Reduction of atherogenic lipoprotein (a) and apolipoprotein B in humans with the selective thyroid receptor beta agonist VK2809

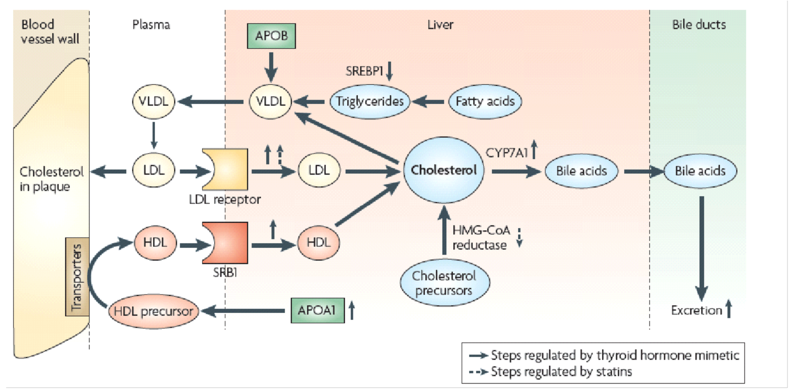
Steven L. Schoenfeld[1], Brian Lian[1], Rochelle Hanley[1], Ken Homer[2]
[1]Viking Therapeutics, San Diego, CA, [2]Integrium, LLC, New Jersey

Introduction

Thyroid hormones are important modulators of lipid homeostasis and metabolism. Overt hypothyroidism in humans is associated with elevated low-density lipoprotein (LDL) cholesterol and apolipoprotein B, due to decreased clearance of LDL, resulting in part from reduced expression of hepatic LDL receptors. Conversely, in hyperthyroidism there is an enhanced excretion of cholesterol and increased turnover of LDL resulting in decreased total and LDL cholesterol (reviewed by Duntas and Brenta, 2012).

Apoliprotein B is the main structural surface protein found on all beta lipoproteins (Chylomicrons, VLDL, IDL and LDL) and can function to traffic cholesterol into the artery wall. Lipoprotein(a) [Lp(a)] is a type of low density lipoprotein and is covalently bound to apolipoprotein B by a disulfide bridge (Steyrer et al. 1994). Lp(a) interferes with fibrinolysis by competing with plasminogen binding to molecules and cells. In addition, Lp(a) binds to macrophages via a high-affinity receptor that promotes foam cell formation and the deposition of cholesterol in atherosclerotic plaques (Zioncheck et al. 1991). The association of Lp(a) with cardiovascular disease has been shown in several studies, including a meta-analysis of over 120,000 subjects which concluded that Lp(a) was particularly involved in vascular outcomes such as CHD and stroke (Ergou et al. 2009).

The thyroid hormone receptor isozyme beta-1 (TRβ-1) is a nuclear hormone receptor that is responsible for the effects of T3 on cholesterol, triglyceride, and bile acid metabolism. Cholesterol excretion in the bile as well as hepatic hepatic expression of LDL and HDL receptors are stimulated by T3 through binding to TRβ (reviewed by Angelin and Rudling 2010). These characteristics suggest potentially promising therapeutic effects in settings where elevated lipids contribute to long-term cardiovascular risks.



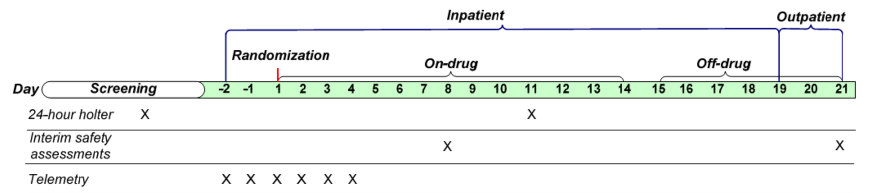
VK2809 is a liver-targeted small molecule prodrug of a potent, selective TRβ agonist, VK2809A. VK2809 derives its liver-targeting properties via selective activation by the cytochrome P450 isozyme 3A4 (CYP3A4), an enzyme found predominantly in liver tissue. This generates elevated hepatic exposure to VK2809A, with reduced systemic exposure to other tissues, such as heart and skeletal muscle.

In animals, VK2809 has demonstrated potent reductions of plasma cholesterol, triglycerides, and liver fat content.

Hypothesis

In a previous 14-day Phase 1b trial in subjects with elevated LDL-C (>100 mg/dL), treatment with VK2809 at doses of 5 mg to 40 mg daily resulted in placebo-adjusted reductions in LDL-C (LSM) of 15% to 41% (an overview of the study design of this trial is below).

Overview of the previous 1b study



In view of the robust observed reduction in LDL-C, and historical data suggesting TRβ agonists may have broader lipid-lowering effects, we set out to determine if the atherogenic particles lipoprotein(a) [Lp(a)] and Apolipoprotein B-100 (Apo B) were similarly reduced by treatment with VK2809.

Methods

Archival blood samples from subjects who had completed the 14 day Phase 1b study were retrieved and analyzed for Lp(a) and Apo B. The percentage change from baseline (Day 1) to Day 15 in Apo B and Lp(a) was determined using an Analysis of Covariance model with Treatment as the primary effect and the baseline value as the covariate. The placebo-adjusted percent change from baseline with their corresponding 95% confidence intervals were derived using this model.

Results

Apo B

After 14 days of once daily treatment with VK2809, placebo-corrected, least square mean reductions in levels of plasma Apo B ranged from 5% to 40%. Higher doses resulted in greater Apo B reductions, which appeared to peak in the 40% range. The observed reductions were highly statistically significant at doses above 2.5 mg per day.

VK2809-102: Apo B

	Treatment Group							
	PBO	**0.25 mg**	**1.0 mg**	**2.5 mg**	**5.0 mg**	**10.0 mg**	**20.0 mg**	**40.0 mg**
Baseline	**(N=14)**	**(N=6)**	**(N=6)**	**(N=6)**	**(N=6)**	**(N=6)**	**(N=6)**	**(N=6)**
Mean (SD)	107.5 (10.4)	107.7 (23.1)	102.7 (13.5)	109.3 (11.0)	109.8 (10.8)	116.7 (31.4)	95.8 (8.8)	122.7 (7.4)
(Min, Max)	(90, 125)	(85, 150)	(85, 124)	(94, 128)	(94, 126)	(77, 153)	(83, 110)	(112, 129)
Day 15	**(N=14)**	**(N=6)**	**(N=6)**	**(N=6)**	**(N=6)**	**(N=6)**	**(N=6)**	**(N=5)**
Mean (SD)	96.6 (13.2)	96.2 (26.3)	88.0 (15.9)	88.5 (16.3)	76.5 (10.6)	68.2 (13.8)	51.2 (7.4)	58.2 (5.8)
(Min, Max)	(75, 118)	(68, 141)	(74, 116)	(65, 105)	(68, 192)	(54, 87)	(40, 60)	(52, 65)
Percent Change – Day 15	**(N=14)**	**(N=6)**	**(N=6)**	**(N=6)**	**(N=6)**	**(N=6)**	**(N=6)**	**(N=5)**
Mean (SD)	-9.6 (12.4)	-10.6 (16.5)	-13.7 (15.3)	-18.7 (15.2)	-30.3 (7.2)	-40.1 (9.1)	-46.7 (4.6)	-52.0 (4.1)
(Min, Max)	(-34.2, 5.1)	(-27.7, 15.3)	(-32.1, 9.4)	(-38.1, -3.2)	(-38.6, -17.9)	(-54.8, -29.9)	(-51.8, -38.8)	(-58.6, -49.2)

*Data is Mean (SD), (Min, Max)

VK2809-102: Least Squares Mean (LSM) Analysis of Percent Change from Baseline to Day 15 for Apo B

Treatment Group	n	LSM	95% CI		PBO-Adjusted LSM	PBO-Adjusted 95% CI	P value versus placebo
PBO	14	-9.8	(-16.0, -3.6)				
0.25 mg	6	-10.7	(-20.1, -1.3)		-0.9	(-12.2, 10.4)	0.87
1.0 mg	6	-14.8	(-24.3, -5.3)		-5.0	(-16.3, 6.3)	0.38
2.5 mg	6	-18.6	(-28.0, -9.1)		-8.7	(-20.0, 2.5)	0.12
5.0 mg	6	-30.0	(-39.5, -20.6)		-20.2	(-31.5, -8.9)	0.0008*
10.0 mg	6	-38.4	(-48.0, -28.8)		-28.6	(-40.0, -17.2)	<0.0001*
20.0 mg	6	-49.3	(-59.1, -39.5)		-39.5	(-51.0, -27.9)	<0.0001*
40.0 mg	5	-49.4	(-60.1, -38.7)		-39.6	(-52.0, -27.2)	<0.0001*

Lp(a)

After 14 days of once daily treatment with VK2809, placebo-corrected, least square mean reductions in plasma Lp(a) ranged from 13% to 60%. The reductions were highly statistically significant at doses above 5 mg per day.

VK2809-102: Lp(a)

	Treatment Group							
	PBO	**0.25 mg**	**1.0 mg**	**2.5 mg**	**5.0 mg**	**10.0 mg**	**20.0 mg**	**40.0 mg**
Baseline	**(N=12)**	**(N=5)**	**(N=5)**	**(N=5)**	**(N=5)**	**(N=5)**	**(N=6)**	**(N=6)**
Mean (SD)	11.6 (11.3)	30.2 (31.9)	19.8 (10.4)	44.6 (64.7)	41.0 (25.9)	20.2 (18.8)	19.3 (9.5)	12.5 (9.4)
(Min, Max)	(3, 42)	(3, 83)	(8, 36)	(5, 156)	(5, 75)	(4, 52)	(7, 34)	(3, 29)
Day 15	**(N=10)**	**(N=4)**	**(N=5)**	**(N=4)**	**(N=5)**	**(N=4)**	**(N=5)**	**(N=1*)**
Mean (SD)	11.8 (12.0)	34.0 (29.5)	13.8 (4.9)	43.0 (58.3)	27.4 (18.4)	11.3 (12.6)	8.4 (6.4)	14(.)
(Min, Max)	(3, 42)	(6, 74)	(6, 18)	(3, 127)	(3, 49)	(3, 30)	(3, 18)	(14, 14)
Percent Change – Day 15	**(N=10)**	**(N=4)**	**(N=5)**	**(N=4)**	**(N=5)**	**(N=4)**	**(N=5)**	**(N=1*)**
Mean (SD)	-5.6 (57.6)	-12.0 (23.4)	-23.6 (26.9)	-30.1 (21.6)	-34.7 (14.6)	-60.6 (12.2)	-59.8 (19.3)	-51.7 (.)
(Min, Max)	(-46.2, 150)	(-45.5, 5.6)	(-50.0, 20.0)	(-62.5, -18.6)	(-55.6, -17.1)	(-66.7, -42.3)	(-85.0, -42.9)	(-51.7, -51.7)

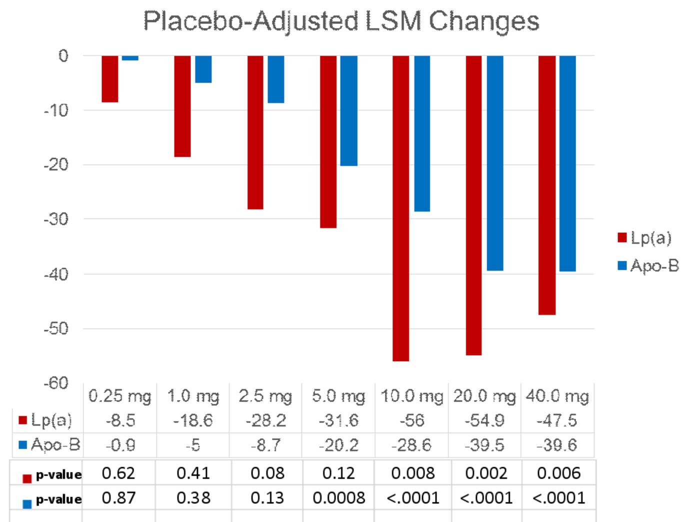
*4 pts in the 40 mg VK2809 group had Lp(a) values that were BLQ at Day 15 (< 2)

VK2809-102: Least Squares Mean (LSM) Analysis of Percent Change from Baseline to Day 15 For Lp(a)

Treatment Group	n	LSM	95% CI		PBO-Adjusted LSM	PBO-Adjusted 95% CI	
PBO	10	-4.4	(-28.8, 20.1)				
0.25 mg	4	-12.9	(-50.4, 24.6)		-8.5	(-54.1, 37.0)	0.62
1.0 mg	5	-22.9	(-56.4, 10.5)		-18.6	(-59.5, 22.3)	0.41
2.5 mg	4	-32.5	(-72.0, 6.9)		-28.2	(-76.4, 20.0)	0.08
5.0 mg	5	-35.9	(-69.9, -2.0)		-31.6	(-74.5, 11.3)	0.12
10.0 mg	4	-60.3	(-97.6, -23.1)		-56.0	[-100.0, -11.6)	0.0081*
20.0 mg	5	-59.2	(-92.6, -25.8)		-54.9	(-95.8, -13.9)	0.0023*
40.0 mg	1*	-51.9	(-126.4, 22.6)		-47.5	(-126.0, 30.9)	0.0056*

* 4 pts in the 40 mg VK2809 group had Lp(a) values that were BLQ at Day 15 (< 2)

Placebo-Adjusted % Changes in Lp(a) and Apo-B: Baseline to Day 15



Conclusions

Statistically significant reductions of the atherogenic proteins Lp(a) and Apo B were observed after 14 days of daily treatment with the selective TRβ agonist VK2809. These effects may suggest unique differentiation relative to thyromimetic-based agents and could provide additional therapeutic benefit beyond improvement in LDL and triglyceride profile. For example, while thyroid hormone replacement in patients with hypothyroidism is known to improve lipid profiles, the effects on Apo B and Lp(a) have been inconsistent (Triguero et al.,1998; Monzani et al., 2004).

Reduction in atherogenic protein levels could be important for patients with elevated cardiovascular risks, such as those with obesity, metabolic syndrome, dyslipidemia, and NASH. Multiple studies have discussed the importance of atherogenic proteins in CVD. Nordestgaard et al. (2010) concluded that there was a "robust and specific association between elevated Lp(a) and increased cardiovascular disease." Barter et al. (2006) discussed the utility of Apo B versus cholesterol in estimating cardiovascular risk in order to guide physicians in treatment of their patients, concluding that "Evidence from fundamental, epidemiological and clinical studies indicates that apo B is superior to any of the cholesterol indices to recognize those at increased risk of vascular disease and to judge the adequacy of lipid-lowering therapy." Harper and Jacobson (2010) similarly commented in the Mayo Clinic Proceedings, "Using Apolipoprotein B to Manage Dyslipidemic Patients: Time for a Change?" Thus, the preponderance of evidence speaks to the importance of Lp(a) and Apo B in cardiovascular disease. Few single-agent treatments outside niacin (which is often poorly tolerated), have demonstrated the ability to significantly lower both Lp(a) and Apo B.

VK2809 is a prodrug that is selectively activated in the liver to release a potent TRβ agonist in tissue with high receptor density. Such liver-targeted, subtype-selective TRβ agonists may offer advantages over less-selective thyromimetics, or over treatment with thyroid hormone itself, due to reduced activity at the thyroid alpha receptor, which has a role in cardiac function and bone metabolism.

In conclusion, the data presented herein suggest that VK2809 may represent a promising potential new therapy for the treatment of patients with elevated markers of CV risk such as Lp(a)/Apo B.

A proof of concept study is underway to evaluate the effects of VK2809 on atherogenic lipids and liver fat content in patients with hypercholesterolemia and fatty liver disease.

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Author Disclosure Information

S.L. Schoenfeld: Full time employee Viking Therapeutics

B. Lian: Full time employee Viking Therapeutics

R. Hanley: Retired employee Viking Therapeutics

K. Homer: Full time employee, Integrium LLC, under contract to Viking Therapeutics