Leveraging Model-Informed Drug Development to Expedite Phase 2b Initiation for an Oral Peptide Targeting PCSK9

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Aim

- The abstract focuses on leveraging PKPD modelling to expedite the initiation of phase 2b trials for an oral peptide targeting PCSK9.
- Using data from a single-dose phase 1 trial with subcutaneous administration, a PKPD model was developed to inform a 12-week phase 2b trial with oral administration.
- The model predictions were used for internal decision-making and regulatory acceptance.
- The simulations demonstrated the possibility of extrapolation from early phases to later stage trials with confidence.

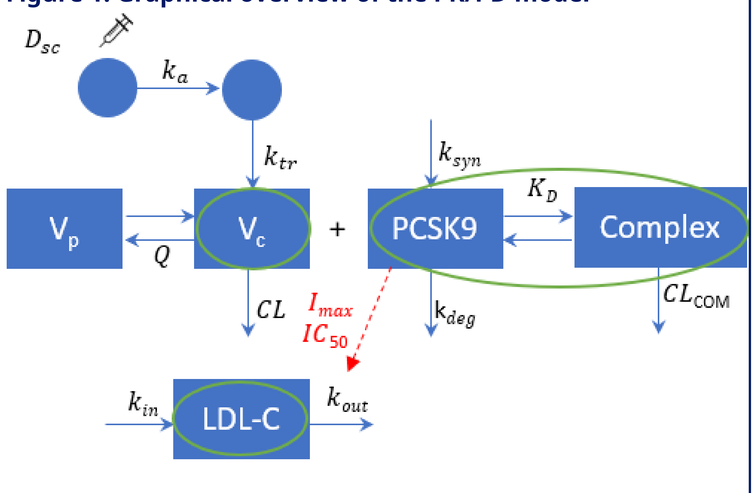
Objective

The rapid initiation of phase 2 studies is increasingly vital in modern drug development. Pharmacokinetic/pharmacodynamic (PKPD) modelling provides early-stage prediction tools to aid internal decision-makers in assessing risk, potential trial outcomes, and facilitating interactions with regulatory authorities. This case study details the development of a PKPD model using data from a single-dose phase 1 trial with subcutaneous (s.c.) administration, informing a 12-week phase 2b trial with oral administration. This approach harnesses PKPD modelling as a pivotal tool for informed decision-making and dosage regimen optimization.

Methods

PK, total PCSK9, and LDL-C data from a first human dose (FHD) study involving s.c. administration of NNC0385-0434 (PCSK9i: PCSK9 inhibitor peptide) were used to develop a PKPD model. The trial included three different dose arms ranging from 10 to 250 mg in healthy subjects, and one arm with 200 mg in patients with hypercholesterolemia. Data from all 28 individuals treated with PCSK9i were included in the model. The PK data of PCSK9i was described using a 2-compartment model with fast and slow first-order absorption from the subcutaneous tissue and first-order clearance. The total PCSK9 data was described using the quasi-steady state approximation to the target-mediated drug disposition (TMDD) model[1]. The LDL-C data was described using an indirect effect model, with free PCSK9 affecting the clearance of LDL-C. All model parameters were simultaneously estimated.

Figure 1: Graphical overview of the PK/PD model



D_{sc}: subcutaneous dose, k_a: absorption rate constant; k_{tr}: transit rate constant, V_c and V_p: central and peripheral volume, Q: inter-compartmental clearance, CL: clearance of PCSK9i, PCSK9: proprotein convertase subtilisin/kexin type 9, k_{syn}: PCSK9 production rate constant, k_{deg}: PCSK9 elimination rate constant, K_D, dissociation constant, CL_{com}: PCSK9i-PCSK9 complex clearance, *LDL-C*: low-density lipoprotein-cholesterol, I_{max}: maximal inhibition, IC_{50}: PCSK9 concentration associated with half-maximal inhibition, k_{in}: LDL-C production rate constant, k_{out}: LDL-C elimination rate constant. The three green circles represents the observed quantities used for parameter estimation for PK, total PCSK9 and LDL-C

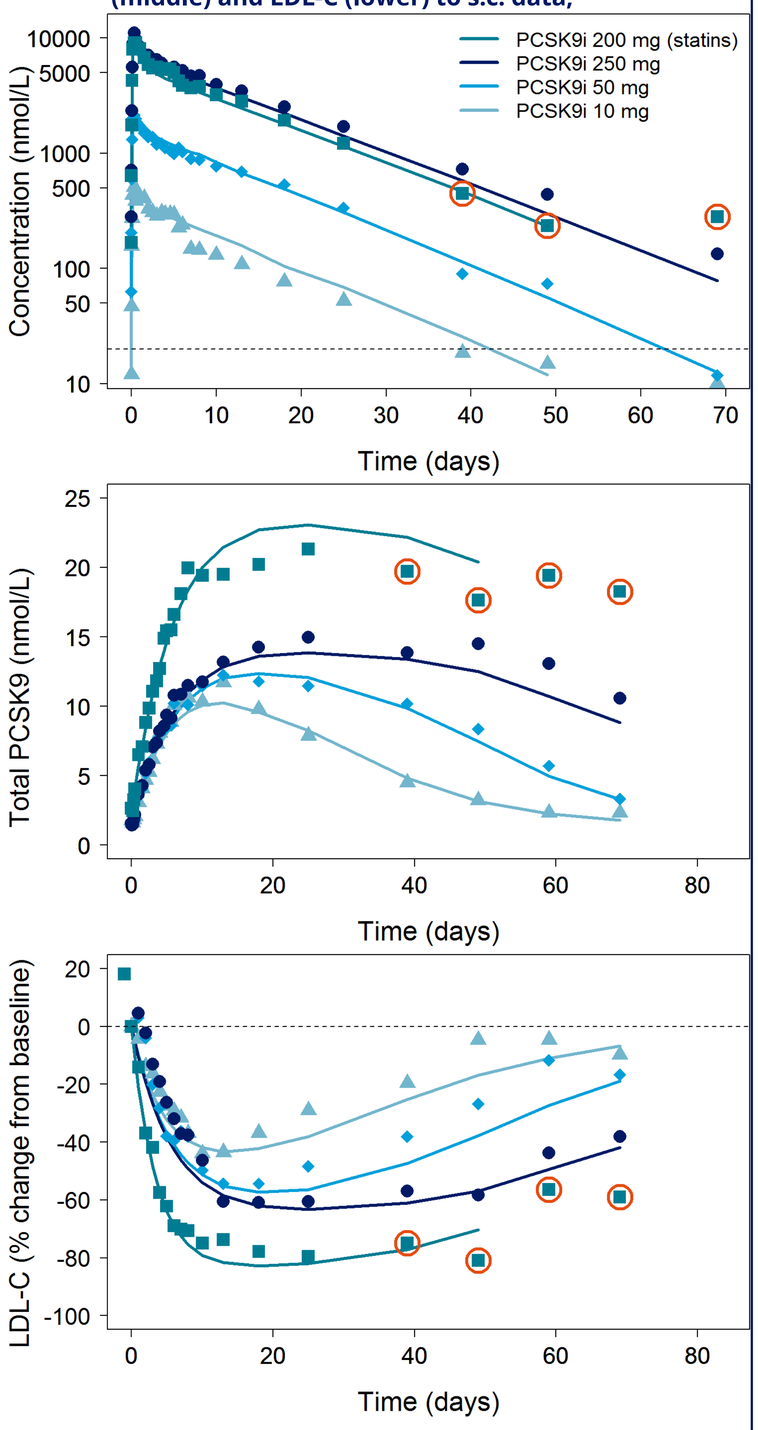
The model's validity for trial simulation was assessed using standard goodness-of-fit evaluations and visual predictive checks.

Oral absorption of PCSK9I was assumed to be similar to that of another orally administered peptide[2] based on a comparability study in dog for simulating the phase 2b trial with daily oral dosing of 15, 40, and 100 mg of PCSK9i. The model predictions for both PK and LDL-C were used both in internal decisions of optimal trial design as well as in the argumentation leading to regulatory acceptance of the clinical development approach.

Results

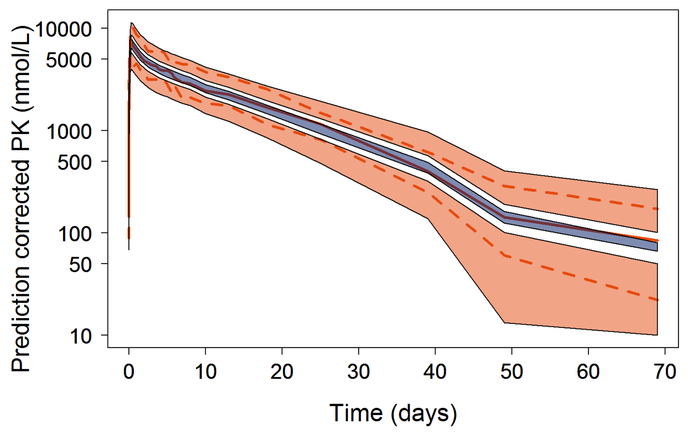
The data from the s.c. trial was well described with the PKPD model, and the evaluation showed its suitability for trial simulations.

Figure 2: Goodness-of-fit figures for PK (upper), total PCSK9 (middle) and LDL-C (lower) to s.c. data,



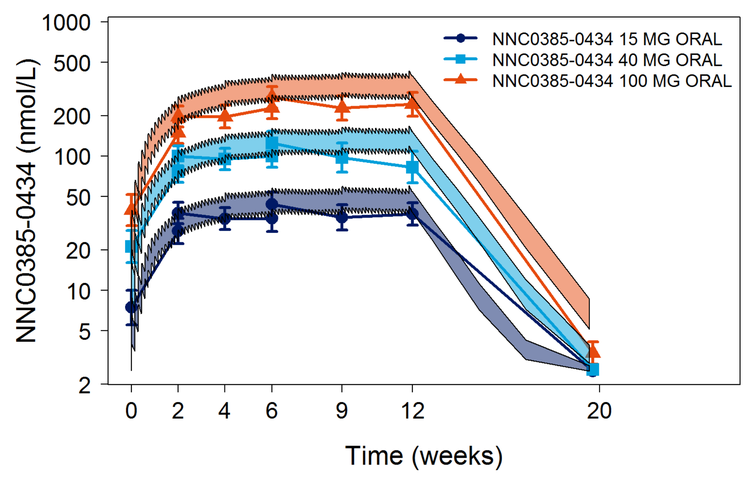
Data points are geometric mean (PK and total PCSK9) or mean (LDL-C) of observed concentrations in the P1 s.c. trial. Lines are population predictions. Dashed line is the lower limit of quantification for PK. Red circles mark sample visits where subjects with missing data or where samples have taken outside visit window due to COVID-19.

Figure 3: Visual predictive check for PK



Data are prediction corrected observed (lines) and simulated (shaded areas, reflect the 95% CIs based on 10000 simulations) medians, 5th and 95th concentration percentiles.

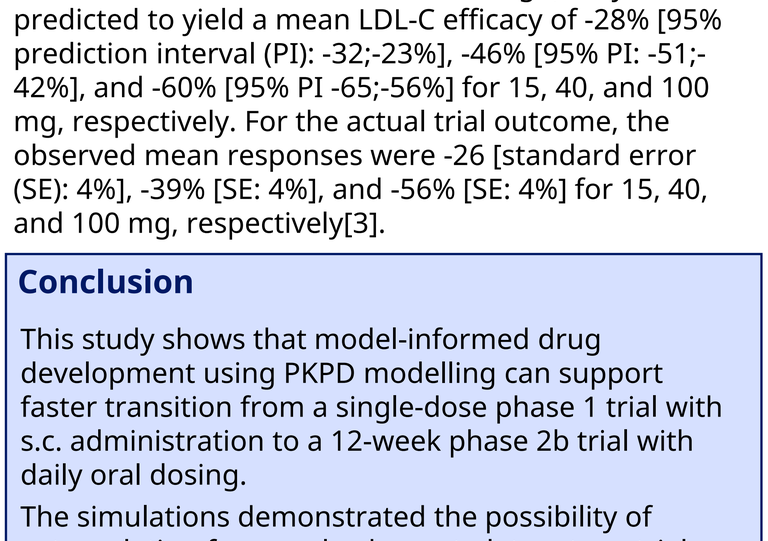
Figure 4: Comparison of the pretrial PK simulations and the actual geometric mean of the observations in the phase 2b trial



Thick lines and points represent respectively geometric mean value of exposure in each dose group and bars indicate 95 % confidence interval of the geometric mean value. Coloured areas indicate the 95 % prediction interval of the three doses using the PK/PD model from the FHD trial with PCSK9i with an assumption that oral PCSK9i has an oral absorption similar to an oral peptide and 51 subjects in each arm. The data points in the figure only includes data from subjects who have taken 5 or more doses the preceding 7 days.

The phase 2b trial was simulated with baseline covariates reflecting a patient population with hypercholesterolemia, between-subject variation in PKPD parameters, and within-individual variation in bioavailability. The simulations results were shared with internal stakeholders as well as regulatory authorities prior to initiation of the phase 2b trial.

Figure 5: Comparison of the pretrial LDL-C simulations and the actual mean of the observations in the phase 2b trial



Thick lines and points represent respectively mean value of LDL-C B quantification in each dose group and bars indicate 95 % confidence interval of the mean value. Coloured areas indicate the 95 % prediction interval of the three doses using the PK/PD model from the FHD trial with PCSK9i with an assumption that oral PCSK9i has an oral absorption similar to an oral peptide and 51 subjects in each arm. The data points in the figure only includes data from subjects who have taken 5 or more doses the preceding 7 days.

After 1000 simulations of the trial design, they were predicted to yield a mean LDL-C efficacy of -28% [95% prediction interval (PI): -32;-23%], -46% [95% PI: -51;-42%], and -60% [95% PI -65;-56%] for 15, 40, and 100 mg, respectively. For the actual trial outcome, the observed mean responses were -26 [standard error (SE): 4%], -39% [SE: 4%], and -56% [SE: 4%] for 15, 40, and 100 mg, respectively[3].

Conclusion

This study shows that model-informed drug development using PKPD modelling can support faster transition from a single-dose phase 1 trial with s.c. administration to a 12-week phase 2b trial with daily oral dosing.

The simulations demonstrated the possibility of extrapolation from early phases to later stage trials with confidence.

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References:
[1]: Gibiansky, L., Gibiansky, E., Kakkar, T. et al. Approximations of the target-mediated drug disposition model and identifiability of model parameters. J Pharmacokinet Pharmacodyn 35, 573–591 (2008). [2]: Overgaard, R.V., Navarria, A., Ingwersen, S.H. et al. Clinical Pharmacokinetics of Oral Semaglutide: Analyses of Data from Clinical Pharmacology Trials. Clin Pharmacokinet 60, 1335–1348 (2021)
[3]: PCSK9 inhibition with orally administered NNC0385-0434 in hypercholesterolaemia: a randomised, double-blind, placebo-controlled and active-controlled phase 2 trial. The Lancet Diabetes & En-docrinology, ISSN: 2213-8587, Vol: 12, Issue: 3, Page: 174-183 (2024)