# Comparison of a typical PK/PD model versus a mechanistic QSP model to predict the Phase II of a PSCK9 inhibitor, using MonolixSuite

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## QUESTION & METHODS

Compared to PK/PD models, QSP models incorporate more mechanistic details and model entities which have not been measured experimentally. By putting more emphasis on the biological relevance, QSP models are believed to be more capable of extrapolating from preclinical to clinical or from healthy volunteers to patients.

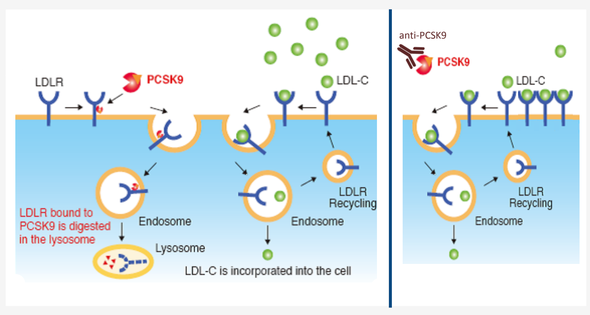
### What is the benefit of QSP models compared to simpler PK/PD models?

**Methodology:**
- Develop 3 models of increasing complexity on Phase I PK/PD data
- Compare the predictions of the 3 models for a Phase II design

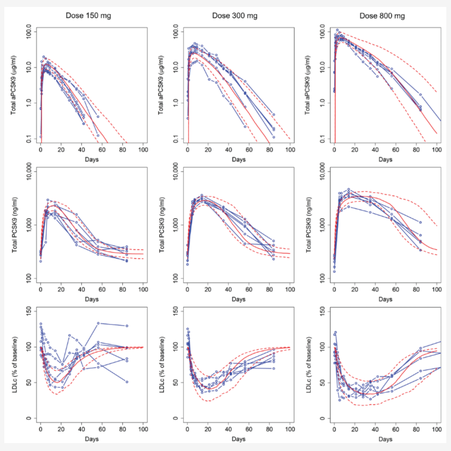
## ANTI-PCSK9 mAb FOR CHOLESTEROL LOWERING

RG7652 [1] is a fully human monoclonal antibody antagonizing PSCK9 activity. It is developed as cholesterol (LDLc) lowering therapy and can be given in patients already treated with statins.

**Without anti-PSCK9:**
=> high PCSK9
=> low LDLr on membrane
=> high LDLc in plasma




**With anti-PSCK9:**
=> low PCSK9
=> high LDLr
=> low LDLc




### Phase I data

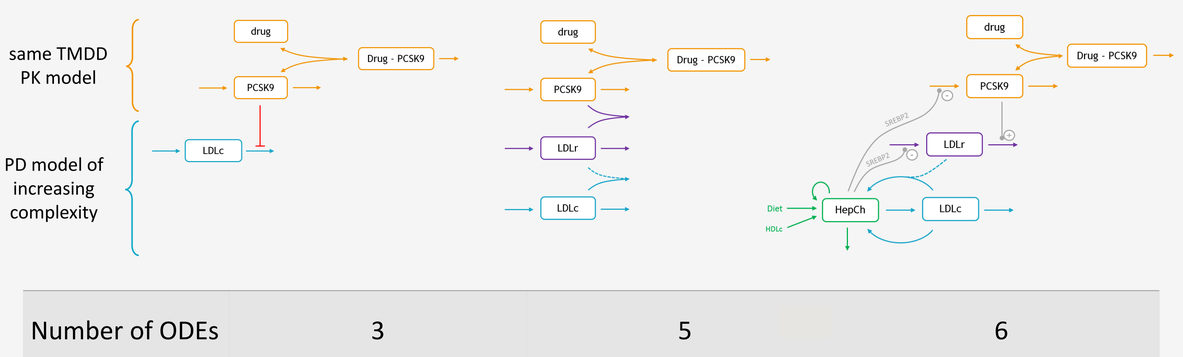
In the Phase I trial, RG7652 elicited substantial and sustained dose-related LDL-C reductions with an acceptable safety profile [1].

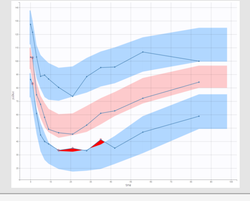
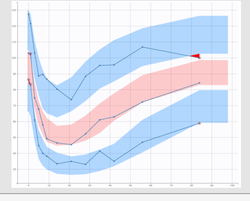
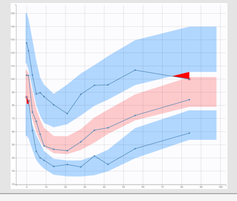
Individual phase I data for 3 dose levels [2]:
- Total PCSK9
- Total drug
- LDLc (relative to baseline)

## MODEL DEVELOPMENT ON THE PHASE I DATA

Three models of increasing complexity are developed on the Phase I data. Part of the parameters are fixed (from literature) and part are estimated with Monolix.

Identifiability assessment in Monolix:
— RSE and correlation matrix of the estimates
— Multi-start convergence assessment in GUI
— Bootstrap with Rsmlx
— Profile likelihood with Rsmlx




| | Model A<br>Typical PK/PD | Model B<br>Mechanistic PK/PD | Model C<br>QSP |
|---|---|---|---|
| Number of ODEs | 3 | 5 | 6 |
| Number of parameters | 10<br>(10 estimated) | 14<br>(11 estimated + 3 fixed) | 21<br>(13 estimated + 8 fixed) |
| Identifiability issues | None | Some (investigated via RSE and profile likelihood) | Unclear |
| Estimation run time | 1 min | 5 min | 1 hour |
| Literature search required | None | A little | A lot |
| Likelihood | 4110 | 4130 | 4157 |
| VPC |  |  |  |

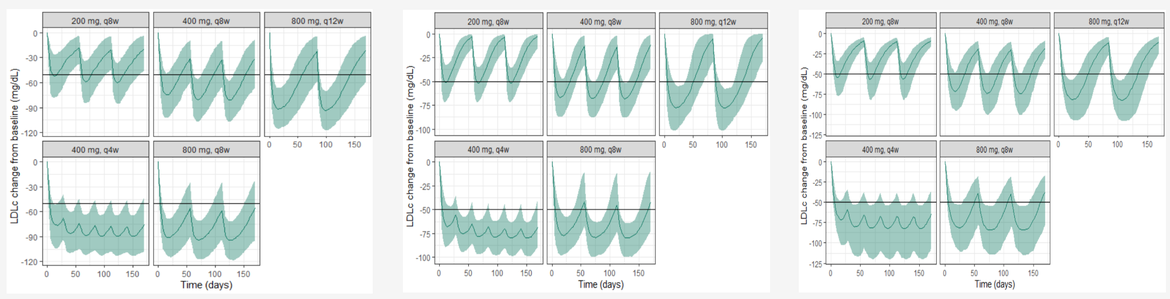
## PREDICTION OF PHASE II TRIAL VIA SIMULATIONS

In phase II, statin-treated patients will be recruited. To simulate this, the parameter values are modified to obtain baseline LDLc and PSCK9 concentrations representative of statin patients. Different dosing regimens and mutation effects are then investigated.

The Monolix model can be imported into Simulx to simulate new situations in just a few clicks.

**Q1: Which dose regimens achieve an LDLc reduction of at least 50 mg/dL?**

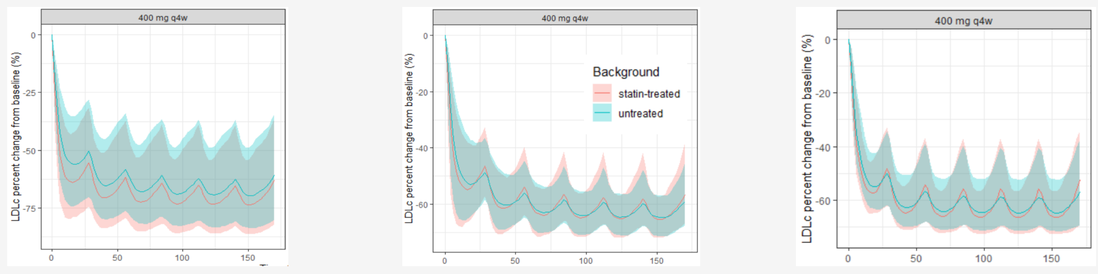
(A) Typical PK/PD (B) Mechanistic PK/PD (C) QSP




All models give similar predictions in favor of the 400 mg Q4W regimen.

**Q2: Is there a difference in response for statin-treated patients and untreated patients?**

(A) Typical PK/PD (B) Mechanistic PK/PD (C) QSP



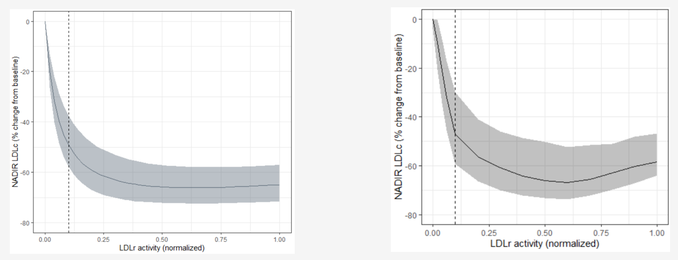

Only a minor difference between statin-treated and untreated patients.

**Q3: What is the response of patients with familial hypercholesterolemia? (low LDLr receptor concentrations due to mutations)**

(A) Typical PK/PD

*Cannot be simulated because LDLr does not appear in the model.*

(B) Mechanistic PK/PD (C) QSP

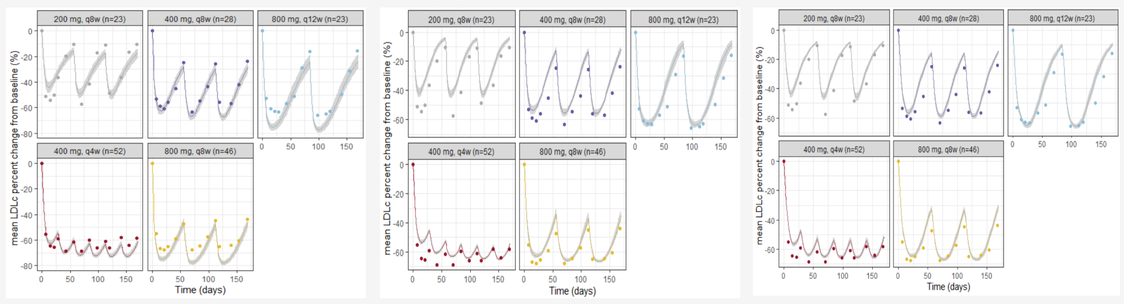



Patients with less than 10% LDLr activity will have only a weak response to anti-PCSK9.

## VALIDATION OF THE MODEL PREDICTIONS

Phase II data has been published [3] (colored dots) and can be compared to the predictions obtained from the three models (grey prediction intervals).

(A) Typical PK/PD (B) Mechanistic PK/PD (C) QSP




Predicted phase II cholesterol response is very accurate

## CONCLUSION

In this example:
- all three models allowed to correctly predict phase II efficacy data
- the typical PK/PD model (A) required the least development efforts
- more specific questions related to familial hypercholesterolemia could only be investigated with more mechanistic models (B and C) which incorporate intermediate chemical species.

## REFERENCES

**[1]** Baruch et al., *Clin. Cardiol.* 40, 503–511 (2017)
**[2]** Gadkar et al., *CPT Pharmacometrics Syst. Pharmacol.* 3, (2014)
**[3]** Baruch et al., *Am. J. Cardiol.* 119, 1576–1583 (2017).

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