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CASE REPORT

A case-study of model-informed drug development of a novel PCSK9 anti sense oligonucleotide. Part 1: First time in man to phase II

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Abstract

Here, we show model-informed drug development (MIDD) of a novel antisense oligonucleotide, targeting PCSK9 for treatment of hypocholesteremia. The case study exemplifies use of MIDD to analyze emerging data from an ongoing first-in-human study, utility of the US Food and Drug Administration MIDD pilot program to accelerate timelines, innovative use of competitor data to set biomarker targets, and use of MIDD to optimize sample size and dose selection, as well as to accelerate and de-risk a phase IIb study. The focus of the case-study is on the cross-functional collaboration and other key MIDD enablers that are critical to maximize the value of MIDD, rather than the technical application of MIDD.

INTRODUCTION

AZD8233 is an antisense oligonucleotide that targets PCSK9 protein synthesis and thus lowers circulating LDL-C.[1] In 2022, the ETESIAN phase IIb study showed that AZD8233 lowers LDL-C up to 79% in patients with hypercholesterolemia on statins.[2] This magnitude of LDL-C reduction exceeded the range of other agents targeting the PCSK9 pathway as well as what has been observed by statin therapy alone.[3–5]

A key success factor for the streamlined early-phase development of AZD8233 was an in-depth understanding of the relation of PCSK9 and LDL-C. An abundance of data from older PCSK9 inhibitors could be used to establish a quantitative link from the biomarker (PCSK9), to the surrogate end point (LDL-C).

This case study starts with the first-in-human (FIH) study and ends with the read out of the ETESIAN phase II study that demonstrated potential for a best-in-class risk/benefit profile. We tell the drug development story of AZD8233 from a model-informed drug development (MIDD) perspective showing data and insights as they were emerging. We relied on "off the shelf" methodologies that have been previously developed and applied by others. When possible, we give references to helpful tutorials, examples, and original publications to the methodologies used in this work. In our experience, the biggest challenge of MIDD is often not technical in nature. Instead, the real issue is making MIDD seamlessly blend with the reality of drug development and the challenges it presents.

OVERVIEW OF THE MIDD STRATEGY FROM FIH UP TO PHASE II

A graphical overview of the MIDD strategy starting with the FIH study and ending with the design of the ETESIAN phase II study is shown in Figure 1a. In the first two steps, the relationship between PCSK9 and LDL-C is quantified and used to select the target level of PCSK9 reduction. Steps three and four outline the preparation for live dose prediction based on single ascending dose (SAD) data and subsequent model development and validation on multiple ascending dose (MAD) data, as well as an overview on the strategic use of the US Food and Drug Administration (FDA) MIDD pilot program. Finally, in step five, we discuss how doses and sample size for the phase II study were determined.

THE RELATIONSHIP BETWEEN PCSK9 AND LDL-C AND SETTING TARGET PCSK9 INHIBITION–STEP ONE AND TWO

To evaluate potential for differentiation and a best-in-class profile, the team needed to understand the level of PCSK9 reduction required in the SAD study to offer LDL-C reduction >70% in later studies. The target of mean reduction of 70% or more was jointly derived by the team and based on commercial insights and evaluation of existing therapies.

The abundance of prior clinical data allows for the derivation of the quantitative relationship between PCSK9 and LDL-C as exemplified by Sokolov and colleagues.[6] Underlying data from two modes of PCSK9 reduction are available: intracellular inhibition of PCSK9 synthesis with siRNA and monoclonal antibodies targeting circulating PCSK9. Gibbs et al. quantified the relationship between PCSK9 and LDL-C after single and multiple doses of evolocumab ranging from seven to 420 mg using a PK-PCSK9-LDL-C model.[7] Steady-state simulations based on the Gibbs model show a clear relationship between PCSK9 and LDL-C change from baseline, indicating that a 90% inhibition of PCSK9 levels is required to reduce LDL-C levels by 70% (Figure 2, black line, and dark gray ribbon). Kathman et al. derived a similar relationship based on PCSK9 synthesis inhibition by inclisiran after single and multiple doses ranging from 100 to 500 mg.[8] Simulations based on the Kathman model show an almost identical relationship (Figure 2, red line, and light gray ribbon).[8] Furthermore, digitized PCSK9 and LDL-C data from the literature showed good

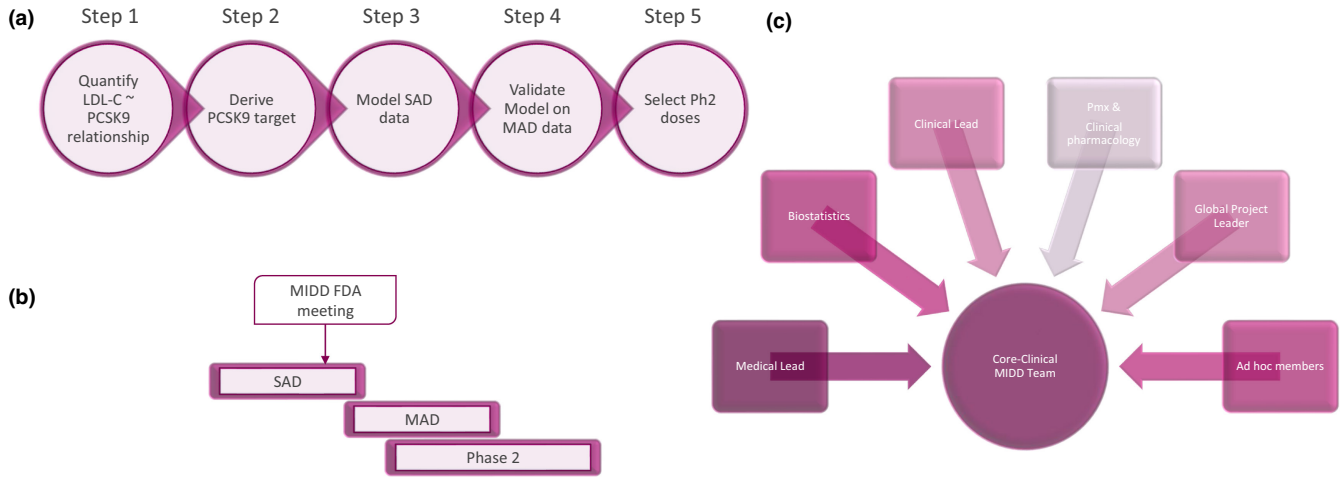

FIGURE 1 Overview of MIDD strategy (a), early clinical program (b), and the core clinical MIDD team composition (c). FDA, US Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; MAD, multiple ascending dose; MIDD, model-informed drug development; PCSK9, proprotein convertase subtilisin/kexin type 9; Ph2, phase II; PMX, pharmacometrics; SAD, single ascending dose.

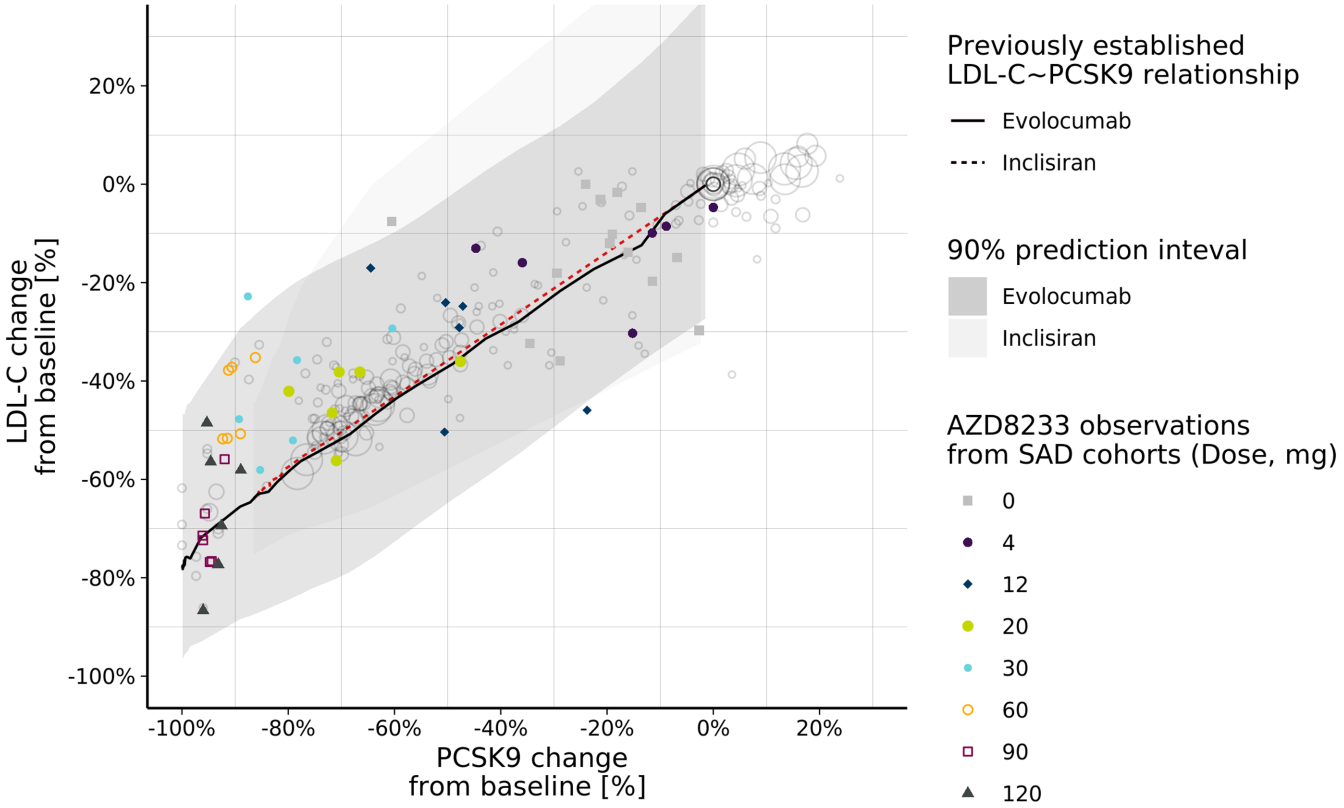

FIGURE 2 Quantitative relationship between PCSK9 and LDL-C. Mean digitized evolocumab and inclisiran data (gray circles) at steady-state levels. The size of the gray circles is proportional to the sample size. Colored points represent nadir observations in the SAD study. Lines represent mean steady-state PCSK9~LDL-C relationship by inclisiran (red) K-PD model and evolocumab (black) PK-PD model; corresponding shaded areas represent 90% prediction intervals. Model simulations and observed data from evolocumab and inclisiran are at steady-state. The observed AZD8233 data are nadir observations from a single dose. K-PD, kinetic-pharmacodynamic; mAb, monoclonal antibody; PK-PD, pharmacokinetic-pharmacodynamic; SAD, single ascending dose; siRNA, small interfering ribonucleic acid.

agreement with the simulations, lending further support to the derived target level of 90% PCSK9 inhibition (Figure 2, gray circles). The relationship was also validated by internal SAD data once it became available, increasing the confidence further (Figure 2, colored points).

The decision to rely on PCSK9 as opposed to LDL-C for dose selection was possible due to the strong and causative relationship between PCSK9 and LDL-C (Figure 2), but other factors motivated the decision as well (e.g., AZD8233 acts by inhibiting production of PCSK9 directly and PCSK9 is therefore considered to be closer to the mechanism of action). Prior experience with older PCSK9 inhibitors shows that PCSK9 is more responsive (greater effect size) than LDL-C with smaller variability.[9,10] These considerations are of special importance because of the small sample size ($n = 6$ per cohort) in the SAD study and non-steady-state evaluation of the pharmacodynamic (PD) effect due to single dose administration (Figure S1).

MODELING PCSK9 REDUCTION IN FIH SAD STUDY–STEP THREE

Continuously updated dose-prediction based on PCSK9 reduction in the SAD study

The human dose prediction based on the non-human primate (NHP) data was 30 mg.[1] At the fourth data delivery, interim data from the 60 mg cohort showed convincing 90% PCSK9 reduction (Figure 3). Data delivery 4 was also identified by the stochastic simulation and re-estimation (SSE) analysis as sufficiently robust to update the NHP model with clinical data and for the first time update the therapeutic dose, now predicted to be ~20 mg QM (Figure 3, March 12, 2019).[11] This inconsistency is explained by change in other PD parameters that governed steepness in PCSK9 inhibition, potency, rate of PCSK9 elimination, and elimination rate from the effect compartment (Figure S2). The predicted therapeutic

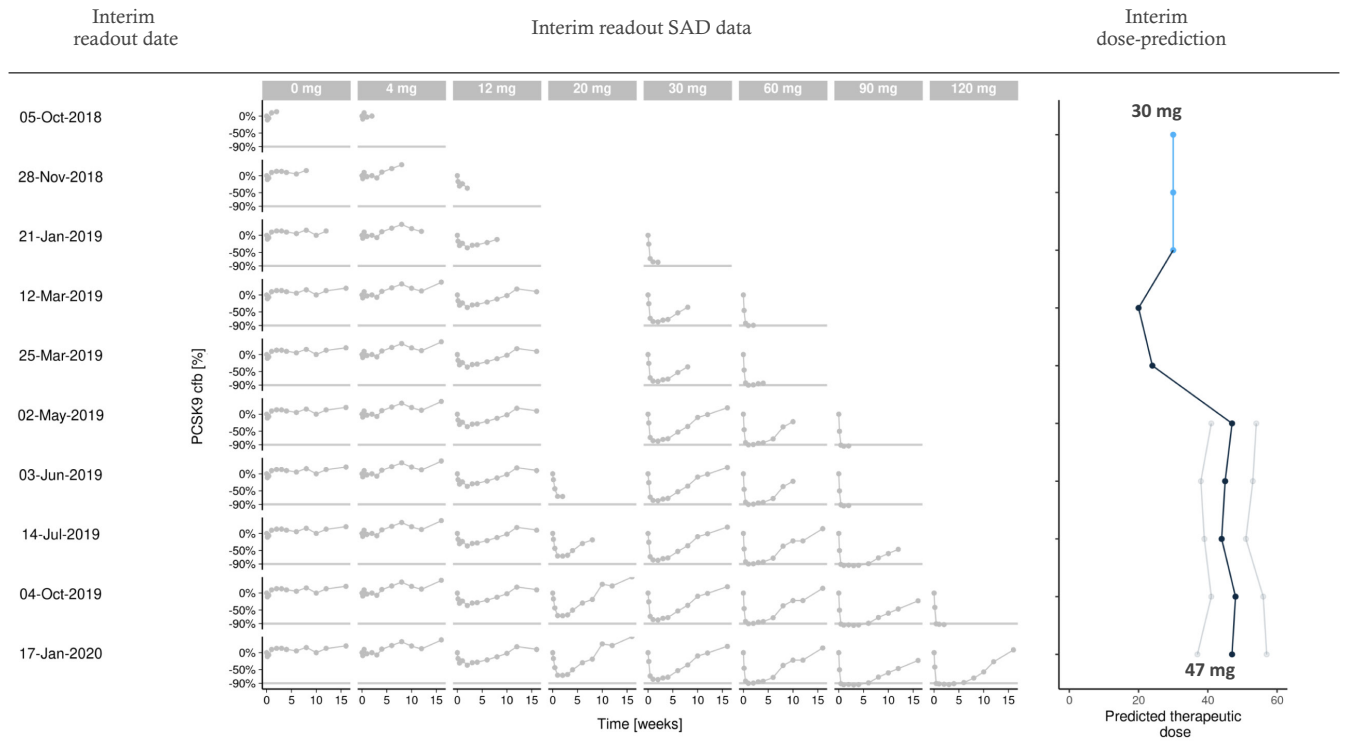

FIGURE 3 Continuous dose prediction based live data stream from the SAD in healthy volunteers. Left panel indicates date of data delivery. Middle panel shows the PCSK9 change from baseline at each delivery by dose. Right panel indicates the dose prediction at time of data delivery. The light blue line indicates dose prediction based on NHP data. The dark blue line and gray lines indicate the dose prediction based on the PCSK9 data from the SAD study. The gray lines indicate the 90% confidence interval. NHP, non-human primate; SAD, single ascending dose.

dose continued to be updated based on data from subsequent data deliveries. Subsequent data deliveries showed a consistent dose prediction of 40 to 50 mg QM. It can be questioned if the SSE used to evaluate when robust dose predictions can be made were successful in their task. As seen in Figure 3 and Appendix S1, dose predictions and model parameters did not stabilize until data delivery 6. Most likely, we can attribute this to a too optimistic assumption about model parameter uncertainty and translatability of the preclinical model used for SSE. This oversight is an important lesson learned that, fortunately in this case, did not have a significant impact.

Therapeutic dose predictions were based on the probability of a dose to lower PCSK9 by 90% during the entire monthly dosing interval. Initial uncertainty in fixed effect parameter estimates was accounted for by resampling the variance–covariance matrix estimated in NONMEM.[12,13] However, as the sample size increased (from delivery 6 and onward), nonparametric bootstrap was favored over the variance–covariance matrix methods. In this example, the confidence intervals (CIs) estimated by the two methods were similar and did not impact any decisions. Simulations used to estimate the therapeutic dose accounted for variability (between subject variability and residual error) as well as uncertainty in parameters (random and fixed effects). Use of the R package mrgsolve increased efficiency in the workflow and was instrumental.[14] A detailed online tutorial presented by Baron on using the mrgsolve package for simulations accounting for both uncertainty and variability as well as for estimating probability of technical success is available online.[15] Additional methodological details are available in the supplement. The full concentration time profiles for PCSK9 and LDL-C after a single dose are shown in Figure S2.

FDA MIDD pilot program

The FDA MIDD pilot program was initiated as part of performance goals of the sixth iteration of the Prescription Drug User Fee Act (PDUFA VI). The program provides a platform for drug developers and the FDA to discuss the application of MIDD approaches as well as provide advice about how MIDD approaches can be applied in specific drug development programs.[16] In February 2020, the team submitted a request for an MIDD meeting with the FDA.[17] The meeting request focused on using MIDD approaches for dose selection. The final briefing book was submitted in April 2020 and showed simulations illustrating the data available for dose selection at each decision point. Simulations were

based on PCSK9 modeling from the SAD study coupled with the historical LDL-C ~ PCSK9 relationship. The briefing book showed the strategy for dose selection for phase II as well as dose selection for the final dose to be tested in the phase III program. Once again, SSE was used to show the robustness of the data at each decision point and in extension the confidence in the dose selection.

Several information requests were received from the FDA focusing on the safety dataset but also requests for R code, NONMEM models, and the underlying data. A face-to-face meeting was not possible due to the ongoing coronavirus disease 2019 (COVID-19) pandemic. A written response was obtained in June 2020 with agreement on the overall dose selection strategy, including phase II sample size and dose selection strategy based on SAD PCSK9 data in combination with interim MAD data from two cohorts. Effectively, this allowed the phase II study to be started as soon as the safety review committee (SRC) cleared the 90 mg MAD dose (Figure 1b). Starting the phase II study prior to completion of the MAD study saved 6 months in development.

One can argue that the underutilized end of phase I (EOPI) meeting could have been used to reach similar goals. In our case, we saw advantages in the MIDD pilot program and how it is set up with several internal FDA meetings where all meeting participants from all review disciplines had internal alignment on the application of the modeling approach and modeling was allowed to take center stage.

PREDICTION OF MAD STUDY RESULTS AND VALIDATION OF THE MODEL–STEP FOUR

Up to this point, only SAD PCSK9 data from healthy volunteers was used to inform the MIDD approach. Furthermore, the LDL-C prediction was based on the prior established LDL-C ~ PCSK9 relationship. To be competitive, LDL-C must be reduced by 70% in patients on statins. Showing accurate predictions of LDL-C reduction in patients on background statins in the MAD study was therefore crucial.

The MAD study randomized eight patients into each active arm at three dose levels (15, 30, and 90 mg). These dose levels were estimated to reduce PCSK9 by ~65%, 85%, and >90% at week 12. In addition to doses at weeks 0, 4, and 8, a booster dose at week 1 was planned to ensure that PCSK9 and LDL-C levels would be at their steady-state levels at week 12. The MAD study would start with the 30 mg cohort, followed by the 90 mg cohort, after approval from the SRC to escalate the dose. The expected PCSK9 data available from the MAD study (Study D7990C00002) was simulated and presented to the team in January 2020 (Figure S5).

In September 2020, the 30 mg cohort data from the MAD study arrived showing ~70% LDL-C reduction in patients on statins. The PCSK9 reduction was well-predicted, and so was the nadir and LDL-C reduction (Figure S5). Although, the sample size in the 30 mg MAD cohort was small ($n = 8$), two key conclusions could be made based on the accuracy of these predictions: (1) induction of PCSK9 by statins does not impact the LDL-C lowering effect, and (2) LDL-C reduction by 70% at doses lower than 90 mg QM is possible. Additional methodological details are available in the supplement. It should be noted that our ability to predict future outcomes of a study was found impressive not just within the project team but also by very senior leaders in the organization. One can argue that being able to predict steady-state data from single dose data is a reasonable request for these types of models, but outside of our field, this was found very impressive.

PHASE II DESIGN AND ACCELERATION–STEP FIVE

Finding an optimal dose that would satisfy the therapeutic goals is of tremendous importance to achieve a best-in-class profile and fulfill an unmet medical need in hypercholesteremia. Therefore, design aspects, such as sample size, treatment duration, and doses, to be investigated in the phase II dose finding study were continuously updated as more data became available.

Furthermore, a flexible protocol (with only placeholder doses) was written, and the investigational product was prepared in vials of different concentrations to allow for maximal flexibility in doses. Patients were prescreened and front loaded to ensure fast recruitment. All together, these activities allowed the first patient to be dosed 2 weeks after we selected the final doses. Because of the high confidence and the prioritization of this project, the team invested additional resources in recruitment of the phase II study, fully recruiting the study 5 weeks ahead of schedule. This was a monumental achievement from a study operations perspective only possible through cross-functional collaboration on a new level. Without these key enablers (Table 1), MIDD would just be a modeling and simulation activity, as opposed to the integrated approach to MIDD, advocated here and elsewhere.[17–20]

The size of the phase II study was informed by extensive SSE to evaluate probability of picking the "right dose" as determined by LDL-C lowering criteria, similar to the approach proposed by Smith et al.[21] The dose selection criteria were based on the estimated 95% CI for LDL-C lowering and picking the lowest dose whose 95%

TABLE 1 Enablers of MIDD

Key enablers of MIDD	
Flexible protocols	• Allows on the fly changes to doses, as well as addition of cohorts. Key for seamless transition from SAD to MAD and starting phase II based on interim MAD data. Use of vials and syringes in studies allowed for more flexibility to select doses.
CMC front loading	• Drug substance availability for a range of possible doses produced at risk to minimize "white space" between studies. This allowed starting phase II within days after dose selection based in interim MAD data.
Optimized recruitment strategy	• Patient prescreening at a priori identified sites allowing fast recruitment rates. Over 30 patients randomized and dosed in phase II 1 week after dose selection based on interim MAD data.
Live data-stream	• A tight network of vendors to facilitate a continuous "live data stream" at regular intervals. Continuous updates of the dose prediction to inform cost of goods predictions, CMC planning, and forward clinical development plan.
Cross-functional teamwork	• Tight collaboration between the key functions made possible by long-term consistent investment in building trust and enhancing collaboration.
Organizational support	• Support from the organization to implement and follow through on an MIDD strategy providing upfront at-risk investments.
Clear communication	• Communication strategy that is free from technical jargon that focuses on opportunity, risk, and impact.

Note: Flexible doses were achieved by setting the upper range to be evaluated in the dose justification section of the protocol based on exposure limits and max level of PCSK9 inhibition. Doses were also justified based on their desired level of PCSK9 reduction. Protocol language was added to allow adjustment of doses to meet the desired level of PCSK9 reduction.

Abbreviations: CMC, chemical manufacturing and controls; MAD, multiple ascending dose; MIDD, model-informed drug development; SAD, single ascending dose.

CI excludes 65% LDL-C reduction and includes 70% reduction. For example, assuming a true effect of 70% for the higher dose and 65% for the lower dose, power to pick the "right dose" was evaluated for a range of sample sizes, showing that a sample size of >20 subjects in the phase II study together with the SAD and MAD data is sufficient (Figure 4a**)**. In addition to a model-based analysis, a Bayesian analysis was conducted to support the sample size. Posterior probability of reaching >69% LDL-C reduction was estimated based on median of 10,000 simulations using the observed variance and point estimate of the 90 mg dose in the SAD study and assuming a point estimate of 70% LDL-C reduction in future trials. This analysis showed that increasing the sample size in the phase II study to 50 subjects per arm showed no significant improvement in certainty to reach 70% LDL-C reduction **(**Figure 4b**)**.

Doses to be investigated in the phase II study were based on the predicted PCSK9 reduction. Three doses were proposed to be investigated. A low dose that would be used to show that lower doses result in lower LDL-C lowering, a middle dose (the predicted therapeutic dose), and a high dose that would be used to show that higher doses do not lead to increased LDL-C lowering.

Modeling of all available data up to this point (SAD and interim MAD data) was used to predict the therapeutic dose. The simulations included uncertainty in both random and fixed effects. The therapeutic dose was predicted to be ~50 mg (90% CI: 42, 59; Figure 4c**)**. However, the dose needed to reach >90% probability of technical success (PTS) of observing a mean PCSK9 reduction of 90% in the proposed phase II study was estimated to 53 mg (Figure 4d**)**. Whereas the middle dose aimed to lower PCSK9 by 90% on average, the top dose aimed to lower PCSK9 by 90% in >90% of subjects during the entire dosing interval. A dose of 97 mg was needed to reach >90% PTS of reducing PCSK9 by 90% in >90% of subjects (Figure 4d**)**. Although there are advantages of designing a study based on optimal design theory to increase precision or decrease sample size,[22] we valued generating safety data on what we believed to be a therapeutic dose more, especially considering the intended large and broad patient population.

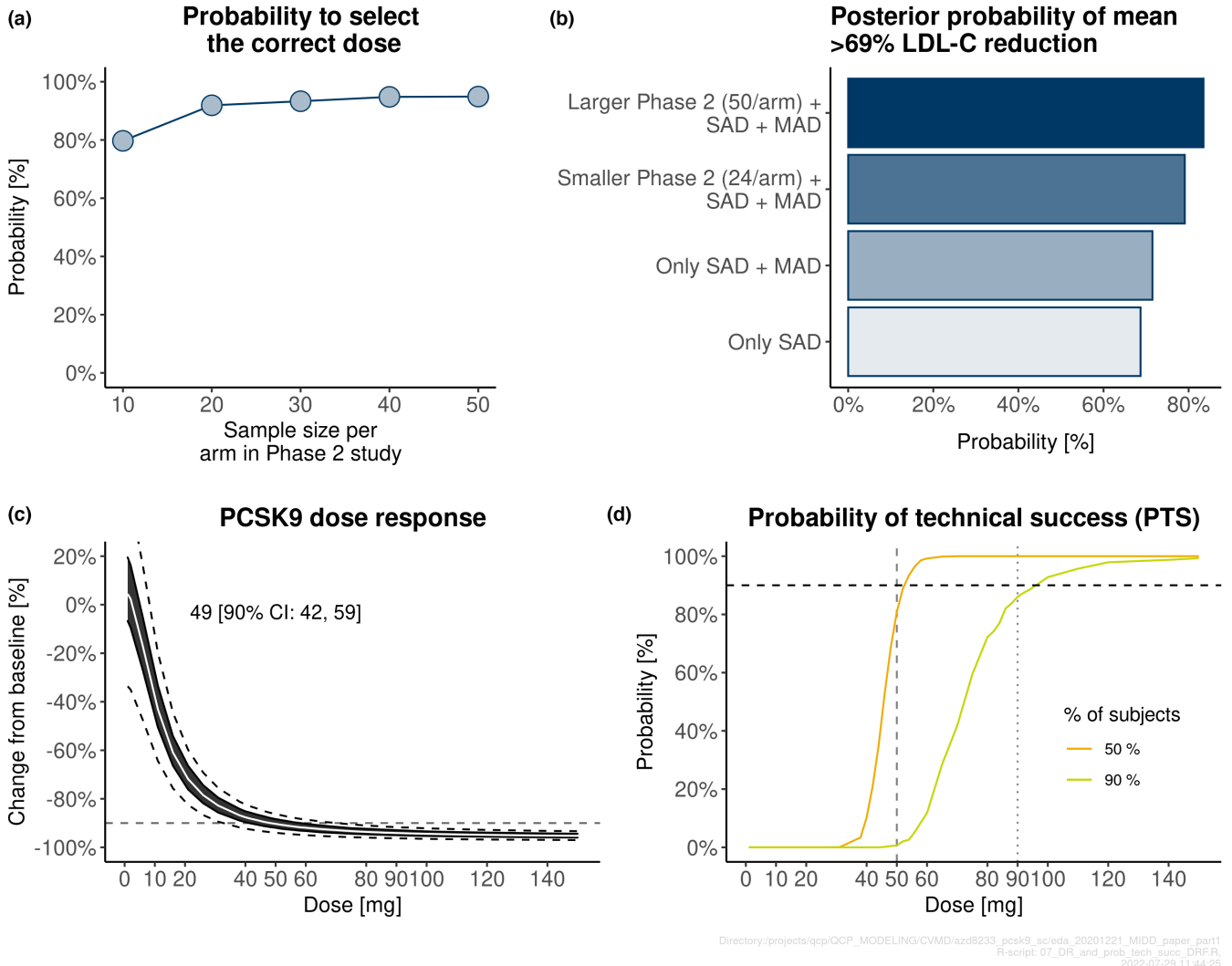

FIGURE 4 Justification of phase II study sample size (top row) and dose selection (bottom row). Probability to select the correct dose by sample size (a), posterior probability of observing an LDL-C reduction >69% in future studies with various sample size (b), PCSK9 dose–response curve (c), probability of technical success to reach 90% PCSK9 inhibition in 50% of subjects (orange), and 90% of subjects (green) by dose (d). CI, confidence interval; MAD, multiple ascending dose; SAD, single ascending dose.

Based on these analyses, the 15, 50, and 90 mg doses were selected to be investigated in the phase II study. This decision was made 2 weeks after the SRC cleared the 90 mg dose in the MAD study. This was possible due to the prespecified dose selection criteria that was agreed within the team and key stakeholders. Again, illustrating the strength of the cross-function MIDD approach.

DISCUSSION

In this case study, we tell the MIDD story that led to the read out of the ETESIAN phase IIb study that showed a potential best in class LDL-C reduction of up to 79%.[2] We begin the case study before the FIH study, with the derivation of PCSK9 target values based on competitor's data and models. Continuing with establishment of a live data stream that would fuel continuous dose-prediction (based on FIH data) used to justify and inform front loading of future studies and early engagement with the FDA. The FDA MIDD pilot program created an arena where we could engage FDA scientists on a sufficiently detailed level that allowed us to use MIDD methods to justify the phase II study start prior to the readout of the MAD study. This collaboration with the FDA decreased the length of the program by 6 months. Finally, in this case study, we outline the MIDD strategy used to select the doses, sample size, and inform other aspects of the phase II study design.

This case study focuses on the benefit side of the benefit–risk. Due to the limited sample size, an MIDD approach could only be applied to the risk of QT prolongation. A concentration-QT analysis was performed based on the SAD data, concluding that AZD8233 does not induce QTcF prolongation at the high clinical

exposure scenario.[23] It should be noted that the preclinical modeling work was fundamental for the successful application of MIDD principles in this case study. Prediction of human efficacy based on preclinical data was pivotal to support clinical phase investment. Please see Gennemark et al. for an example of preclinical MIDD applications as well as prediction of an oral formulation of AZD8233.[1]

To effectively use MIDD, data must be obtainable and quantifiable, full alignment and collaboration within the cross-functional team is necessary, and the team needs to be supported from an organization committed to quantitative decision making. All these requirements were present in this case study. An abundance of prior information made it possible to set quantitative targets for LDL-C lowering and prior modeling work allowed for direct translation from PCSK9 reduction to LDL-C reduction. The PCSK9 inhibition was achievable after a single dose and modeling predicted response at steady-state in patients. The cross-functional collaboration in the MIDD team was responsible for maximizing the value provided by the MIDD approach.

It is our ambition that this case study will serve as a real-life application of MIDD showing how data are analyzed as it emerges, including a transparent account of discussions when theories are challenged by unexpected observations. We also conclude that with cross-functional collaboration and organizational support, the value and impact of MIDD is greatly increased with the ability to reduce timelines, cost, and to increase certainty in decision making.

AUTHOR CONTRIBUTIONS

D.R., J.K., and C.N. wrote the manuscript. D.R., J.K., C.N., B.C., L.W., A.H., P.E., R.J.L., B.H., and T.R.B. designed the research. D.R., J.K., R.I., A.H., and B.C. performed the research. D.R., J.K., and R.I. analyzed the data.

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CONFICT OF INTEREST

All authors were employed by AstraZeneca at the time of this study and may own stock.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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