be collected on Case Report forms (CRFs) designed by the research team.
Data up until hospital discharge will be recorded in each subject's Case Report Form by the research team. Submitted data will be anonymised and reviewed for completeness before entering onto the database. Data will be stored securely against unauthorised access and accidental loss. All essential documents and trial records will be archived in conformance with the applicable regulatory requirements and access to these archives will be restricted to authorised personnel. Data Collected will include demographic details, as well as physiological and ventilatory variables that will act as indicators of disease severity.

Data from the study will be held on a bespoke database. Linked anonymised data will be single entered in to the database. The database will be stored securely on a password protected computer at the University of Birmingham. The database will be checked for accuracy and then locked prior to unblinding and analysis. Trial data will be archived for 20 years after the completion of the trial. It will initially be stored within locked filing cabinets within locked rooms at the Centre for Translational Inflammation research, University of Birmingham. Following all analysis, the data may be moved to a secure off-site archive.

Definition of the end of the study

The end of the study will be defined as the date of the final day of the final participant undergoing follow-up

Annual Progress Reports will be sent to the main REC and to the sponsor on the anniversary date on the REC "favourable opinion" letter.

EXPERIMENTAL SAMPLE COLLECTION AND ANALYSIS

Up to 60ml of blood will be taken from the patient as specified in the schedule.
Laboratory Methods
Neutrophil methods: Neutrophils will be extracted from blood using a Percoll (Sigma-Aldrich) density gradient that yields preparations that are 95% pure and 95% viable by cytopsin and propidium iodide staining.

NET production: In separate experiments isolated neutrophils will also undergo immunofluorescent staining of their nuclei and subsequently be stimulated to produce NETs using PMA and fMLP, which will be assessed by fluorescence videomicroscopy.
Chemotaxis assays: Isolated neutrophils are placed over a modified Dunn chamber in a chemotactic shallow gradient. The chamber allows direct viewing of the pathway and speed of migrating cells and establishment of a linear steady state chemokine gradient. Medium alone or medium containing the appropriate concentration of chemoattractant to be assessed is then placed in the slide system and migration of neutrophils is recorded

with a time lapse video-microscopy. Function will be assessed by measuring their chemotactic ability against IL-8.
Markers of tissue degradation/ NE activity, will be measured as per published protocols.
Inflammation. Systemic inflammation will be assessed by a commercially available multi-plex ELISA as per manufacturer guidelines.

PHARMACOVIGILANCE

Timely, accurate and complete reporting and analysis of safety information from clinical trials is crucial for the protection of patients and are mandated by regulatory agencies.

Definition of Adverse Events

The EU Clinical Trials Directive 2001/20 provides the definitions in Table 4.

Table 4: Terms and Definitions for Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	All untoward and unintended responses to an investigational medicinal product related to any dose administered
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).
Serious Adverse Event (SAE) **Serious Adverse Reaction (SAR)** **Suspected Unexpected Serious Adverse Reaction (SUSAR)**	Respectively, any adverse event, adverse reaction or unexpected adverse reaction that: a) results in death; b) is life-threatening; c) requires hospitalisation or prolongation of existing hospitalisation; d) results in persistent or significant disability or incapacity; e) is a congenital anomaly or birth defect; f) is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

Assessment of Causality

Each AE should be clinically assessed for causality based on the information available, i.e. the relationship of the AE to the study drug. For the purposes of this trial the causality should be assessed using the categories presented below. Drug related AEs are defined as those considered by the PI to have a possible, probable or definite relationship to the study drug. The PI at each site will evaluate all AE's for causality using the following guide:

- Unrelated – clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease, or other drugs or chemicals
- Unlikely – clinical event whose time relationship to study drug administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals
- Possible – clinical event with reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals

- Probable – clinical event with a reasonable time relationship to study drug administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals
- Definite – clinical event with plausible time relationship to study drug administration, and that cannot be explained by concurrent disease or other drugs or chemicals

Notification and Reporting of Adverse Events or Reactions

All SAEs irrespective of the causal relationship with the trial medications will be reported to the Sponsor within 24 hours of awareness by the investigator.

Notification and Reporting of Serious Adverse Events / SUSAR

As the IMPs used in this project are licensed in the UK, the expected SARs (outlined in the SmPC) will be recorded in the CRF. All SAEs irrespective of the causal relationship with the trial medications will be reported to the Sponsor within 24 hours of awareness by the investigator.

All SAEs will be recorded in the CRF and on the sponsor SAE form and reported to the JRO within 24 hours of the PI or co-investigators becoming aware of the event. The co-investigators listed in this protocol will be authorized to sign the SAE forms in the absence of the PI. SUSARs arising during the trial will be reported to the JRO and the main REC within one working day of the PI or co-investigator becoming aware of the event.

Procedures for reporting Blinded SUSAR
The allocation of any study participant experiencing a suspected SUSAR will be unblinded according to the Trial Standard Operating Procedure for emergency code breaking, and reported to the Sponsor. If allocation is to vitamin D, the sponsor will report the SUSAR to the MHRA.

Expected SAEs/ SARs and non-reportable events
Expected SAEs / SARs and non-reportable events will be recorded in subjects' case report forms.

REGULATIONS, ETHICS AND GOVERNANCE

The trial will comply with the principles of GCP, the requirements and standards set out by the EU Directive 2001/20/EC and the applicable regulatory requirements in the UK, the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, the European Communities (Clinical Trials on Medicinal Products For Human Use) Regulations, 2004 and subsequent amendments.

ETHICAL CONSIDERATIONS

Regulatory and Ethical Approvals

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Local Research Ethics Committee (LREC) for UK sites. The trial will be conducted in accordance with the EU Directive 2001/20/EC and adhere to the appropriate regulatory requirements in each jurisdiction. A CTA will be obtained from the MHRA and IMB before the start of the trial. The trial will be registered with the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database. The trial will be registered with the UK National Institute for Health Research (NIHR) Clinical Research Portfolio. In order that the trial remains on the NIHR Portfolio and receives the appropriate level of support through the relevant Local Research Network, accrual data on patient recruitment will be forwarded to the UK Clinical Research Network (UKCRN) Co-ordinating Centre on an annual basis.

Protocol Compliance

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the Ethics Committee and the appropriate regulatory authority. Changes to the protocol will require competent authority/ethics committee approval/favourable opinion prior to implementation, except when modification is needed to eliminate an immediate hazard(s) to patients.
Any amendments to the final protocol will be clearly documented and forwarded to the Research Ethics Committee for approval prior to implementation

Indemnity

The University of Birmingham has in force a Public Liability Policy and/or Clinical Trials policy which provides cover for claims for "negligent harm" and the activities here are included within that coverage. The research will take place at NHS Trust sites only and the usual indemnity through provided through NHS schemes and professional indemnity will also apply.

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