Modeling & Simulation
Decisions

Visual abstract + annotation

Use of a quantitative systems pharmacology modeling to benchmark the anti-PCSK9 treatment modalities

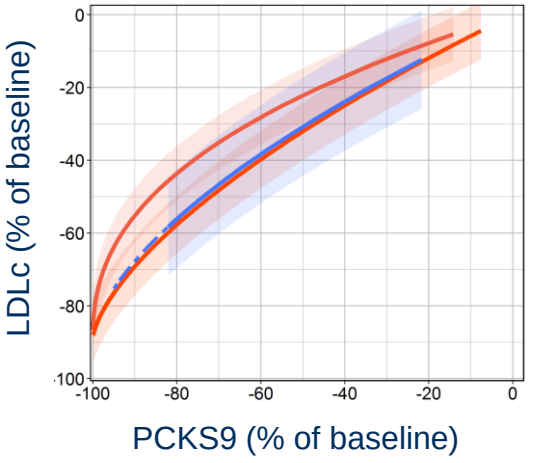
The challenge: PCSK9 inhibition therapies are an actively expanding field in hypercholesterolemia treatment, as a substitute or an add-on therapy in dyslipidemic patients. Multiple PCSK9 compounds are already on the market or are currently being developed, thereby creating a strong competition environment. Thus, understanding the differences and assessing potential advantages of various anti-PCSK9 modalities in different patient populations under wide range of doses and regimens becomes critical on early stages of development.

The achievement: Through collaboration of M&S Decisions and AstraZeneca, a quantitative systems pharmacology model was developed to describe lipoprotein metabolism. This allowed to evaluate the effects of various anti-PCSK9 treatments on major dyslipidemia biomarkers (LDLc, PCSK9, VLDLc, HDLc, Non-HDLc, ApoB, total cholesterol, Lp(a)), to quantify the differences between treatment modalities, and to understand the impact of background statin treatment on anti-PCSK9 efficacy. The models suggests that the anti-PCSK9 siRNA has potential to be at least as effective as the mAbs.

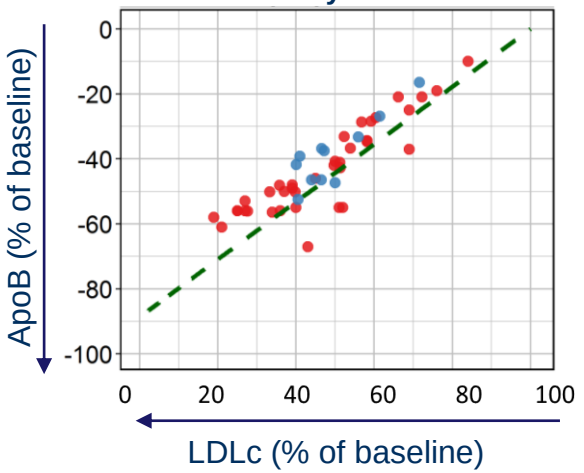
Quantitative Systems Pharmacology modeling helps understand the differentiation potential of PCSK9 siRNA in relation to key competitors

Examples of key model simulations showing…

In silico benchmarking of siRNA vs mAbs in patients with elevated cholesterol



Experimental data analysis and model predictions show similar ApoB reduction under mAbs and synthesis inhibitors



Left: plasma LDLc reduction relative to plasma PCSK9 reduction after treatment with wide arrange of doses of anti-PCSK9 antibodies or the PCSK9 synthesis inhibitor siRNA. Red lines – mAbs predictions. Blue solid and dashed lines – siRNA predictions within and outside available range of data respectively. Shaded area – 95% CI.

Right: pre-dose LDLc levels under different alirocumab (blue dots), evolocumab (red dots) and inclisiran (green dots) doses were compared with pre-dose ApoB levels, suggesting that if synthesis inhibitors had the capacity to interrupt ApoB expression in contrast to mAbs, stronger ApoB reduction would be observed under treatment with synthesis inhibitors. Dotted curve is model prediction.

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Compact work review:

Joint Comparative quantitative systems pharmacology modeling of anti-PCSK9 therapeutic modalities in hypercholesterolemia

Anti-PCSK9 therapies – innovative approach to cholesterol lowering

siRNA cholesterol-lowering compound – a new modality with significant benefits in price and compliance

Saturated, extremely competitive market

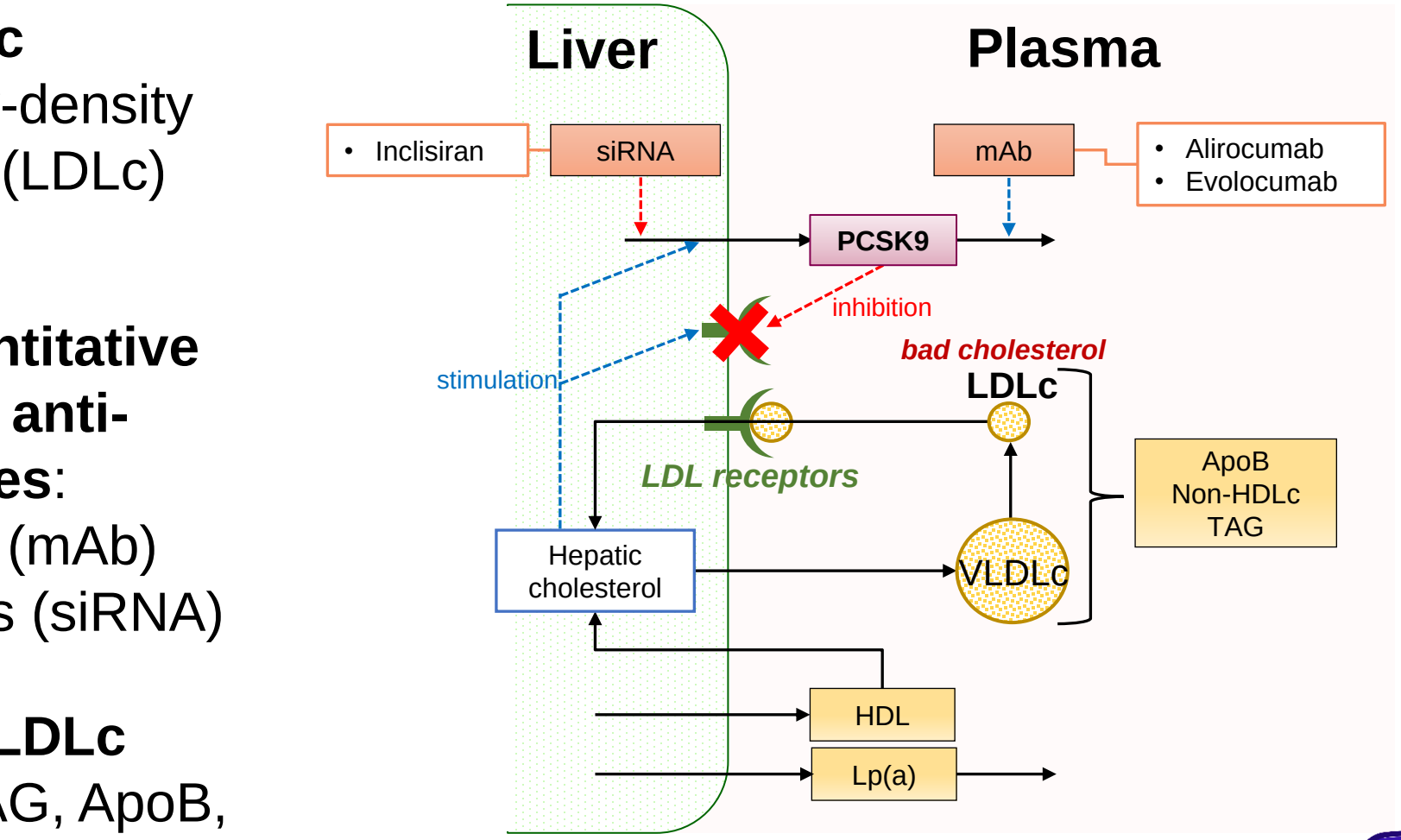
Can siRNA-based compound compete with other therapies on the market?

Investment decision required even before the compound is tested in clinic

QSP modeling of lipoprotein metabolism based on competitor data

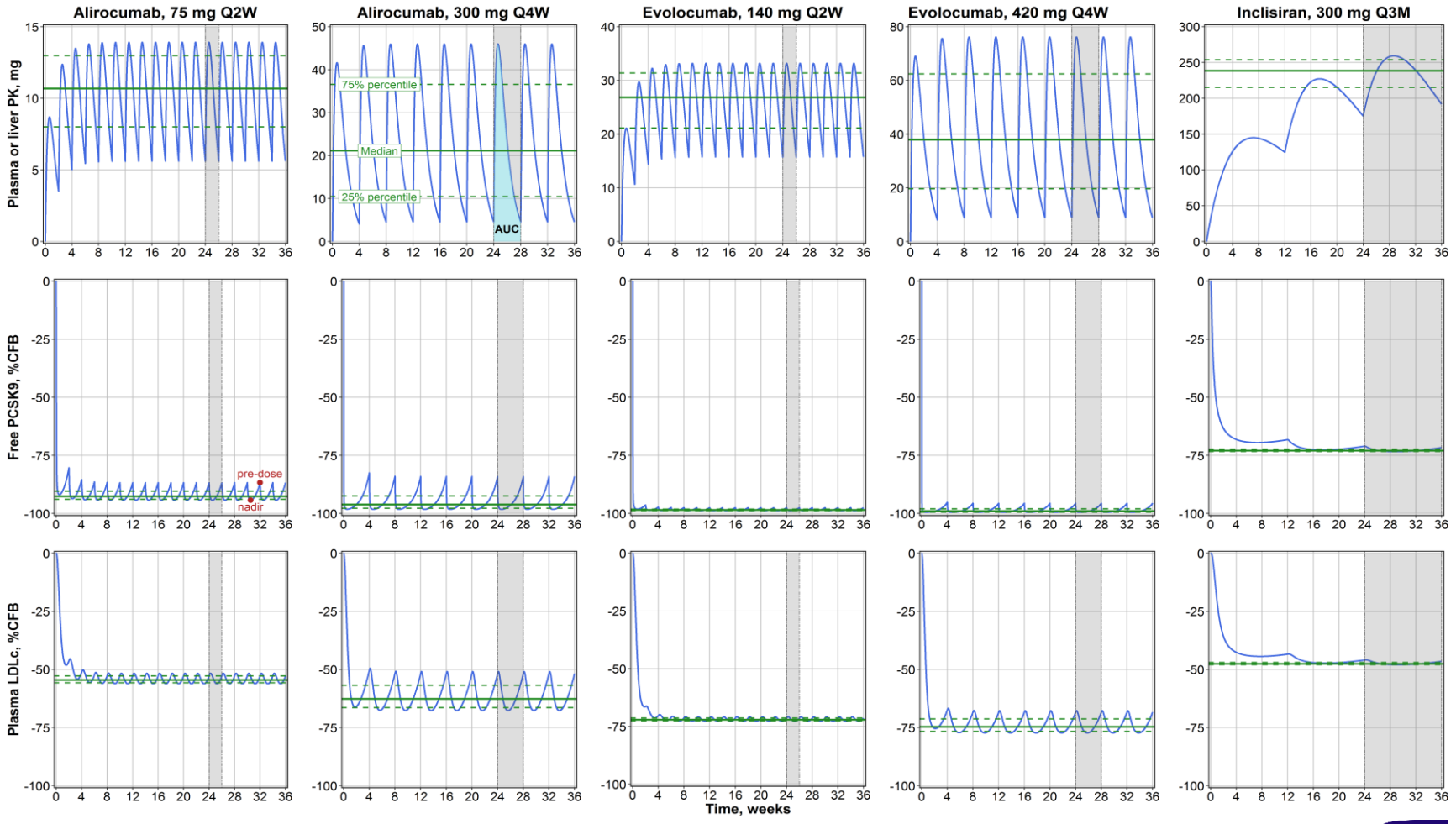
How to position new drug modality in the exhausted therapeutic space?

- Describes the **dynamic interplay** between low-density lipoprotein cholesterol (LDLc) and PCSK9
- Sets the stage for **quantitative benchmarking of two anti-PCSK9 drug modalities**: monoclonal antibodies (mAb) and synthesis inhibitors (siRNA)
- Includes multiple **non-LDLc biomarkers:** HDLc, TAG, ApoB, Lp(a), etc.



Model-based predictions illustrating the dynamic interplay among PK, key biomarkers, plasma PCSK9 and LDLc

- Plasma PCSK9 follows PK, while LDLc response follows with a delay
- Trough inhibition of plasma PCSK9 is approximately 25% more effective for mAbs vs. inclisiran
- The lack of time-dependent fluctuations in lipoprotein profiles under inclisiran treatment might bring a beneficial effect in terms of clinical endpoint efficacy

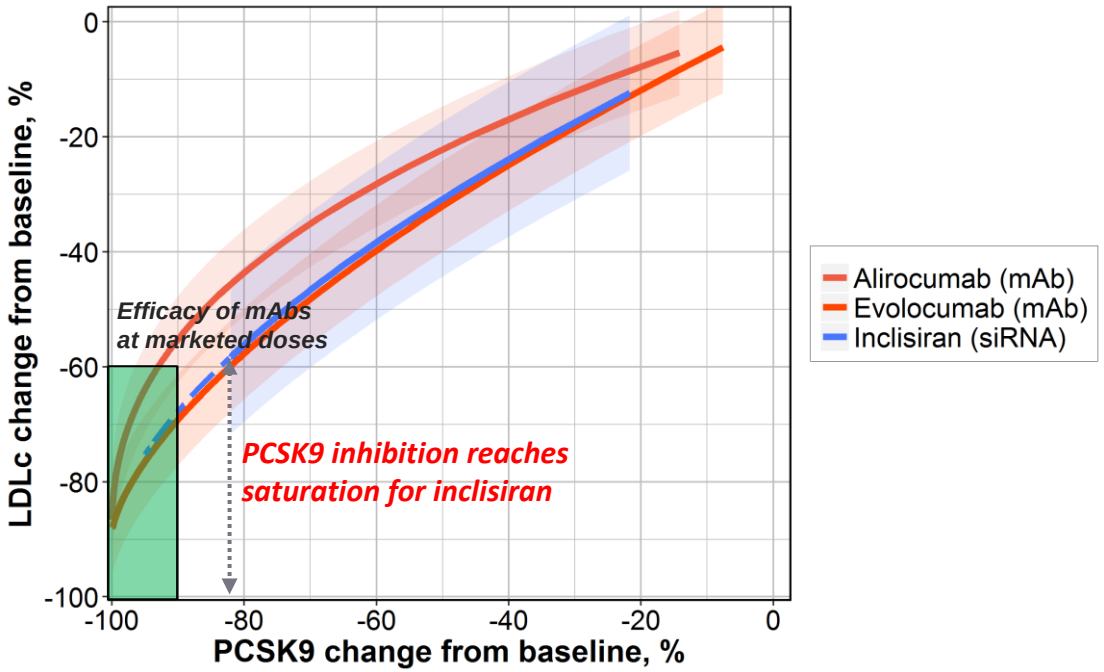


Benchmarking of mAbs and siRNA

- Inclisiran (siRNA) efficacy is limited by 80% PCSK9 reduction and is **inferior to mAbs**

- Anti-PCSK9 siRNA can compete with mAbs if **plasma PCSK9 will be decreased by ~95%**

Comparing efficacy: LDLc reduction in response to PCSK9 reduction



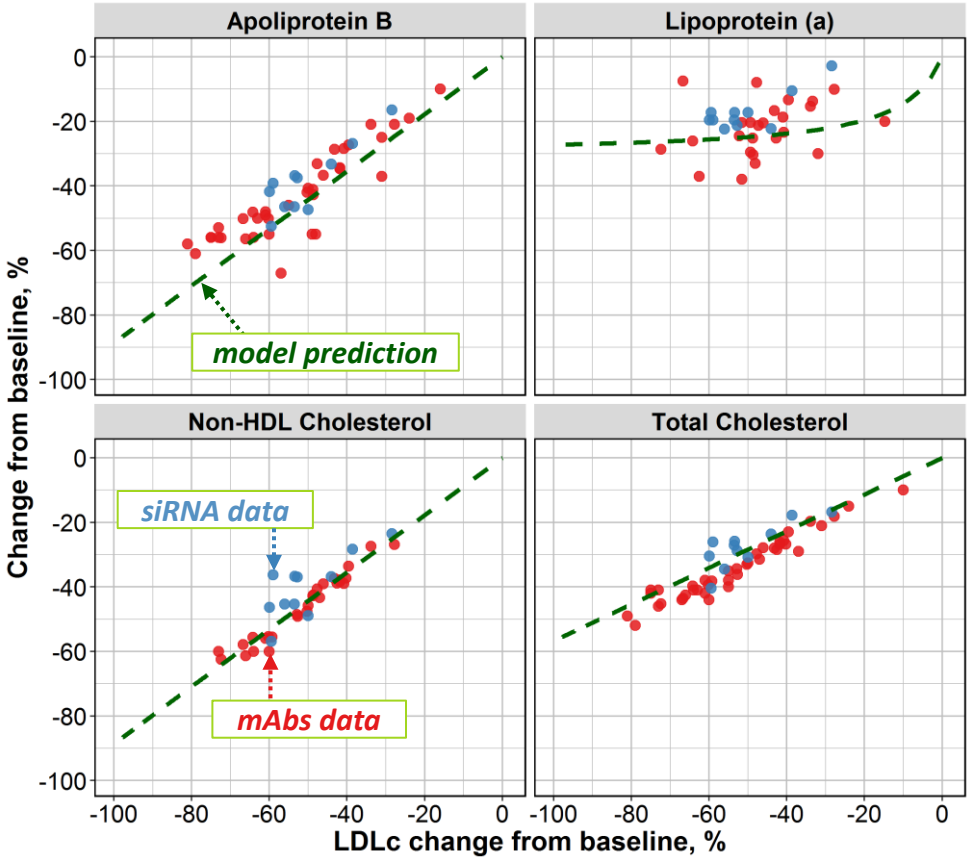
Shaded area: 95% CI

Deep dive into mechanisms

- The model describes the **dynamics of non-LDLc biomarkers**

- **No quantitative differences** were observed in behavior of non-LDLc lipid biomarkers for the different modalities considered

LDLc decrease *versus* decrease in other biomarkers



Conclusions

- At equal levels of plasma PCSK9 lowering, levels of LDLc reductions are comparable across drug modalities
- Anti-PCSK9 siRNA will be able to compete with mAb if plasma PCSK9 will be decreased by ~95%
- The lack of time-dependent fluctuations in lipoprotein profiles under inclisiran treatment might bring a beneficial effect in terms of clinical endpoint efficacy
- No quantitative differences were observed in behavior of non-LDLc lipid biomarkers under treatment with different modalities