Division: Worldwide Development
Information Type: Synoptic Clinical Study Report

Title:	Methodology Study to develop sinerem enhanced 3T MR Imaging of Atherosclerotic Plaques within the Carotid Arteries and Thoracic Aorta, and to compare sinerem MRI to contrast enhanced ultrasound

Phase: II

Compound Number: None

Effective Date: 05-FEB-2010

Subject: Magnetic Resonance Imaging (MRI), Atherosclerotic Plaques, Carotid Arteries, Thoracic Aorta, Cardiovascular Disease Subjects, Ultrasmall Supraparamagnetic Particles Iron Oxide (USPIO), 3 Tesla (3T), Transcranial Doppler (TCD), contrast enhanced ultrasound (CEUS).

Author(s): PPD

Indication Studied: Cardiovascular

Initiation Date: 05 Feb 2009

Early Termination Date: 29 Oct 2009

Date of Report: February 2010

Earlier CSRs

Clinical Study Report Revision History

Sponsor Signatory: Dr Paul M Matthews
(and Medical Officer) VP for Imaging, Genetics and Neurology
GlaxoSmithKline

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

Synopsis

Study Number: EMI111784\

Title: Methodology Study to develop sinerem enhanced 3T MR Imaging of Atherosclerotic Plaques within the Carotid Arteries, and to compare sinerem MRI to contrast enhanced ultrasound

Investigator(s): PPD

Study center(s): GSK Clinical Imaging centre, Hammersmith Hospital, London, UK

Publication(s): None at the time of this report.

Summary:

This clinical study aimed to develop imaging techniques to identify vulnerable atherosclerotic plaque (within the carotid arteries and the thoracic aorta) using two diagnostic agents: Sinerem for enhanced magnetic resonance imaging (MRI) and Sonovue for enhanced ultrasound.

Sonovue has Marketing Authorisation while Sinerem is an investigational MRI contrast agent under development by Guerbet.

This study was terminated early following GSK (the sponsor of the study) being informed of Guerbet's decision not to continue development of Sinerem.

Study Period: 05 Feb 2009 - 29 Oct 2009

Phase of Development: II

OBJECTIVES

Primary

- To develop Sinerem enhanced MRI data acquisition and analysis methods at 3T in order to characterize macrophage uptake in atherosclerotic plaques within the carotid artery.

Secondary

- To determine the optimal Sinerem dose for use of MRI scanning of carotid atherosclerosis at 3T.
- To evaluate the test-retest reproducibility of a specific set of structural and T2* related metrics in Part C (which will be developed in Parts A and B) over two scanning sessions in subjects with atherosclerosis.
- To contribute safety data to the Guerbet Sinerem Global Safety Database.

Exploratory

- To develop Sinerem enhanced MRI data acquisition and analysis methods at 3T in order to characterize macrophage uptake in atherosclerotic plaques within the thoracic aorta.
- To explore the relationship between plaque inflammation (measured by Sinerem 3T MRI), and intraplaque neovascularisation (measured by contrast enhanced ultrasound).
- To gather preliminary data on the test-retest reproducibility of contrast enhanced ultrasound (CEUS) over two scanning sessions in subjects with atherosclerosis.
- To explore the relationship between plaque inflammation (measured by Sinerem 3T MRI) and arterial concentration of MZ.7375.
- To gather preliminary data on Ultrasmall Superparamagnetic Iron Oxide (USPIO) uptake in thoracic and abdominal fat depots
- To gather preliminary data on contrast enhanced ultrasound signal within pericardial fat.

METHODOLOGY

The study was divided into 4 parts. Up to 30 subjects were to be recruited in total into Parts A, B and C, so as to acquire evaluable data from at least 4 subjects in each of these 3 parts. Part D would require between 6 and 10 patients. Patients from Parts A, B and C were eligible to participate in Part D.

Study Parts A & B

Eligible subjects were allocated into part A or B at the PI's discretion. Subjects attended the Clinical Imaging Centre (CIC) for a single scanning session consisting of a single MRI session. Subjects allocated into Part A had a carotid artery scan, whilst subjects allocated into Part B had a scan of their thoracic aorta. When MRI sequences in Parts A and B had been optimized, recruitment into Parts A and B ceased and recruitment into Part C commenced.

Study Part C

Subjects attended the CIC for two MRI scanning sessions. Safety assessments at each session were identical and consisted of an MRI scan including a carotid artery scan, using parameters optimized in Part A, and a thoracic scan, using parameters optimized in Part B.

The aim of Parts A, B and C was to optimise MRI sequences for scanning carotid and thoracic aorta atherosclerosis.

Study Part D

In Part D, each subject was to receive two MRI scans and two ultrasound scans. Each subject would have been given a single administration of Sinerem and two administrations of Sonovue, with at least a 7 day period in between administration of Sonovue and Sinerem.

STUDY POPULATION

Subject Disposition and Demographics

Number of Subjects	
Number of subjects planned, N:	70
Number of subjects enrolled, N:	26
Number of subjects completed as planned, n (%):	24
Number of subjects withdrawn (any reason), n (%):	2
Number of subjects withdrawn for AE, n (%):	0
Demographics	
Age in Years, Mean (Range)	70 (50-80)
Sex, n (%)	
Female:	6 (23)
Male:	20 (77)
BMI, Mean (Range)	26.5 (22.4-36.6
Height (M), Mean (Range)	1.63 (1.54-1.86)
Weight, Mean (Range)	77 (53.1-98.1)
Race, n (%)	
Asian – South East Asian Heritage	1 (4)
White – White/Caucasian/European Heritage	25 (96)

Twenty six subjects were enrolled into the study, of which 15 completed Part A, 1 completed Part B and 8 completed Part C. Two subjects were withdrawn (one failed screening and one did not attend the study appointments). At the time of early termination no subjects had been enrolled into Part D.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

- Male or female between 18 and 80 years of age inclusive. Women were of non-childbearing potential.
- Atherosclerotic plaque within the carotid artery as assessed by carotid ultrasound either documented prior to screening or detected at the screening visit.

TREATMENT ADMINISTRATION

At the time of early termination Part D had not yet commenced, thus no subjects received either of the diagnostic agents Sonovue or Sinerem.

Sinerem and Sonovue would only have been administered in Part D of the study, in which each subject would have received two MRI scans and two ultrasound scans and would have been given a single administration of Sinerem and two administrations of Sonovue, with at least a 7 day in period in between administration of Sonovue and Sinerem.

The maximum dose of Sinerem that would have been administered (2.6mg/kg) was the standard dose used in clinical studies. It was anticipated that, during the study, the dose of Sinerem may have been reduced to optimise data acquisition. Under no circumstances would the dose would have been increased. The dose of Sonovue that would have been used was the clinical dose recommended in the approved Summary of Product characteristics (SmPC) for vascular imaging (2.4mLs).

RESULTS

As this study was terminated early, no formal statistical analysis was performed and so there are no quantitative results to report.

Part A:

The purpose of Part A was to modify sequences to ensure optimal signal-to-noise ratio (SNR) and reduce scan time. In doing this we were able to develop a T2* sequence with excellent blood flow suppression. In previous studies regions of USPIO -induced hyopintensity in the plaques have been identified following co-registration of T1 black blood sequences on to the T2* maps, as blood signal suppression was not able to be performed on those multi-echo gradient echo acquisitions. Therefore, in this study we were able to use this additional feature to allow measurement of T2* hypointensity directly from the T2* maps. The details of the sequence optimisation procedures are described below.

By defining the period after the final preparation pulse but before each slice's excitation pulse as t, and the remaining period after imaging before the end of the TR (Repetition Time) as Teff, a closed form solution for the steady-state signal can be derived. It can be seen that this is a modified SPGR (Spoiled Gradient Echo) steady-state signal equation, which has additional decay due to diffusion-weighting and T2 decay during the preparation. The flip angle which gives maximal signal (Ernst angle) is greatly increased from that of pure SPGR, due to T2 decay during the prep period. The small RMSE (Root Mean Squared Error) of 0.56% between the Bloch simulations for muscle confirms the solution. Increasing the size of the flow-sensitizing gradients in the preparation reduces the speed at which flowing spins are suppressed, but adds additional T2 weighting to the acquired images. A field of speed (FOS, = 2*Venc) of 37cm/s was empirically chosen as a balance between flow suppression and signal loss. Excellent blood suppression is noted in each, showing the robustness of the flow suppression.

Part B:

As suggested to be a possibility in the protocol, an assessment after imaging one patient in Part B suggested that the objective of refining a USPIO sensitive sequence for application to the thoracic aorta was not feasible given available resources. As this also was not critical to meeting the main study objectives, no further patients were enrolled into Part B.

Part C:

The study was terminated before completion of Part C with formal notification by the manufacturers, Guerbet, that Sinerem could not be made available for use in the study. This decision by Guerbet was as a consequence of recent information received by them from the European regulators and was not anticipated by either Guerbet or the investigators at the start of this study.

Part D:

The study was terminated before initiation of Part D.

Safety

There were no adverse events to report from this study.

CONCLUSIONS:

- Black blood sequences to quantify T2* values with good blood suppression were successfully developed and implemented.
- Neither IMP (Sinerem nor Sonovue) were administered as Sinerem, so no conclusions can be drawn with regards to most objectives of the study.

Date of Report: February 2010