



## CASE STUDY/AEGR-733

Hepatic fat accumulation in hyperlipidemic patients as measured by magnetic resonance spectroscopy and magnetic resonance imaging

### INTRODUCTION

When used in combination, magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI) can offer unique advantages in the study of hepatic fat in hyperlipidemic patients. MRI assesses differences in local environments to produce high contrast images, while MRS is capable of displaying minute differences in the magnetic properties of different chemical compounds to provide a unique biochemical signature. As a result, MRS can quantify important information on cellular activity and metabolism within the imaged region.

Because of its unique capabilities in employing novel imaging technologies in drug development trials, American College of Radiology (ACR) Image Matrix was chosen for a groundbreaking, randomized clinical trial testing the efficacy and safety of an MTP inhibitor.

### ABOUT THE STUDY

Sponsored by Aegerion Pharmaceuticals, a randomized, double-blind, and placebo-controlled parallel-group study was conducted to evaluate the improvement in hyperlipidemic patients given low doses of the MTP-inhibitor AEGR-733. Specifically, the study monitored the effects of low-dose AEGR-733, administered with and without other lipid-lowering agents, on standard laboratory parameters such as lipid profile, hepatic and blood/urine biomarkers, ECG results, and high-sensitivity C-reactive protein.

The primary objective for ACR Image Matrix was to evaluate the impact of low-dose AEGR-733 as monotherapy and in combination with established lipid-lowering on hepatic fat accumulation measured by MRS/MRI. A secondary objective was to assess the correlation between hepatic fat measurements obtained by MRS – the more standard approach – and those generated from the MRI scans on the same patients.

A total of 696 participants were screened for eligibility, of which 460 underwent a screening MRS/MRI scan and 260 were randomized for treatment. During the 11 months of the trial, ACR Image Matrix trained and qualified 17 radiology sites identified by the clinical CRO, PharmaNet, to perform the imaging part of the protocol. ACR Image Matrix received the 1,405 MRS and 1,417 MRI scans from the sites, then archived image and non-image data into its clinical trials management system. ACR Image Matrix researchers and staff evaluated images for quality and protocol adherence then analyzed the data using a novel data processing software, (ACORN) NUTS, validated by ACR Image Matrix for this purpose. Finally, the data was transferred in the sponsor's preferred format to the PharmaNet database.

## BACKGROUND

AEGR-733 is a potent and selective inhibitor of MTP, which is essential for the assembly of lipoproteins containing apolipoprotein B. MTP plays an important role in the synthesis and production of very low-density lipoprotein cholesterol (VLDL-C) in the liver and of chylomicrons in intestinal cells. When MTP is inhibited, chylomicrons and VLDL-C are not released into the circulation, resulting in reduced serum levels of LDL-C. Because chylomicrons serve as transport vehicles for triglycerides and cholesterol ester, MTP inhibition appears to reduce plasma cholesterol and triglycerides derived from both hepatic and intestinal sources.

Because MTP inhibition impairs lipid transport from the liver, the drug may cause an increase in hepatic fat. While the clinical significance of hepatic fat accumulation is unclear, study sponsors hoped to achieve clinically significant reductions in plasma LDL-C and triglycerides while minimizing the potential for adverse events, including hepatic lipid accumulation. Because this drug is expected to be used primarily in combination with other lipid-lowering therapies and because data from other studies had suggested that some lipid-lowering therapies may reduce hepatic fat content, the effect of AEGR-733 administered in combination with these agents was also investigated.

## STUDY CHARACTERISTICS

The study comprised two phases – an initial 35-60 day screening/wash-out period followed by a 12-week treatment phase. All patients attended 11 study-related visits, with vital signs, fasting lipid profile, and standard safety labs monitored at each visit. Patients underwent physical examination at screening and upon discharge. Site researchers charted adverse events, dietary habits, drug compliance, and concomitant medications at each visit. Hepatic MRS/MRI was performed at visits 1, 4, 7, 9, and 11 (screening, baseline, and study weeks 4, 8, and 12). The primary endpoint for this study was the percentage change from baseline in hepatic fat content at 12 weeks, as measured by hepatic MRS and also by MRI for subjects taking AEGR-733 (5 mg) or placebo.

## SPONSOR COMMENTS



“This is one of the largest studies to utilize MRS and MRI for the quantification of hepatic fat and certainly one of the first to do multiple serial measurements. Therefore, we knew from the beginning that this would be a breakthrough study, bringing to bear new technologies in a novel way. Although we had great hopes for the extra dimensions of data collection this technique would allow, we recognized the potential pitfalls were numerous and serious. ACR Image Metrix did an extraordinary job of qualifying and training the radiology labs to a standard protocol, then collecting, analyzing, and archiving over 2,800 separate images. The process was well-designed and well-managed from start to finish.” [William Sasiela, Ph.D., Chief Medical Officer, Aegerion Pharmaceuticals]

## CONCLUSION

Utilizing new MRS and MRI techniques to make available additional depth of study data, ACR Image Metrix provided a comprehensive range of services. In addition to advice on the structure of the study, as well as vetting and training radiology sites, ACR Image Metrix handled all aspects of the images themselves, including archiving, image interpretation/quantitation and processing, and delivery. MRI results were compared to MRS to assess the viability of using MRI as a valid imaging method for future studies.

While AEGR-733 is still in the midst of clinical development, the methodology of utilizing MRS or MRI to measure hepatic fat was determined to be efficient and effective, and in that regard, the study was agreed by all of the involved parties to be a success.