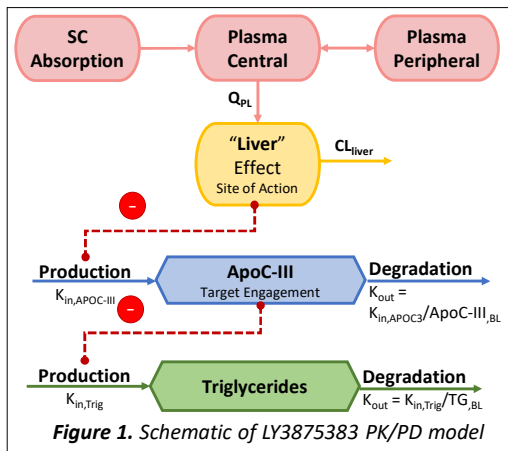


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Introduction

- LY3875383 is a GalNAc-conjugated small interfering RNA (siRNA) targeting apolipoprotein-C-III (ApoC-III), a potent inhibitor of lipoprotein lipase (LPL) activity. The reduction of ApoC-III levels can reduce the level of triglycerides (TG), associated with cardiovascular risk.
- siRNAs prevent the translation of specific target protein by inducing the degradation of mRNA. GalNAc-conjugated siRNAs bind to ASGPR that are abundantly expressed on hepatocytes. Following the hepatocyte internalisation, siRNAs are trapped in the endosomes and released in the cytosol. siRNAs interact with the RNA-induced silencing complex (RISC), leading to the cleavage of mRNA (i.e., degradation).
- siRNAs typically exhibit a transient plasma exposure (half-life less than 10 hr). In contrast, liver exposure is sustained, and half-life is prolonged (several weeks/months). Consequently, the pharmacodynamic (PD) effect is delayed and prolonged compared to plasma pharmacokinetics (PK) and durable, correlating with longer liver exposure.
- The aim of this study is to develop a population PK/PD model describing LY3875383 PK and PD effect on ApoC-III, and the downstream effect on TG.

Methods

- LY3875383 was investigated in a single-ascending dose Phase 1 study. Forty-one healthy participants received a single subcutaneous dose of LY3875383 or placebo.
- Serial plasma PK was collected up to 72h, then bi-weekly up to day 85. ApoC-III and TG levels were monitored up to one year.
- A population PK/PD model was developed in NONMEM v7.5.0. Due to the delay between plasma PK and PD effect, plasma PK was connected to PD by integrating a physiological liver compartment (i.e., surrogate for RISC-bound concentrations). Liver concentrations inhibit the production of ApoC-III. Subsequently, decrease of ApoC-III levels reduces the production of TG. ApoC-III and TG are both described using a turnover model.

Results

- A two-compartment PK model best described plasma PK with a combined zero- and first-order absorption. Body weight effect was added on central volume and clearance (fixed allometric scaling coefficient of 1 and 0.75, respectively). A dose covariate on the absorption rate was also included to account for non-linear increase in maximal concentrations (C_{max}).
- The well-stirred liver compartment enabled to predict liver concentrations (i.e., the main PK driver of PD effect). Liver clearance was slow compared to plasma (plasma vs liver clearance = 14.6 vs 0.000482 L/h, respectively).
- Reductions of ApoC3 and TG followed a dose-response relationship. Durability of effect increased with doses.

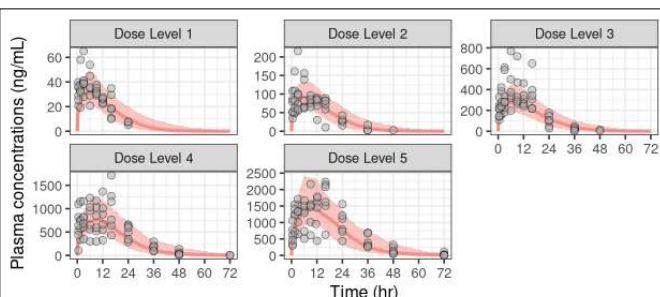


Figure 2. Observed vs predicted PK concentration over time profiles
Shaded area – 90% PI; solid line – median predicted; circles – observations

Table 1. Summary of the population PD model parameters

	Parameter	Definition	Estimate (RSE%)	IIV% (RSE%)
ApoC-III	CL _{liver} (L/h)	Clearance from liver compartment	0.000482 (24)	
	K _{in,APOC-III,0} (mg/dL/h)	synthesis rate of ApoC-III	0.0271 (19)	84.8 (21)
	ApoC-III _{BL} (mg/dL)	ApoC-III at baseline	11.8 (4.8)	30.1 (6.3)
	E _{max}	Maximal drug effect induced by liver conc	1 FIX	
	EC50 (ng/mL)	siRNA conc in liver required to achieve 50% of maximal effect	97900 (24)	109 (26)
TG	Hill	Hill coefficient	0.72 (23)	
	K _{in,Trig,0} (mg/dL/h)	Synthesis rate of triglycerides	5.62 (22)	
	TG _{BL} (mg/dL)	Triglycerides at baseline	131 (8.3)	55.4 (24)
	gamma	Gamma coefficient for ApoC3-TG translation (K _{in,TG} = K _{in,TG,0} × (ApoC _{3,t} /ApoC _{3,BL}) ^{gamma})	0.846 (6.6)	

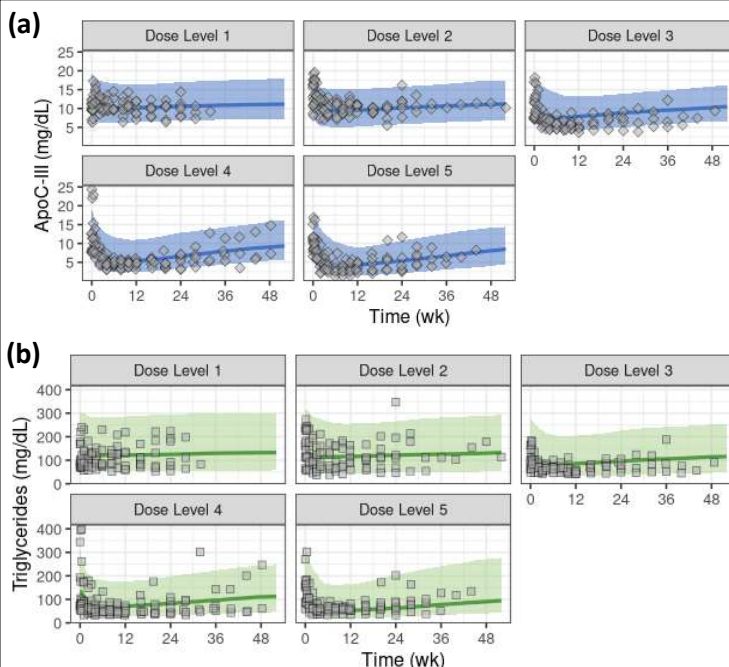


Figure 3. Observed vs predicted ApoC-III (a) or triglycerides (b) over time profiles
Shaded area – 90% PI; solid line – median predicted; diamonds/squares – observations

CONCLUSIONS

- LY3875383 PK was well characterised with a two-compartment model and a dose effect on absorption, indicating a less-than dose proportional increase in exposure.
- LY3875383 demonstrated long durability of effect on two biomarkers and reduction of ApoC-III and TG in a dose-dependent manner.
- This study provides a model-informed drug development (MIDD) framework that can support dose selection and future clinical study designs.