CASE STUDY

Independent, Centralized Image Review and Analyses Supporting Development of VK2809 to Treat NAFLD/NASH

Introduction

Non-alcoholic fatty liver disease (NAFLD) and its progression to non-alcoholic steatohepatitis (NASH), is estimated to become the most common chronic liver condition in Western populations. This increased prevalence is related to the increase in lifestyle-related diseases – due to the shared risk factors of obesity, insulin sensitivity, and poor diet and exercise habits.

However, the etiology of NAFLD/NASH is not well understood – the diseases' multifactorial nature is a contributing factor and challenges drug development. Although sponsors are racing through Phase III trials, there has been limited success, and no drug is currently approved for treatment. Therefore, ongoing research is important for disease understanding as well as identification of effective treatments. To achieve this, we also must be able to appropriately identify patients and monitor treatment efficacy. Medical imaging can play an important role in this process.

ESTIMATED PREVALENCE in the United States:[1]

20–30%
NAFLD

2–5%
NASH

Situation

Viking Therapeutics is a clinical-stage biopharmaceutical company focused on the development of novel therapies for metabolic and endocrine disorders, including VK2809, its novel liver-selective thyroid receptor beta agonist. In a 12-week, multi-center (USA only), randomized, double-blind, placebo-controlled, Phase 2a study, Viking examined the safety, tolerability, and efficacy of oral VK2809 in patients with NAFLD and elevated low-density lipoprotein (LDL) cholesterol.[2] Three doses (5 mg daily [QD], 10 mg QD, 10 mg every other day [QOD]) were compared with placebo. Endpoints included the effects on liver fat content and other liver and lipid markers.

Eligibility criteria included LDL-C ≥110 mg/dL, triglycerides ≥120 mg/dL, and MRI-PDFF liver fat content ≥8% (reduced from the initial criterion of ≥10%). To accurately detect eligible patients as well as statistically and clinically significant changes in fat, accurate, consistent images and analyses are important. To achieve this, Viking required support for independent central image review.

Solution

Bioclinica was chosen to conduct the independent central review, managing the sites and performing the analysis. Responsibilities included site setup and qualification and issuing, tracking, and resolving queries to the sites. Bioclinica's global internal readers also performed rapid eligibility analysis of the images from screened patients, while Bioclinica's internal experts conducted an independent review and quantitative image analysis of the liver images (Figures 1 and 2).

To ensure the highest quality image data from the sites, Bioclinica employs a "Multi-Step Quality Control" process to detect substandard image quality or violations of imaging protocol. If poor quality images or protocol violations were detected in this study, additional site training around imaging techniques and the protocol was implemented.

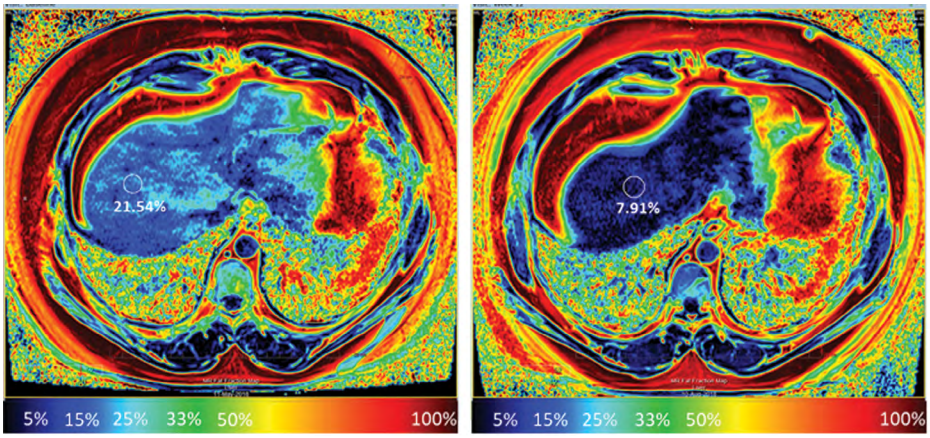

Figure 1. Couinaud segment 8 baseline (L) and 12-week follow-up (R) MRI-PDFF scan from a subject receiving daily 10 mg VK2809. The absolute hepatic fat fraction (HFF) reduction is 18.6% representing a magnitude reduction of 75.6%.

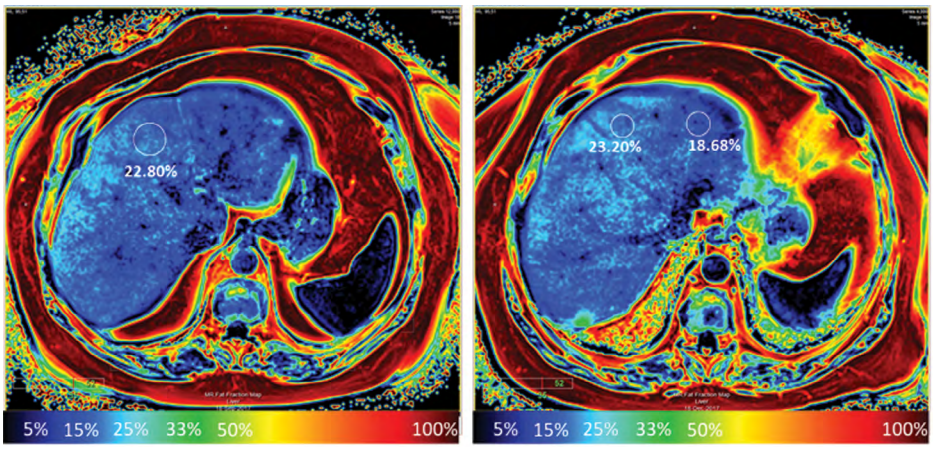

Figure 2. Couinaud segment 4a baseline (L) and 12-week follow-up (R) MRI-PDFF scan from a subject receiving placebo. The absolute HFF was relatively unchanged, increasing slightly 2.3%, representing a magnitude increase of 11.4%.

Outcomes

Based on the results of this 12-week study, Viking will continue development of VK2809 for the improvement of liver fat content, with a Phase 2b study in patients with biopsy-confirmed NASH planned to begin in late 2019.

As detected by MRI-PDFF, liver fat content significantly decreased at all VK2809 doses, compared with placebo, resulting in a ≥50% reduction in liver fat on MRI-PDFF in 70% of treated subjects (p=0.014). In addition, VK2809 was well-tolerated, with no SAEs reported in any cohort.

Summary

A non-invasive, non-ionizing radiation method such as MRI-PDFF can play an important role in drug development for fatty liver disease by confirming eligibility and demonstrating efficacy. An independent central review of MRI-PDFF images by experts provides the ability to recruit subjects capable of producing the desired pharmacodynamic effect and ensures high-quality, robust results throughout the study duration.

VK2809 is a promising low-dose liver-targeted thyroid receptor beta agonist therapy to treat patients with biopsy-proven NASH with fibrosis.

References

1. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34:274–285.
2. Loomba R, Neutel J, Mohseni R, et al. LBP-20-VK2809, a novel liver-directed thyroid receptor beta agonist, significantly reduces liver fat with both low and high doses in patients with non-alcoholic fatty liver disease: a phase 2 randomized, placebo-controlled trial. J Hepatol. 2019;70:e150-e151.

PROPORTION OF PATIENTS WITH ≥30% REDUCTION IN LIVER FAT CONTENT:

100%
5 MG QD*

90.9%
10 MG QD*

76.9%
10 MG QOD*

16.7%
PLACEBO

* P < 0.01

MEDIAN RELATIVE CHANGE IN LIVER FAT CONTENT FROM BASELINE:

53.8%
5 MG QD*

59.7%
10 MG QD*

56.5%
10 MG QOD*

9.4%
PLACEBO

* P < 0.01