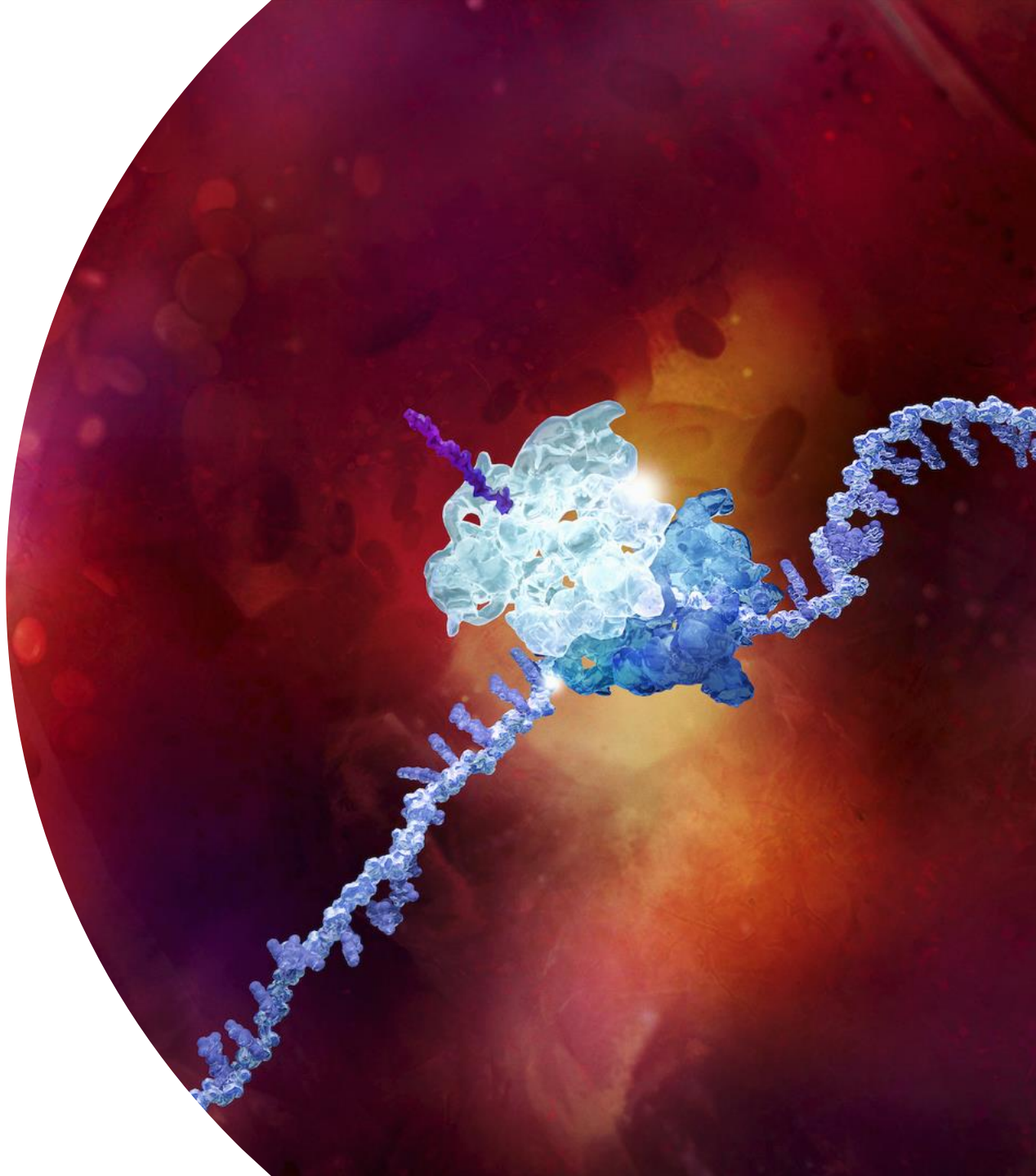
Case study of MIDD for AZD8233 Pre-clinical to Ph3

Jane Knöchel[1], **Dinko Rekić**[1,2]

[1] Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology and Safety Sciences, R&D, AstraZeneca, Gothenburg, Sweden

[2] current affiliation: BioPharmaceuticals, Global CVRM, Gothenburg, Sweden

08.02.2023



Overview

Disease area overview

Unmet medical need yet a highly competitive area

Phase 1 preparation

Early confidence in the program & PCSK9 as biomarker for decision making

Phase 2 preparation

Impact on design including dose selection, sample size justification and probability of success

Justification of Ph2 start prior to MAD readout
(FDA MIDD meeting)

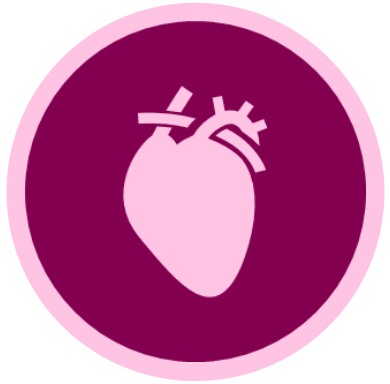
Phase 3 preparation

MIDD supported design of LDL-C phase 3

Knöchel, Jane, et al. "A case-study of model-informed drug development of a novel PCSK9 anti sense oligonucleotide. Part 1: First time in man to phase II." *CPT: Pharmacometrics & Systems Pharmacology* (2022).

Part 2 – manuscript in preparation

Hyperlipidemia overview



A serious medical condition

Hyperlipidemia is one of the key risk factors for cardiovascular disease, the number 1 cause of death in the world [1]. There is a causative link between LDL-C and MACE, LDL-C is recognized as surrogate endpoint [2]

Unmet medical need

~50-80% of patients do not reach treatment goals on top of standard of care consisting of high intensity statins and ezetimibe [3-6]

PCSK9 inhibitors

In 2015 new class (mAb vs PCSK9) of LDL-C lowering drugs introduced (~60% LDL-C reduction)
Cumbersome dosing regimen

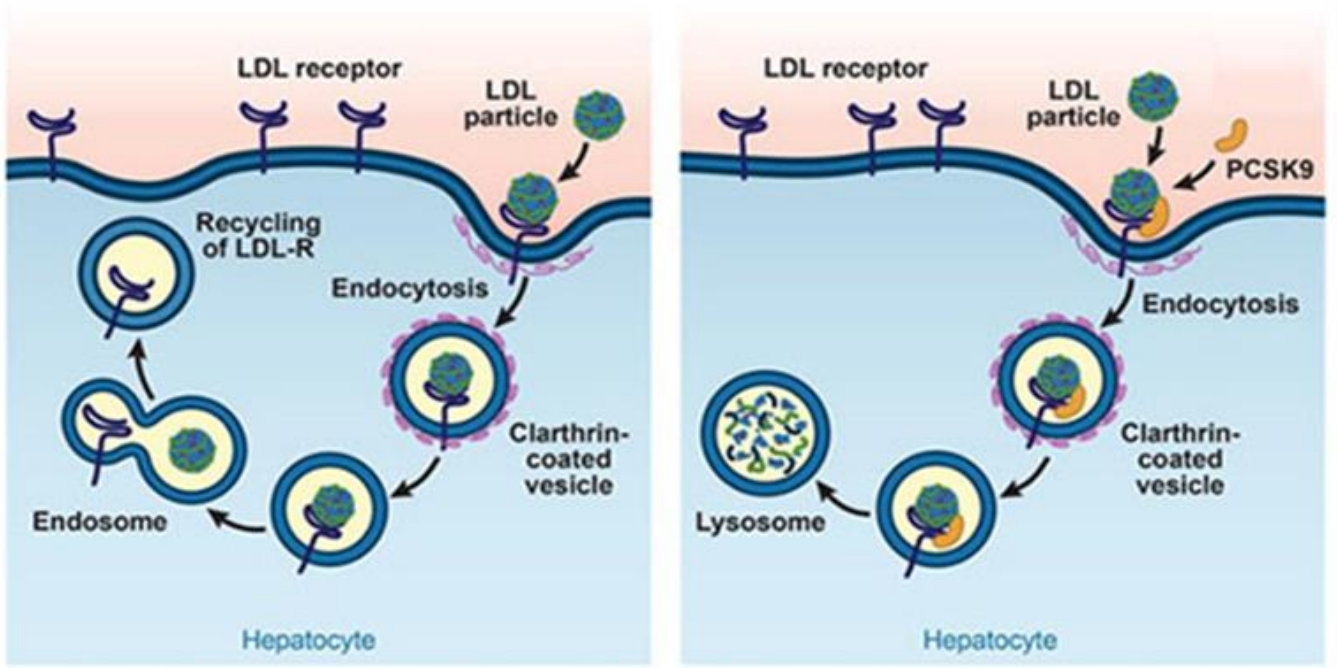
Inclisiran (siRNA vs PCSK9) approved by FDA (Jan 2022) (~50% LDL-C reduction)

[1] WHO: https://www.who.int/health-topics/cardiovascular-diseases/#tab=tab_1
[2] FDA: https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

[3] Sarak, Bradley, et al (2021)
[4] Fox, Kathleen M., et al. (2018):
[5] Allahyari, Ali, et al. 2019
[6] TriNetX data base 2021

LDL-C: low-density lipoprotein cholesterol, MACE: Major adverse cardiovascular events. mAbs: Monoclonal antibody. PCSK9: Proprotein convertase subtilisin/kexin type 9: siRNA: Small interfering RNA

Role of PCSK9 in dyslipidemia



Lambert G, et al. J Lipid Res. 2012

- Protein convertase subtilisin/kexin type-9 (PCSK9) is regulator of cholesterol homeostasis
- ↓PCSK9 → ↑LDL-R levels → ↓LDL-C

Different PCSK9 targeting modalities

- Monoclonal antibodies (mabs) binding extracellular PCSK9

Repatha™ (evolocumab)

Praluent® (alirocumab) Injection 75mg/mL 150mg/mL

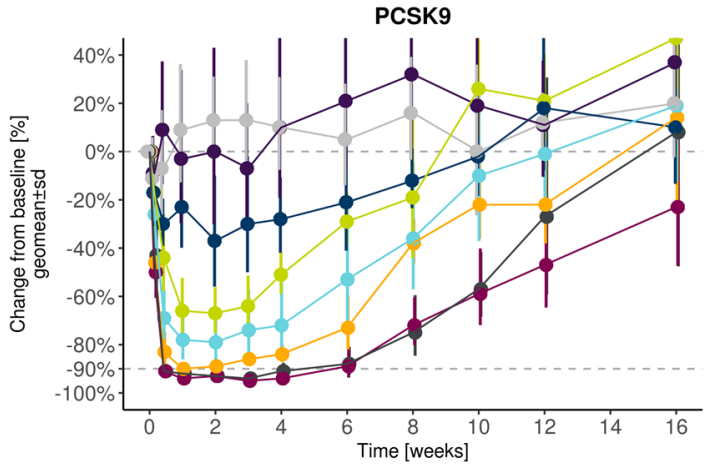
- Short interfering RNA (siRNA) inhibiting PCSK9 translation in the liver by acting on the mature mRNA

LEQVIO® (inclisiran) injection 284 mg/1.5 mL

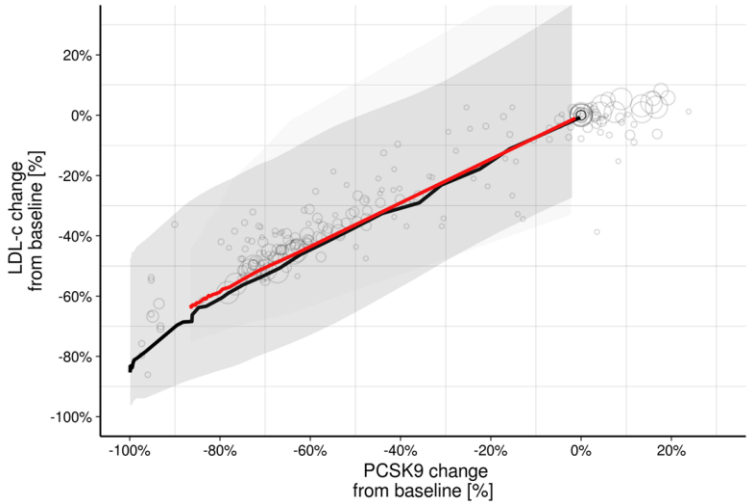
[1] Gu, H., & Zhang, D. (2015). Hypercholesterolemia , low density lipoprotein receptor and proprotein convertase subtilisin / kexin - type 9. Journal of Biomedical Research, 29(5), 356–361. https://doi.org/10.7555/JBR.29.20150067

Well established link between PCSK9 and clinical outcome provides unique opportunity to apply MIDD for AZD8233

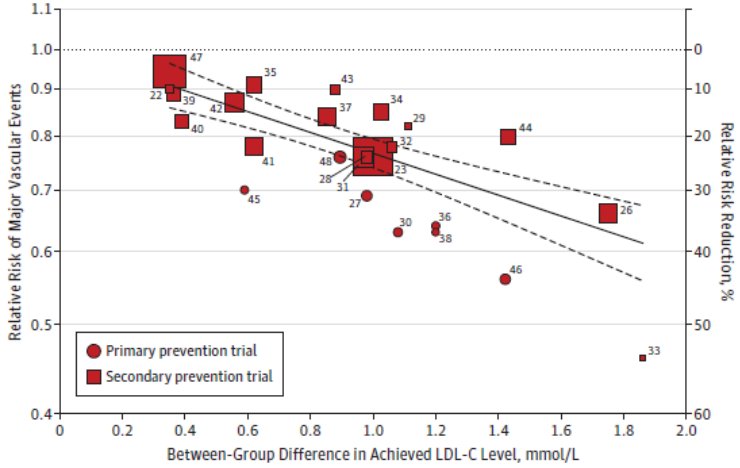
ASO platform has consistent PK and translatable potency for liver targets



Well established relationship between PCSK9 and LDL-C



Well established causal relationship between LDL-C and MACE [1]



MIDD: Model-informed drug development; MACE: Major Adverse Cardiac Events

[1] Silverman, M. G., Ference, B. A., Im, K., Wiviott, S. D., Giugliano, R. P., Grundy, S. M., Braunwald, E., & Sabatine, M. S. (2016). Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: A systematic review and meta-analysis. JAMA - Journal of the American Medical Association, 316(12), 1289–1297. https://doi.org/10.1001/jama.2016.13985

Key challenges for drug development of AZD8233

Speed

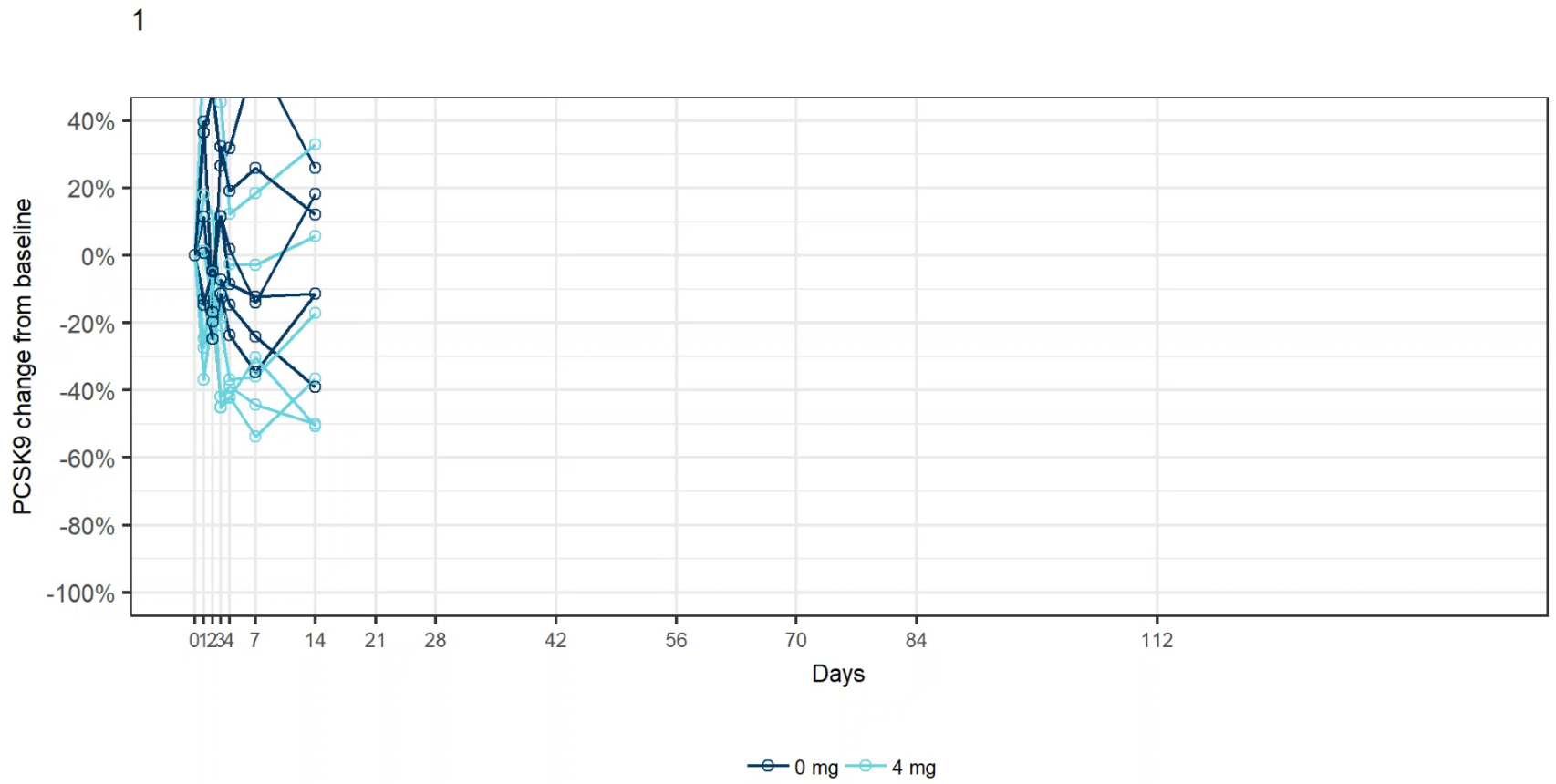
Right dose

Confidence

Acceleration of clinical development of AZD8233 based on SAD data

Translational K-PD model was pivotal to interpret emerging data and define timelines for key decisions

Clinical trial simulation of PCSK9 data available at each data delivery during SAD study



r-script: S04_Data_Delivery_Simulation.R, 2018-10-15 16:09:27

Rekic et al., American Conference on Pharmacometrics 2021

Team building and engagement

A shiny app was created based on the NHP model. The cross functional team could manipulate model parameters and make a “prediction” of PCSK9 reduction prior to each data delivery. The winner is based on the sum of square residuals.

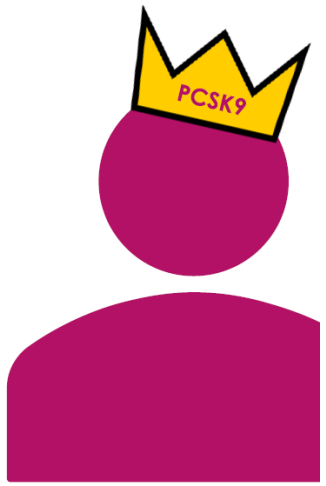
The 2018 PCSK9 prediction contest

subcut. edition

- Every project member, except the organizer, is eligible to compete
- The individual with the best prediction[1] of **PCSK9 concentration time profile** for the 12 mg sc. dose wins a bottle of a fine beverage.
- The winner will be announced in December after data readout of cohort 2

1) A mathematical formula will be used to determine who is the winner

$$RSS = \sum_{i=1}^{n} (y_i - \hat{y}_i)^2$$

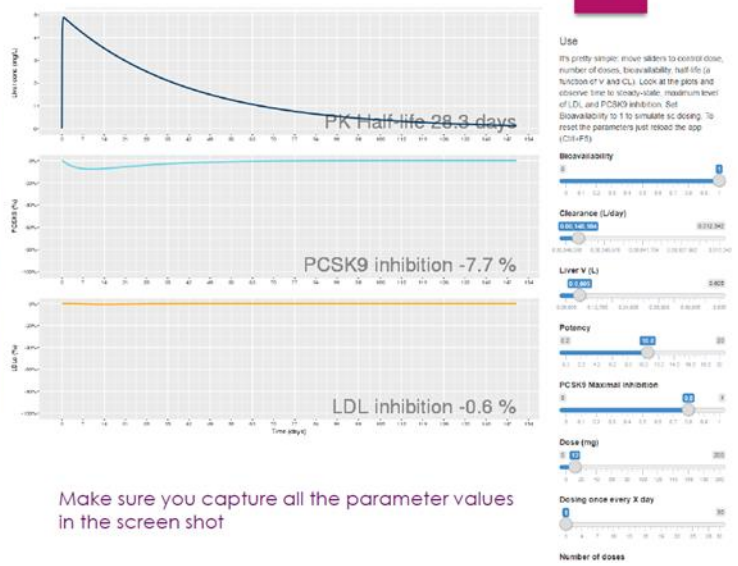


Contest rules

- Use the web app to make your prediction
- Predict the PCSK9 concentration time profile for a single sc. dose of 12 mg
- Take a screen shot and email it to Dinko no later than end of November

Example of a prediction

2

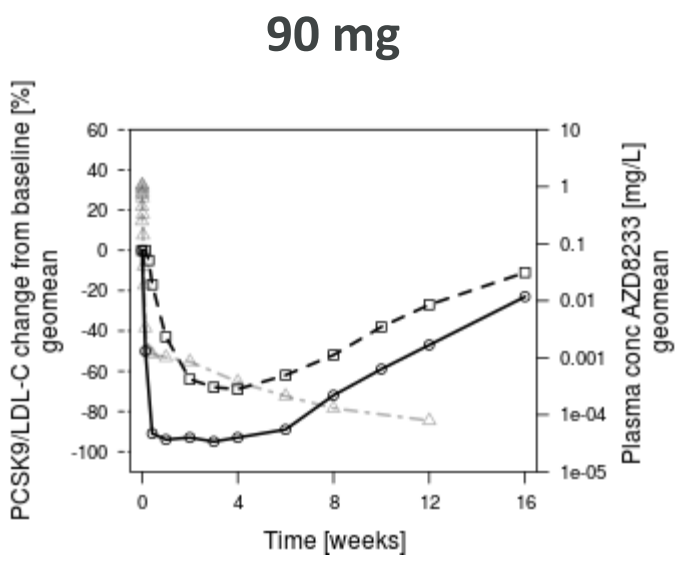


Make sure you capture all the parameter values in the screen shot

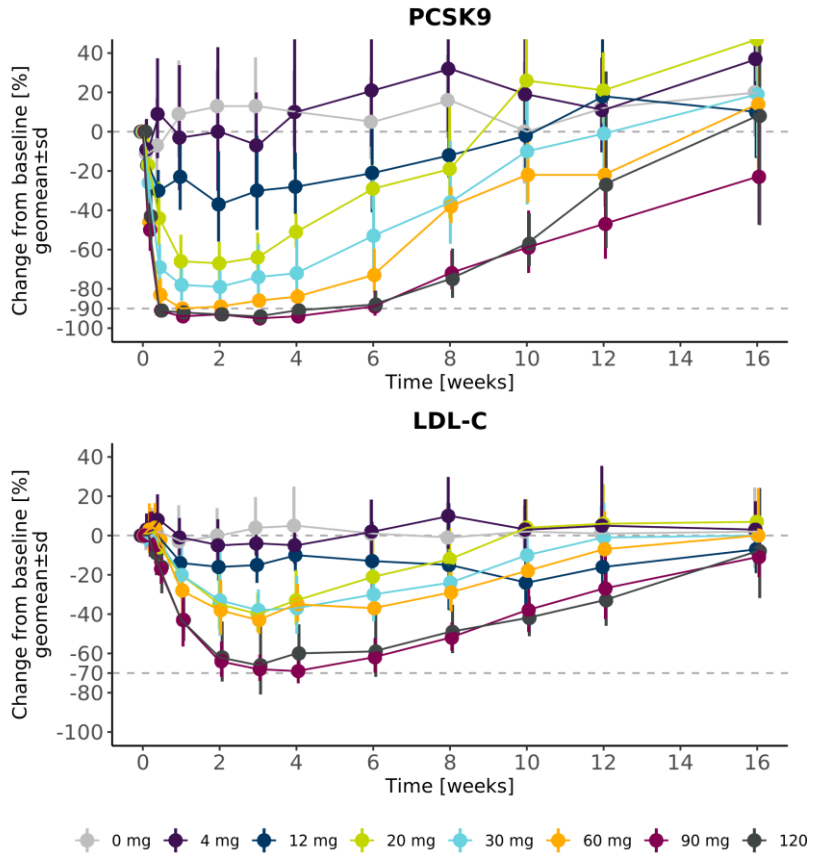
Great tutorial: Wojciechowski, J., Hopkins, A. M. & Upton, R. N. Interactive pharmacometric applications using R and the Shiny package. *CPT: Pharmacometrics and Systems Pharmacology* (2015).doi:10.1002/psp4.21

Choosing to model PCSK9 in K-PD model based on SAD study to set doses for Ph2b

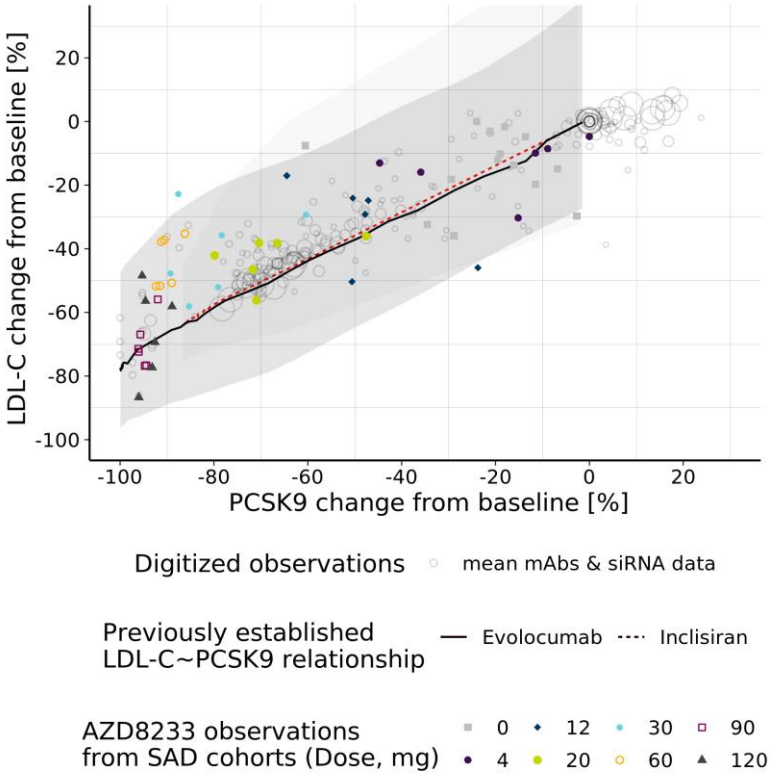
Longer half-life observed in PCSK9 data than in plasma concentration of AZD8233



Clear dose response in PCSK9 but not LDL-C due to small sample size

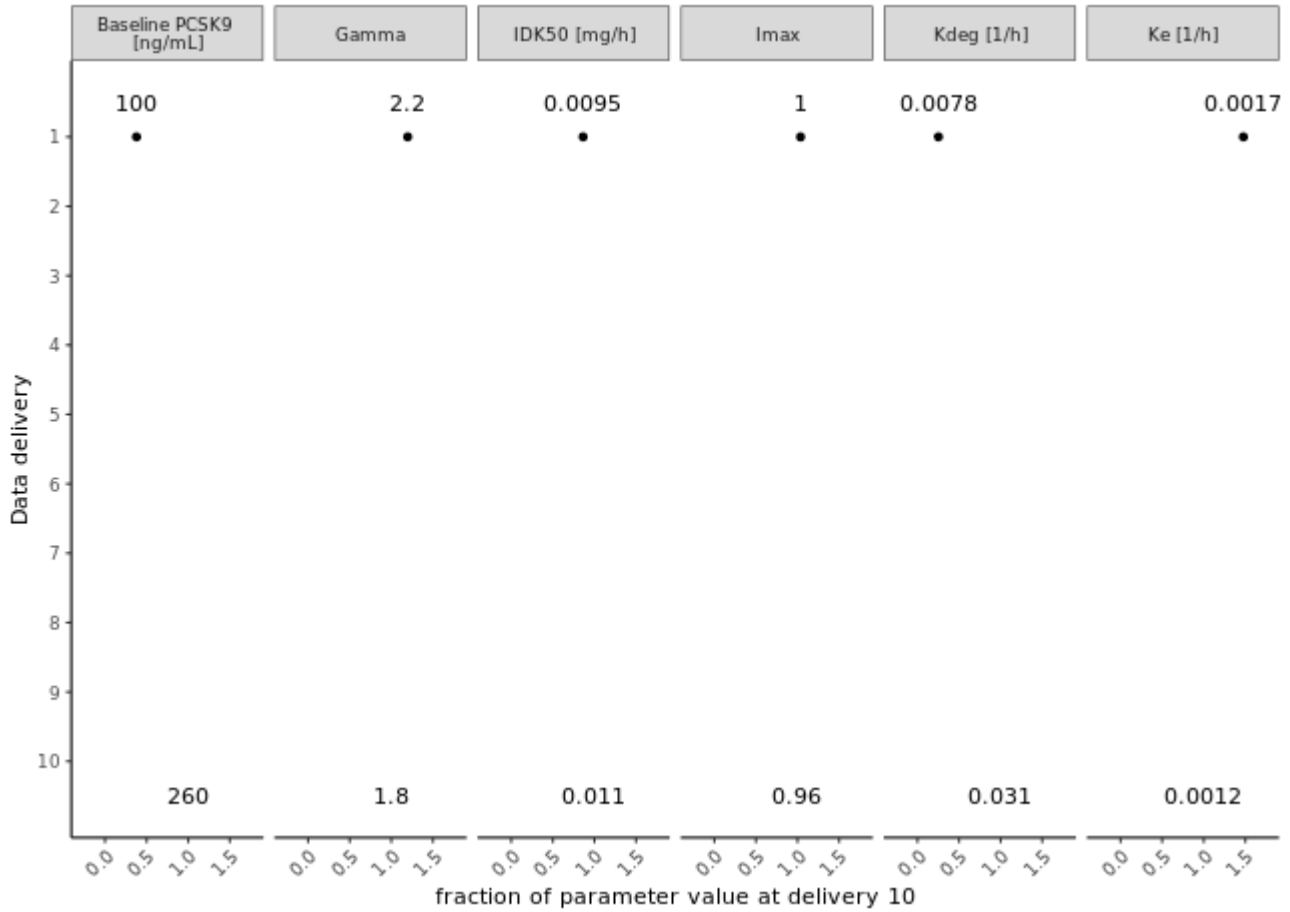


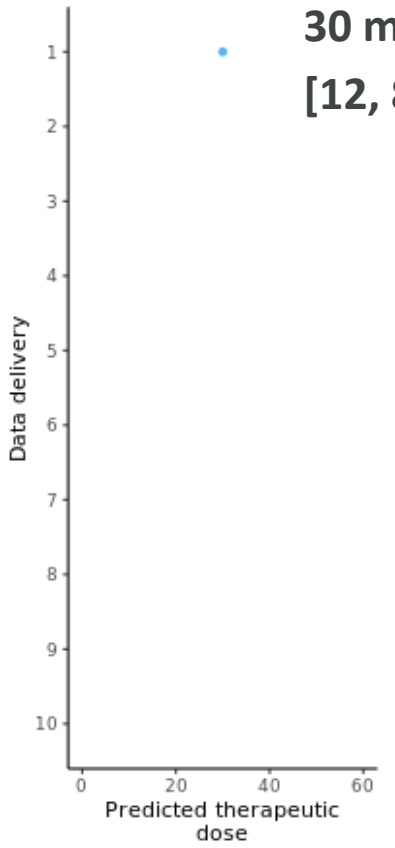
Individual PCSK9 and LDL-C data in line with established LDL-C and PCSK9 relationship



Live modelling of incoming SAD PCSK9 data and update of dose prediction

05-Oct-2018



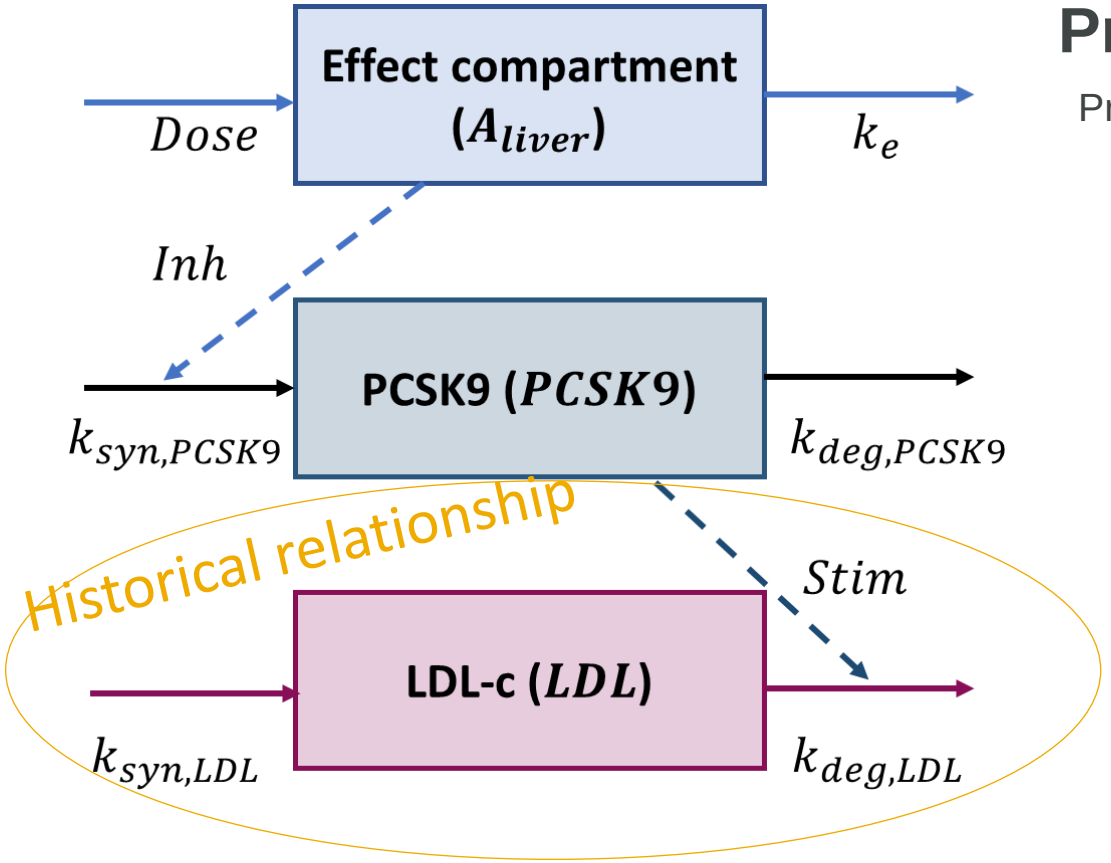


30 mg

[12, 82] mg

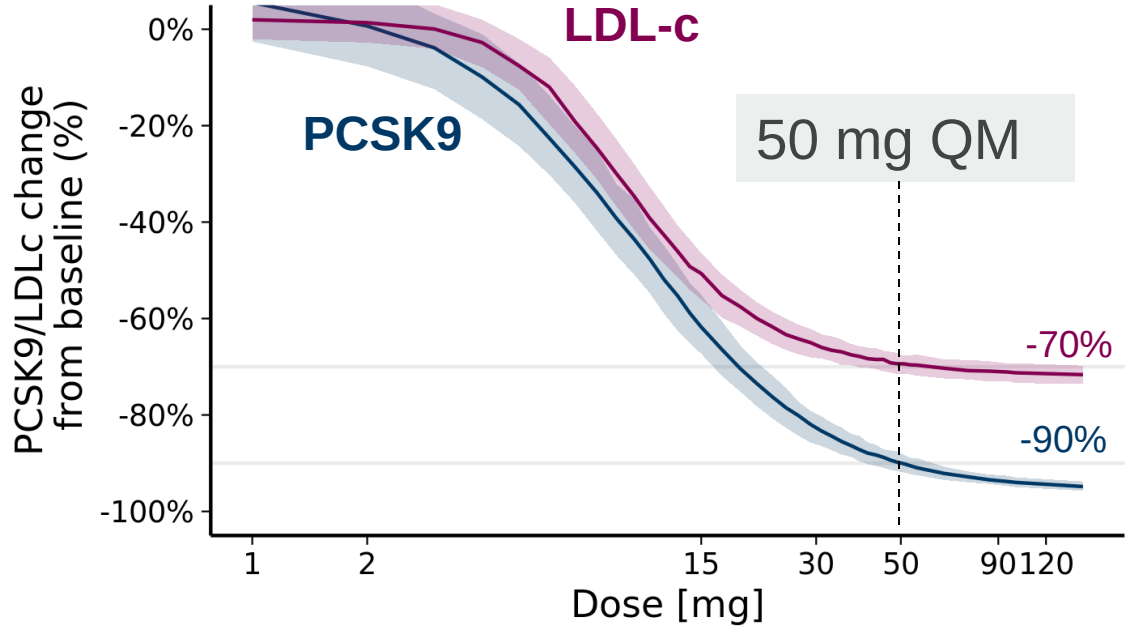
47 mg

50mg QM predicted to reach target of 70% LDL-C reduction based on SAD data



Prediction of dose-response at steady-state

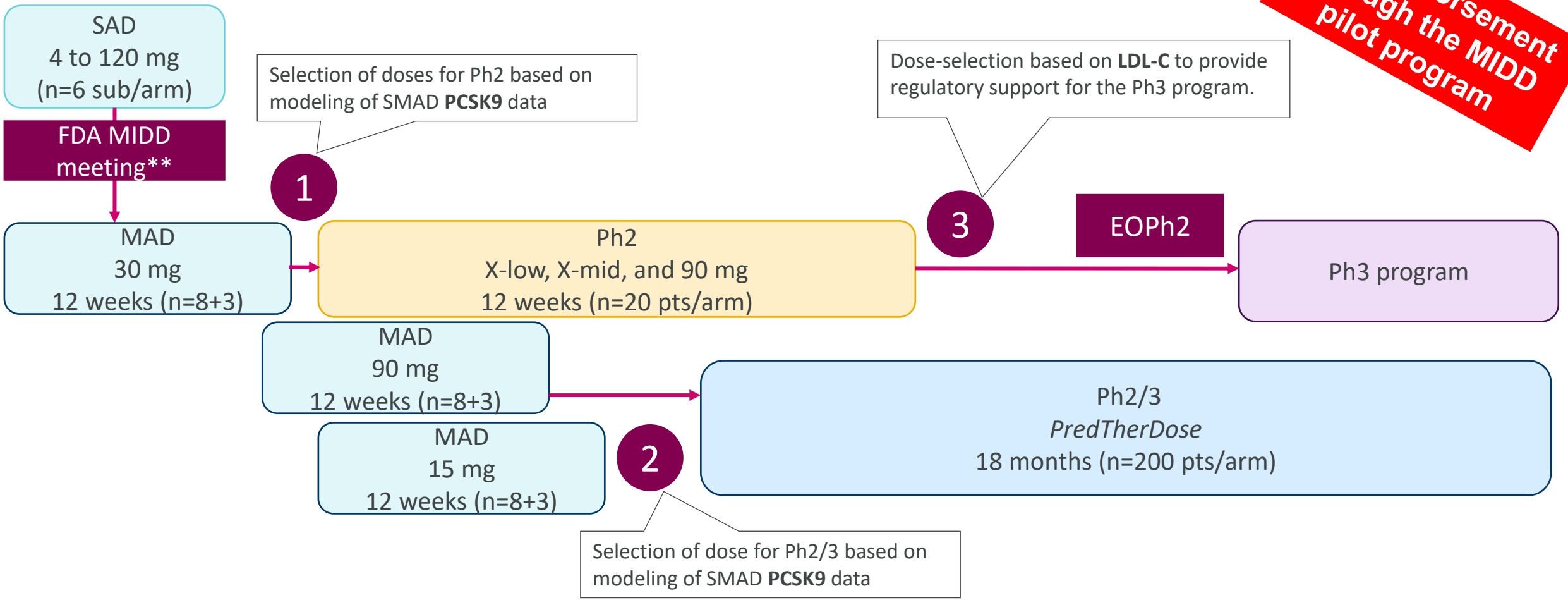
Prediction is based on PCSK9 lowering in SAD and historical LDL~PCSK9 relationship



Dose-response prediction to reach 90% PCSK9 inhibition over the whole dosing interval in steady state based on modeling of sc SAD PCSK9 data as of 2019-10-10. The shaded areas illustrate the simulation based 90% confidence intervals (CI) of the dose-response curves.

Acceleration of clinical program using MIDD

FDA endorsement through the MIDD pilot program



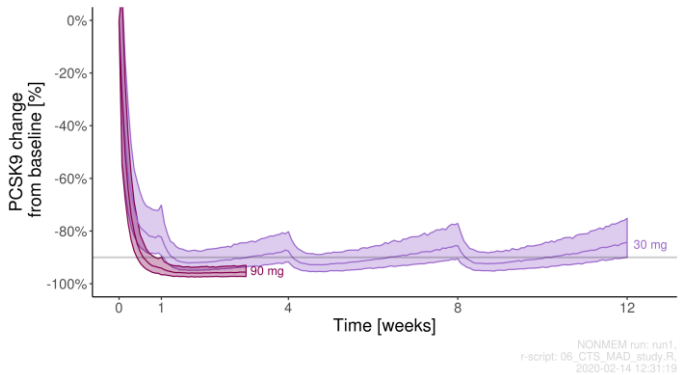
**Model Informed Drug Development (MIDD) pilot program: FDA endorsement of dose selection strategy

Simulation of data available at each decision point

1

MAD data to be available prior to start of Ph2 study (DRF)

N=8/arm
on statins



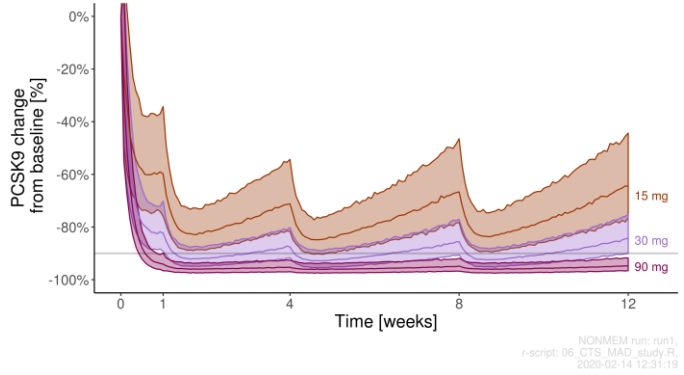
PCSK9 decrease over time[1].
LDL data not shown

- **Select doses for phase 2 study**
- **Confirms efficacy on background statins (70% LDL)**
- **Confirms multiple dose safety and tolerability**

2

Final MAD data

N=8/arm
on statins



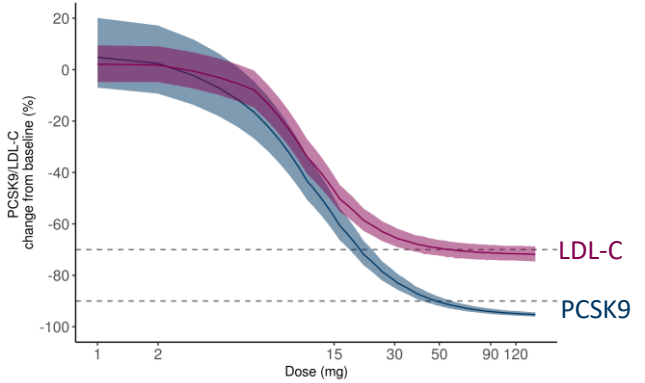
PCSK9 decrease over time[1].
LDL data not shown

- **Confirms or updates dose-prediction based on SAD (50 mg)**

3

Ph2 DRF data[3] to be available to inform Ph3/CVOT

N=25/arm
on statins



- 90 mg dose (~70%[2] or more)
- Minimal effective dose (~70%[2])
- Subtherapeutic dose ~40-50%[2] LDL reduction

- **Characterization of the dose-response relationship and selection of minimal effective dose for phase 3**

1. Median and 90% prediction interval based on simulation of 200 studies with 8 subjects per arm
2. Estimated LDL lowering based on modeling of SAD data

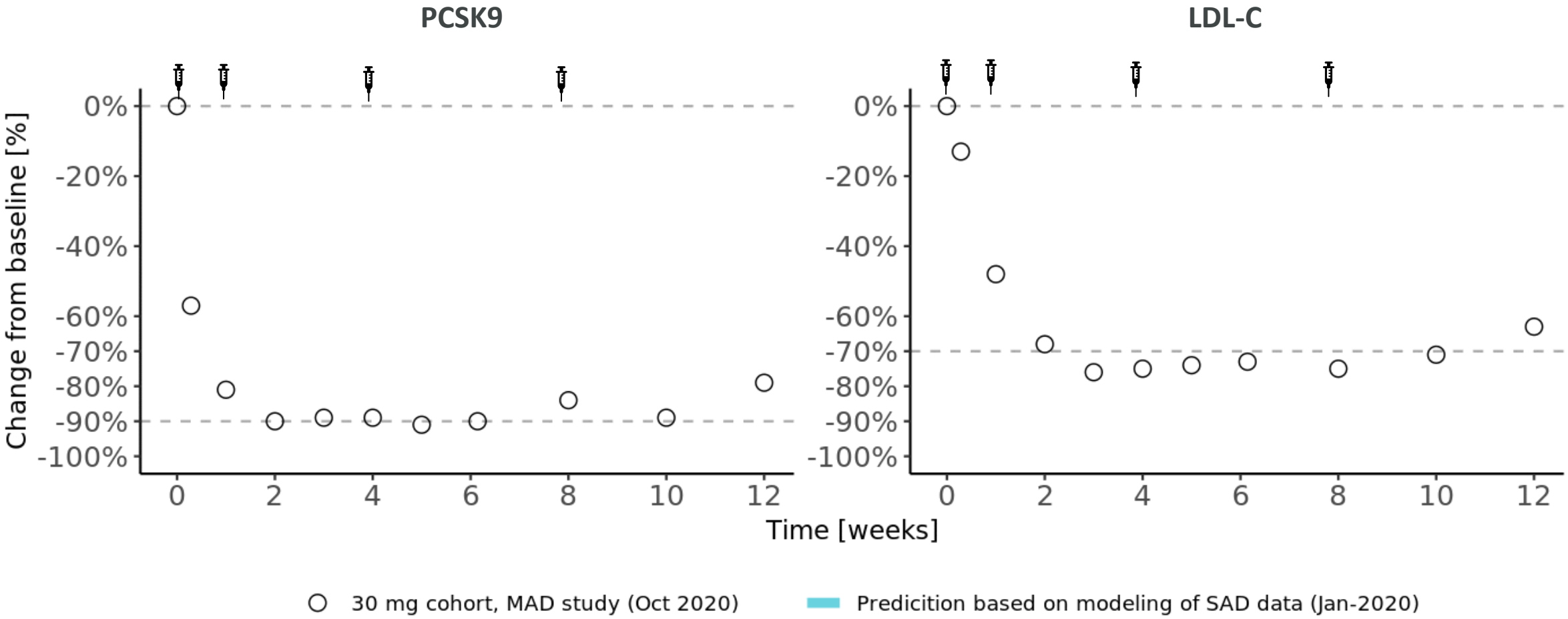
3. Dose-response prediction to reach 90% PCSK9 inhibition over the whole dosing interval in steady state based on modeling of sc SAD PCSK9 data as of 2019-10-10. Lines indicate median and the shaded areas illustrate the simulation based 90% prediction intervals (PI) of the dose-response curves.

Rekic et al., American Conference on Pharmacometrics 2021

Confidence building based on MAD data

Spot on a-priori prediction of PCSK9 data and steady state LDL-C reduction for 30 mg cohort from MAD study

Using the K-PCSK9 model with the historical relationship between PCSK9 and LDL-C



Preliminary data from ongoing sc. MAD study - status 26th September 2020
Plots show mean of observation of 30 mg MAD cohort with indication of number of patients per timepoint.
Blue shaded area represents 90% CI and blue line represents median based on 200 clinical trial simulations with 8 subjects per arm
Rekic et al., American Conference on Pharmacometrics 2021

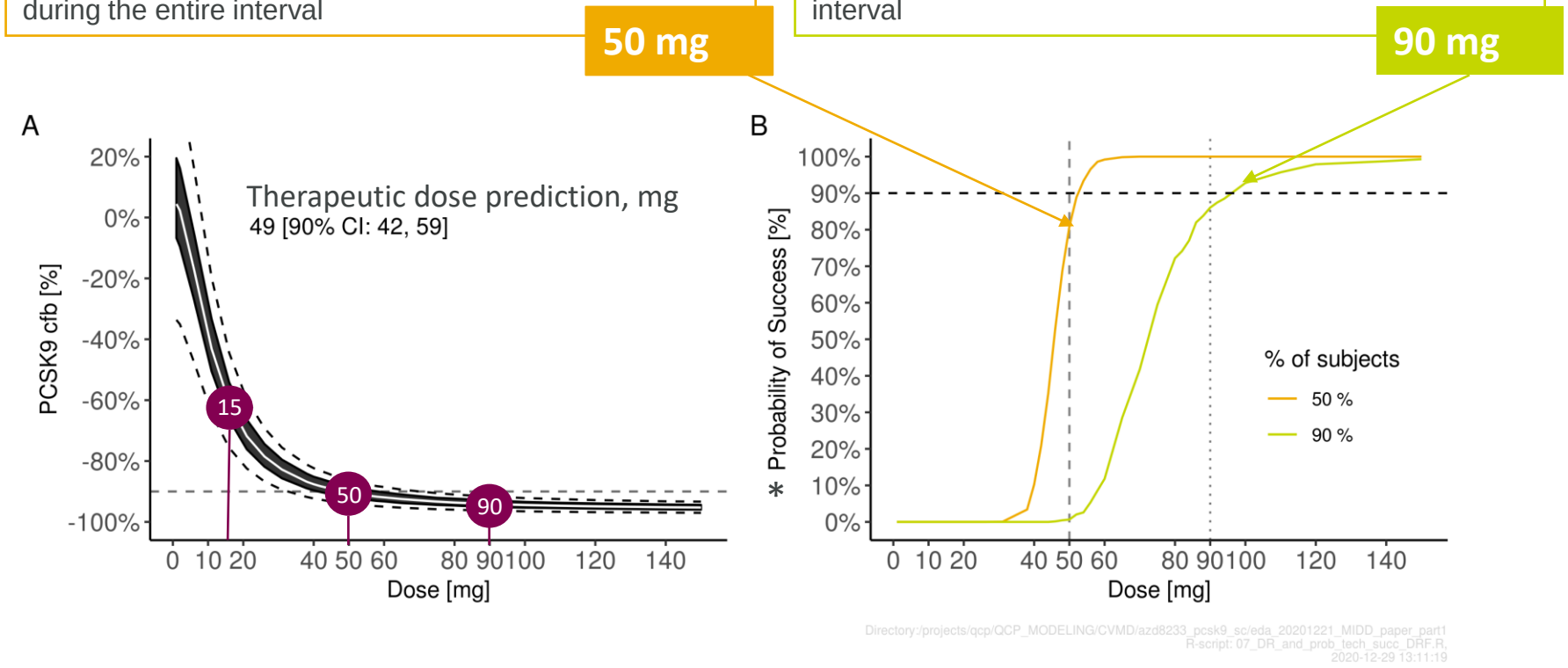
Phase 2 dose selection

15, 50, 90 mg doses selected for phase 2. 50 mg predicted to be the therapeutic dose meeting the best-in-class criteria
(≥70% LDL-C reduction during the entire dosing interval)

Phase 2 study started prior to completion of MAD study. Saving 6 months.

1: For 50% of subjects
This means that ~50% of subject have target levels during the entire interval

2: For 90% of subjects
Almost all subjects reaching target during the entire interval

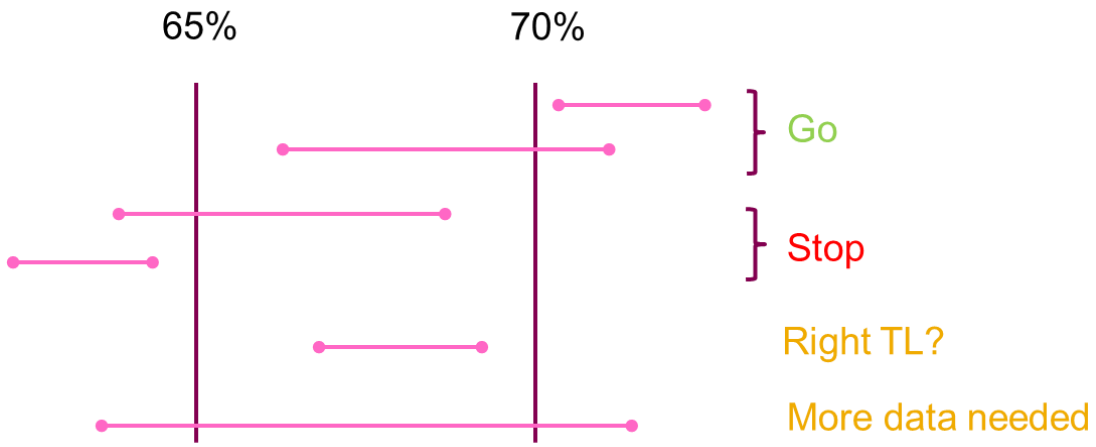


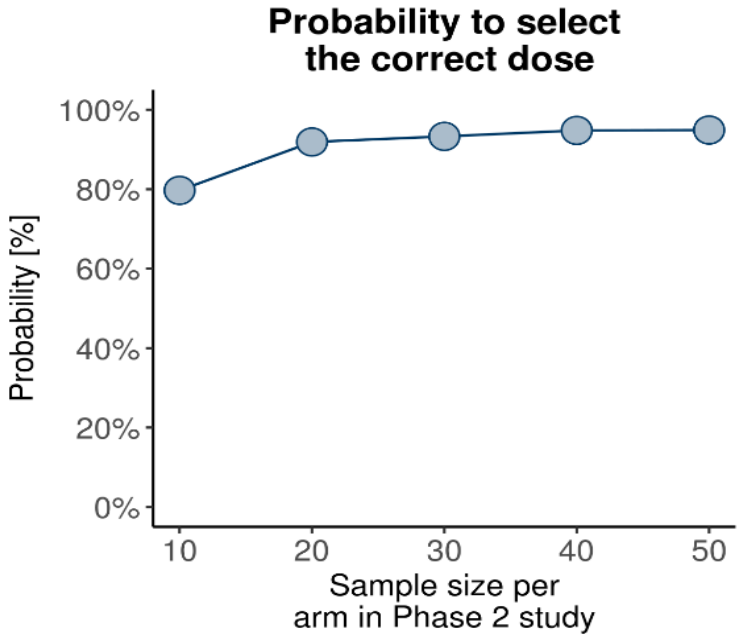
Directory:/projects/qcp/QCP_MODELING/CVMD/azd8233_pcsk9_sc/eda_20201221_MIDD_paper_part1
R-script: 07_DR_and_prob_tech_succ_DRF.R,
2020-12-29 13:11:19

1999 simulations of Phase 2 study. Simulations account for uncertainty in random and fixed effects. PCSK9 target for the therapeutic dose is 90% PCSK9 reduction during the entire dosing interval. A: simulate PCSK9 dose response at steady-state. Band indicates 90% CI. Dotted line indicates 90% PI. B: Technical probability of success (PCSK9 reduction>90%) for 50% of subjects (gold) and 90% of subjects (green) by dose at steady state.

See this great tutorial! Kyle Baron, K. T. Using a PK/PD model for simulation-based assessment of probability of technical success in drug development. (2016).at https://www.youtube.com/watch?v=F_oM1V4Lp90
*Probability of success analysis was not part of the FDA MIDD meeting

MIDD phase 2 sample size justification





Dose-selection criteria in simulation studies:
select the lowest dose that reaches GO*

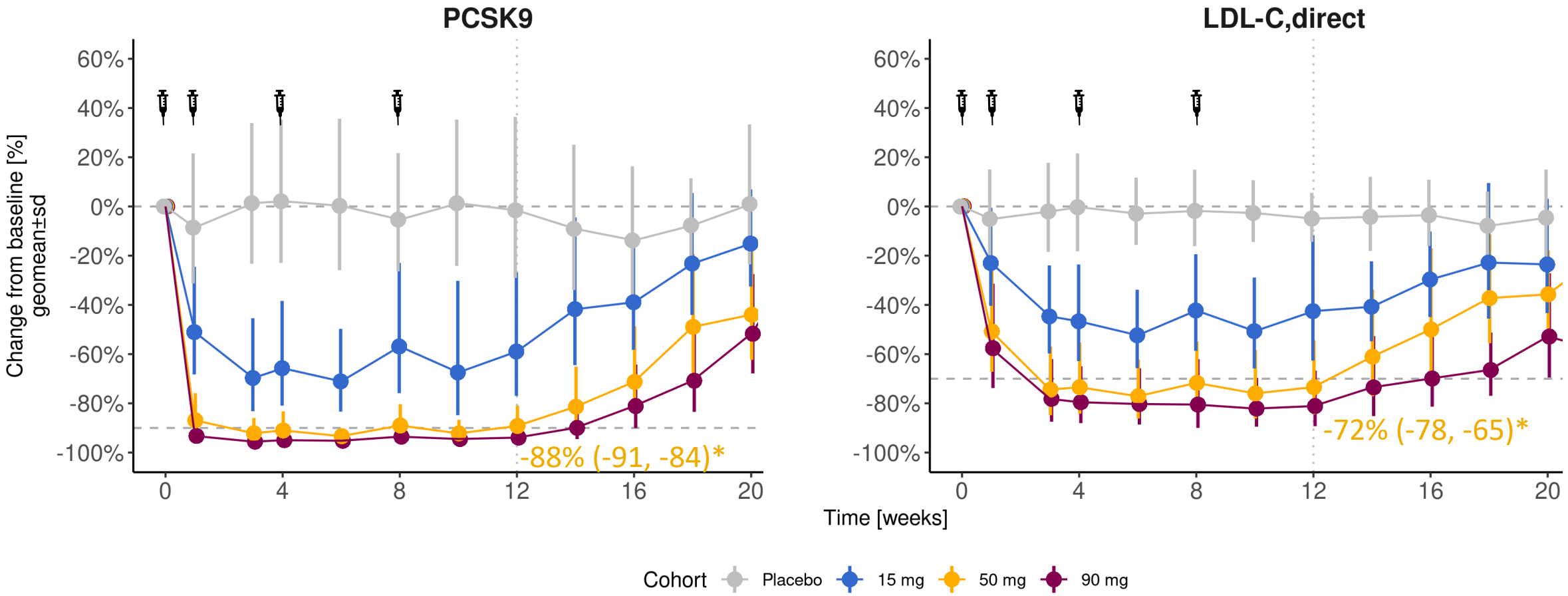
Adapted from: Smith, Mike K., et al. "Decision-Making in Drug development: application of a model-based framework for assessing trial performance." Clinical Trial Simulations. Springer, New York, NY, 2011. 61-83.

Assuming a true effect of 70% for the high dose and 65% for the low dose the correct dose is selected ~95% of cases with a sample size of ~20 sub/arm or more. **

*Analysis not part of MIDD meeting
**Based on stochastic simulations and re-estimations with subsequent effect size predictions based on resampling of the variance covariance matrix.

Readout Ph2b (ETESIAN) and modelling

Clear dose-response in ETESIAN for both PCSK9 and LDL-C

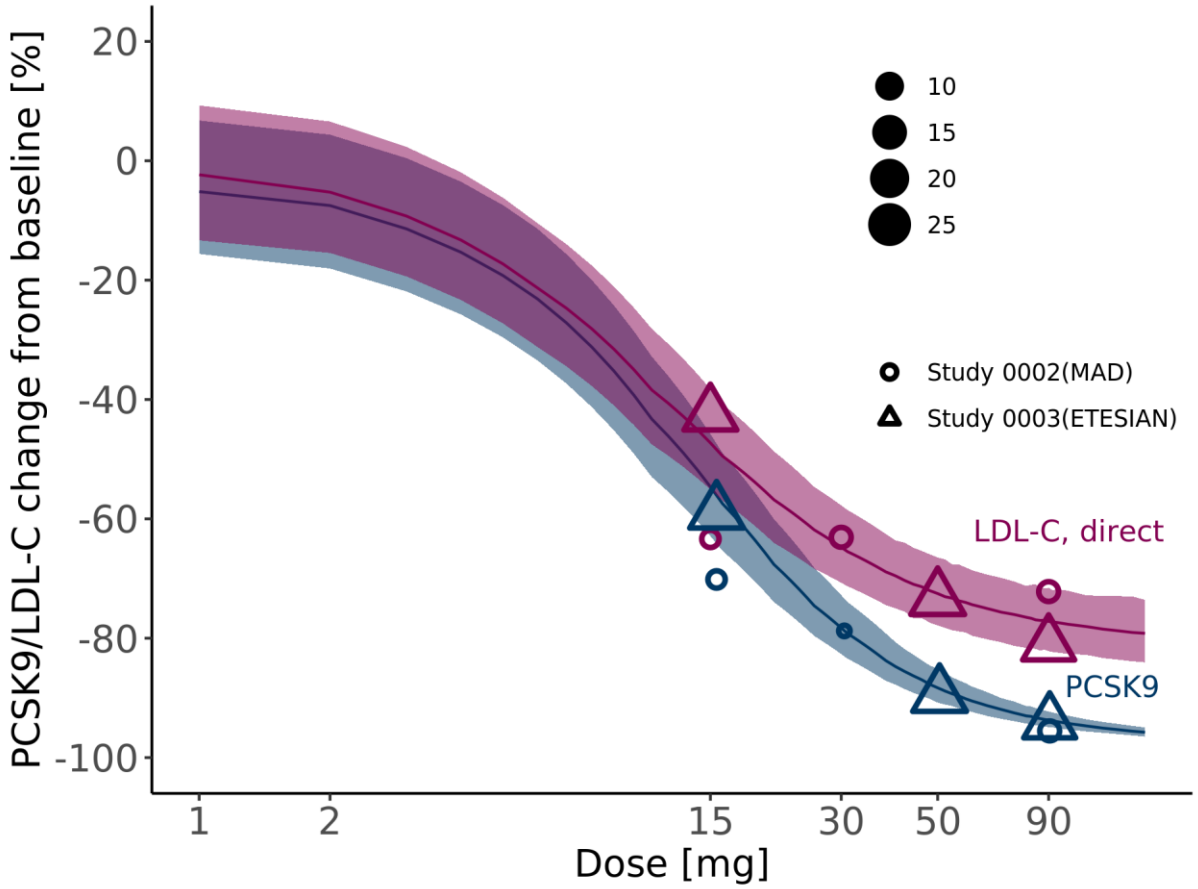


* Placebo corrected change from baseline

Koren, M. J., Hofherr, A., Schumi, J., Rekic, D., Knochel, J., Nilsson, C. A. M., Rudvik, A., Wernevik, L., Ryden-Bergsten, T., & Carlsson, B. C. L. (2022). ETESIAN: A PHASE 2B STUDY OF THE EFFICACY, SAFETY AND TOLERABILITY OF AZD8233, A PCSK9-TARGETED ANTISENSE OLIGONUCLEOTIDE, IN PATIENTS WITH DYSLIPIDEMIA. Journal of the American College of Cardiology, 79 (9), 1475. https://doi.org/10.1016/S0735-1097(22)02466-4

Dose-response curve for PCSK9 and LDL-C overlayed with MAD and Ph2b data

First estimation of PCSK9 and LDL-C dose response curve for AZD8233



Knöchel et al., PAGE 2022

Ph3 Clinical Trial simulations

Clinical Trial Simulation Framework

Components of CTS

Uncertainty and variability

- Residual error and between subject variability
- Accounting for uncertainty in random and fixed effects

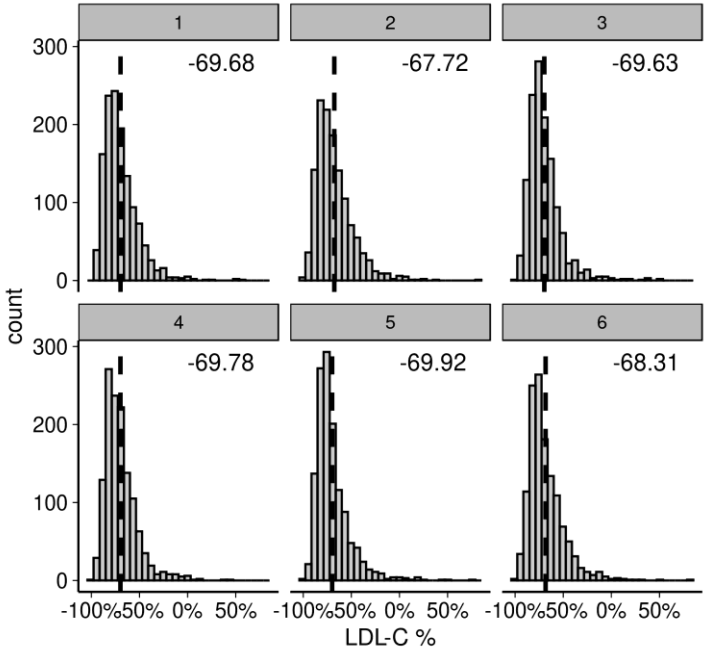
Trial execution

- Simulation with drop out from treatment
- LDL-C measurement time points (observations)
- Dose and regimen, control arm
- Sample size
- Application of inclusion exclusion criteria for baseline LDL-C

Statistical model

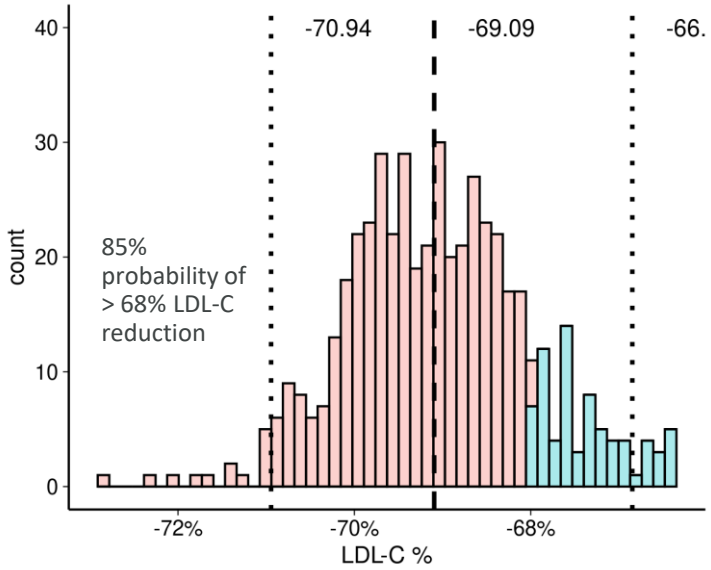
- Same statistical model as used in phase 3

Distribution of individual LDL-C in 6 studies



For each clinical study, an ANCOVA model is used to estimate the treatment effect.

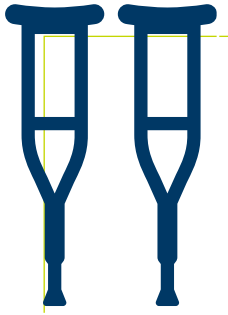
Distribution of means from all simulated studies



Point estimate and CI is estimated based on the percentile method. Alternatively, a distribution can be fitted. Useful for PTS calculations

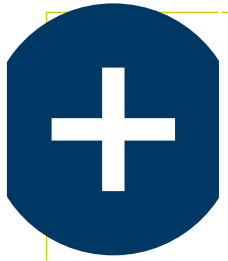
500 simulations, 1200 subjects per arm, 3.4% drop out

Impact of MIDD on pivotal LDL-C Phase 3 studies



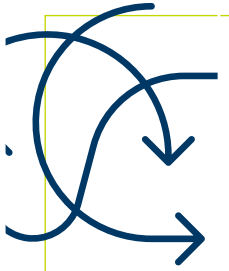
What is the LDL-C reduction without booster dose?

- ETESIAN GO decision is not sensitive to booster dose



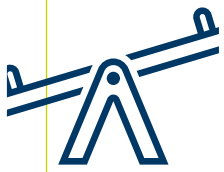
What is the expected effect of increasing dose to from 50 to 60 mg?

- Increase dose to enhance BIC profile



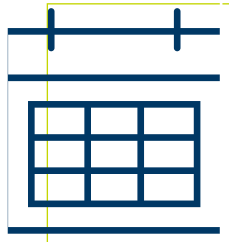
What is the impact of drop-outs on LDL-C?

- Change time point from 6 to 4 months to minimize impact, drop-out important when selecting vendor and sites



When should the primary end-point be?

- Change time point from 6 to 4 months to minimize impact of drop-outs. Steady state reached at 4 months

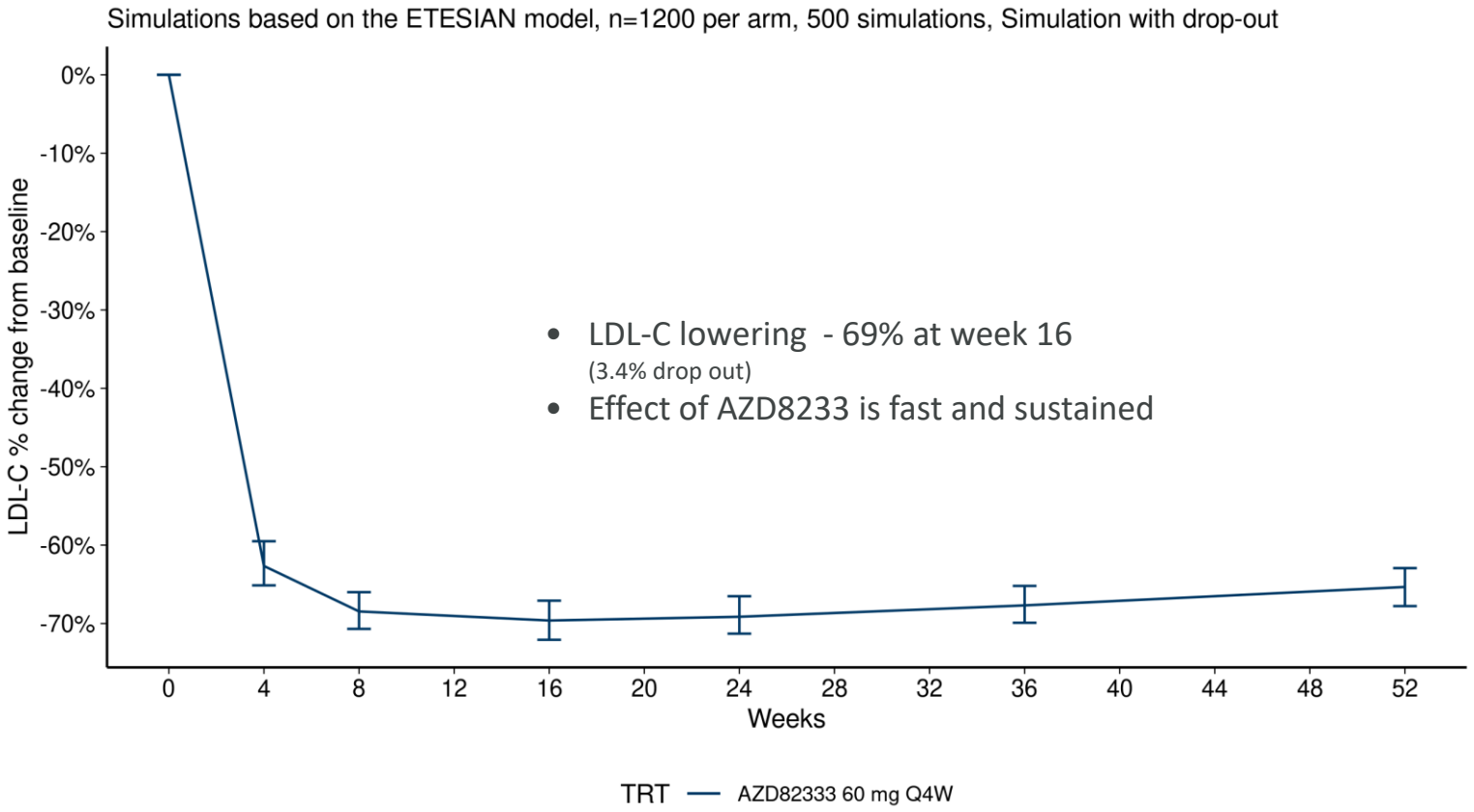


What is the impact changing from QM to Q4W dosing regimen?

- Change from QM to Q4W to enhance BIC profile

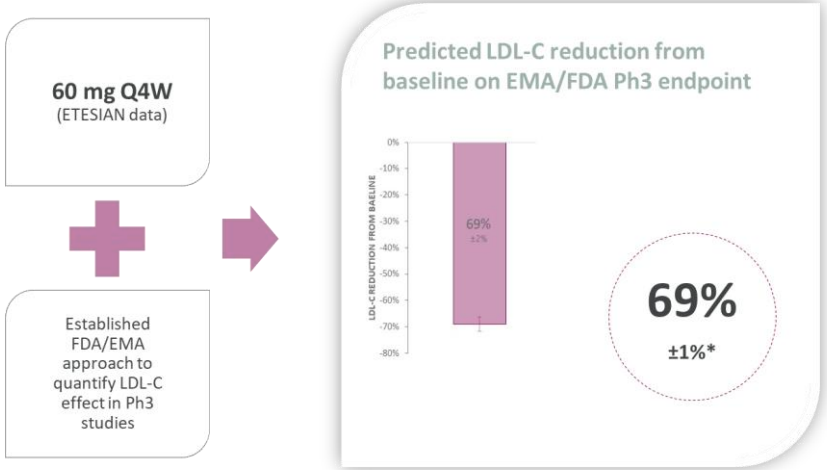
CTS of Phase 3 predict BIC LDL-C lowering in pivotal study

Phase 3 Clinical Trial Simulation AZD8233 60 mg Q4W vs placebo



- LDL-C lowering - 69% at week 16
  (3.4% drop out)
- Effect of AZD8233 is fast and sustained

Therapeutic dose expected to deliver BIC profile



Basis for the Ph3 simulation

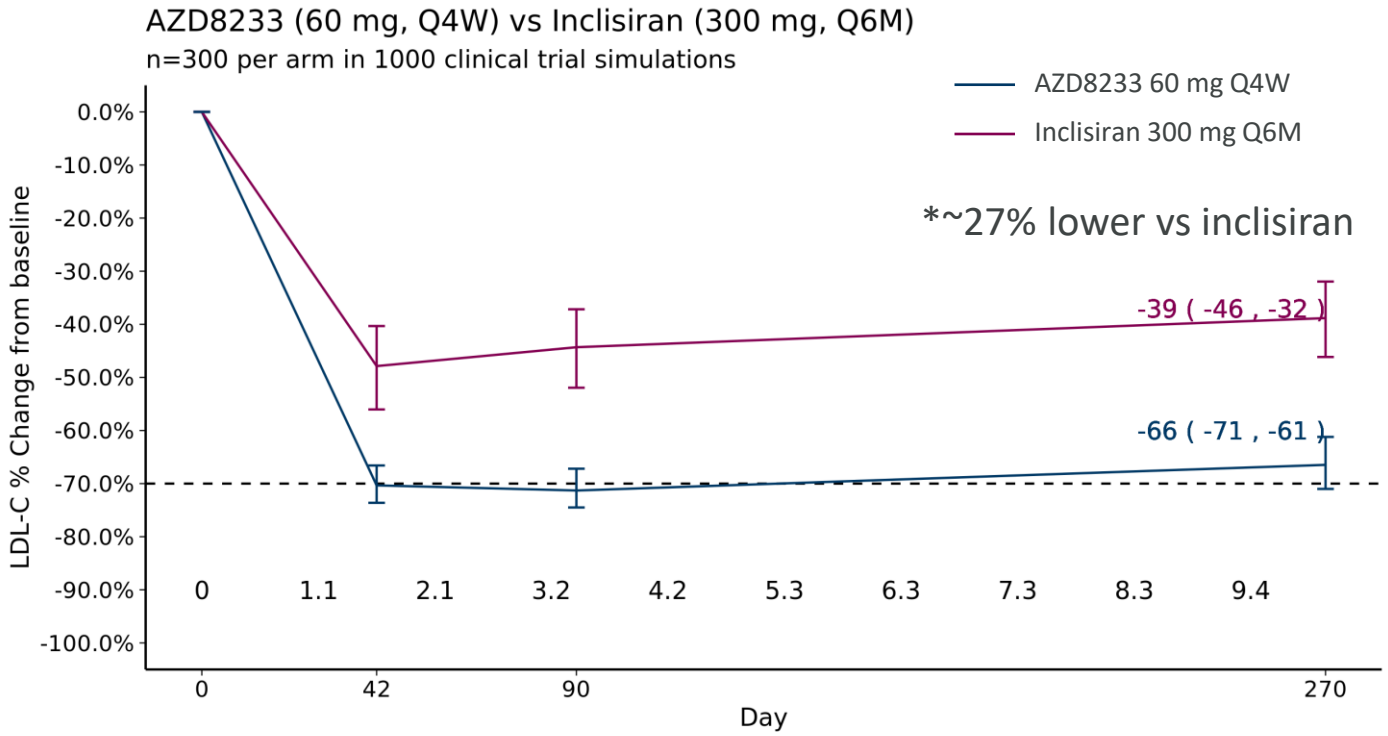
- EMA/FDA full Ph3 endpoint
- LDL-C Primary endpoint at week 16
- 3.4% drop out

Notes: Point estimates are on the linear scale: error bars indicate 95% confidence intervals AZD8233 dosed every 28 days.
*standard deviation

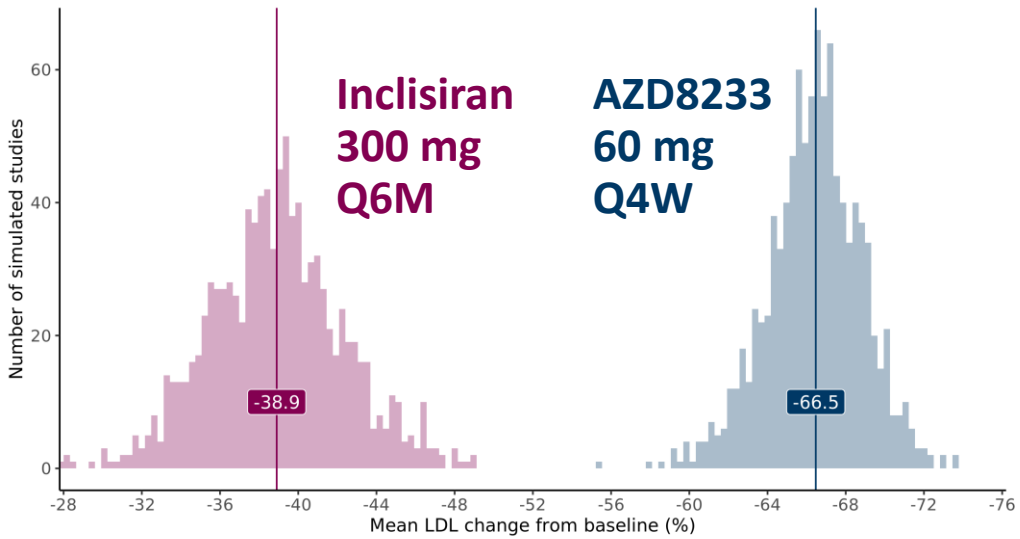
Differentiation

CTS of Head-to-Head study with inclisiran predict superiority of AZD8233

Phase 3 Head-to-Head with inclisiran Clinical Trial Simulation AZD8233 60 mg, Q4W vs inclisiran 300 mg, Q6M



Distribution of predicted mean percent LDL-C cfb at primary endpoint (Day 270)



Notes: Point estimates are on the linear scale: error bars indicate 95% confidence intervals AZD8233 dosed every 28 days.

Summary

Disease area overview

Unmet medical need yet a highly competitive area

Phase 1 preparation

Leverage of established LDL-C-PCSK9 relationship

KPD model for PCSK9 to inform dose selection for MAD and dose selection strategy for Ph2

Early confidence
in the dose selection strategy and clinical program by using PCSK9 as biomarker for decision making

Phase 2 preparation

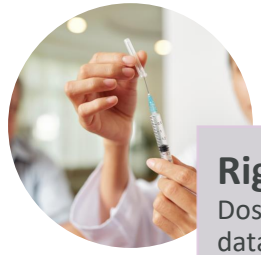
Impact on design including dose selection, sample size justification and probability of success

Justification of Ph2 start prior to MAD readout (FDA MIDD meeting)

Speed
Time to Ph2 shorted by 6 months

Phase 3 preparation

MIDD supported design of LDL-C phase 3



Right dose
Dose selected on SAD data demonstrated expected efficacy in Ph2b study

Knöchel, Jane, et al. "A case-study of model-informed drug development of a novel PCSK9 anti sense oligonucleotide. Part 1: First time in man to phase II." *CPT: Pharmacometrics & Systems Pharmacology* (2022).

Part 2 – manuscript in preparation

Acknowledgments

Clinical Pharmacology & Pharmacometrics Team and CPQP Leadership

Catarina Nilsson, Megan Gibbs, and Bengt Hamrén

AZD8233 Team

Björn Carlsson, Linda Wernevik, Alexis Hofherr, Peter Gennemark, Per Johanson, Lynne Durborow, Rasmus Jansson-Löfmark, Rikard Isaksson, Marielle Andersson, Lynne Durborow, Jennifer Schumi, and Tina Rydén-Bergsten