Opemalirsen antisense oligonucleotide targeting the APOL1 mRNA provides dose-dependent APOL1 reduction in plasma

Magnus Åstrand[1], Peter J Greasley[2], Iain MacPhee[3], Anis Khan[4], Michael McCarthy[5]

Clinical Pharmacology and Quantitative Pharmacology, R&D, AstraZeneca, Gothenburg, Sweden[1]; Research and Early Development, Cardiovascular, Renal and Metabolism, Biopharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden[2]; Late-Stage Development, Cardiovascular, Renal and Metabolism (CVRM), Biopharmaceuticals R&D, AstraZeneca, Cambridge, UK[3]; Clinical Pharmacology and Quantitative Pharmacology, R&D, AstraZeneca, Gaithersburg, USA[4]; Projects, Research and Early Development, Cardiovascular, Renal and Metabolism, Biopharmaceuticals R&D, AstraZeneca, Gaithersburg, USA[5]

Introduction

- APOL1-mediated kidney disease (AMKD) is associated with toxic gain of function variants in people of African ancestry with the high-risk APOL1 genotypes (G1 and/or G2). APOL1 protein is part of the innate immune system but not considered essential.
- Opemalirsen (previously known as AZD2373) is an antisense oligonucleotide (ASO) targeting the APOL1 mRNA. It is currently being evaluated as a potential treatment for AMKD.
- The aim of this work was to characterize APOL1 protein lowering effect in plasma and to characterize the APOL1 protein dose response of opemalirsen using modeling and thereby guide dose selection for a dose ranging study in patients with AMKD

Methods

- Two randomized, placebo-controlled Phase 1 trials in healthy male volunteers were included in the assessment [1,2]. Summary of the studies are shown in Table 1.
- Plasma APOL1 protein levels were quantified based on samples taken at schedules shown in Table 1.

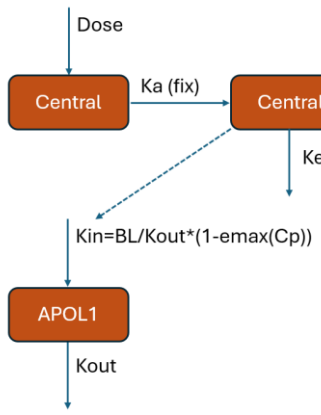
Table 1 Summary of clinical trials included in the analysis

Study	Drug dose and administration	Sampling design
NCT04269031 (SAD)	Placebo (n=8), 10mg (n=6), 30mg (n=5), 75mg (n=6) and 150mg (n=5) mg subcutaneous dose administration	12 plasma APOL1 samples per participant: Pre-dose, 2, 3, 7, 9 days, 2, 3, 4, 5, 6, 8 and 10 weeks post-dose.
NCT05351047 (MAD)	Placebo (n=6), 20mg (n=6), 50mg (n=6), and 150mg (n=6) once weekly subcutaneous dose administration for 6 weeks	13 plasma APOL1 samples per participant Pre-dose, 2, 4, 7 days, 2, 3, 4, 5, 6, 7, 9, 11, 13 weeks post-dose

- ASOs such as opemalirsen often show a rapid distribution phase and high maximum concentration in plasma while the site-of-action concentration in tissue often have longer terminal elimination half-life and much lower peak to trough ratio after repeated dosing [3].
- A kinetic-pharmacodynamic (KPD) model [4] was therefore chosen to describe the time and dose dependent APOL1 plasma protein reduction.
- The model comprised of a one-compartment kinetic component combined with a turnover model component with zero order input to describe the time course of APOL1 protein levels in plasma.

- The hypothetical drug concentration was used to drive the reduction of APOL1 protein via reduction of the input rate according to an inhibitory Emax model

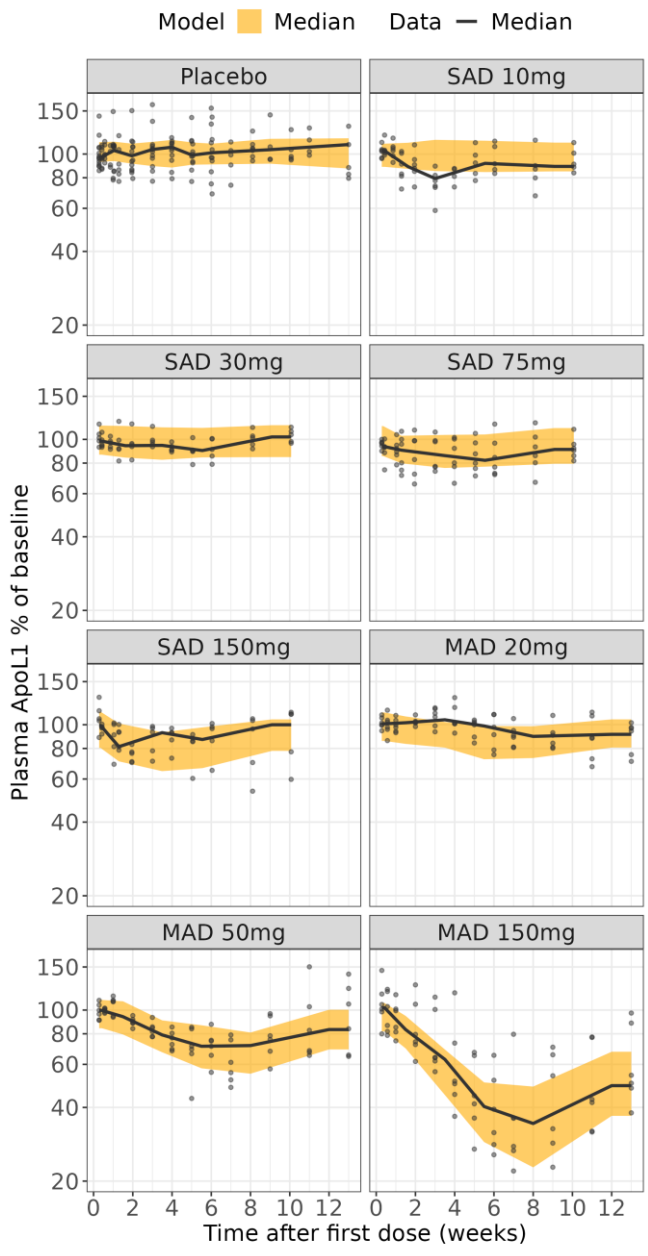
Figure 1. KPD model for Plasma APOL1 reduction



Results

- The KPD model adequately described the APOL1 protein levels over time and across doses based on diagnostic plots confirming the quality and robustness of the final model.

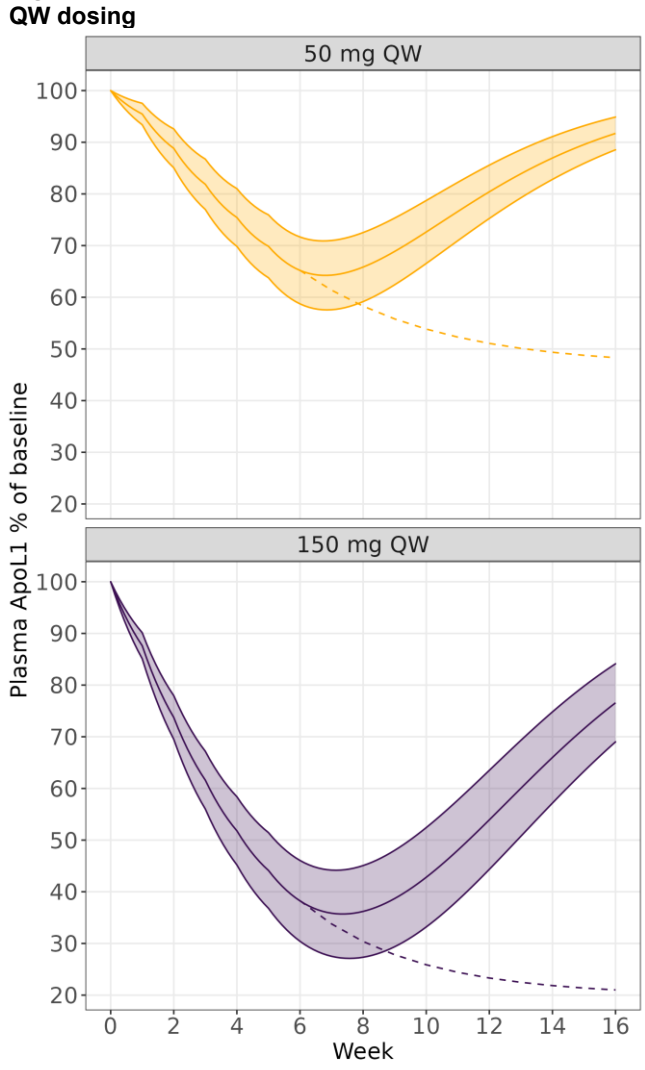
Figure 2. Visual predictive check for the APOL1 KPD model stratified by regimen and dose



Black dots are observed APOL1 and black line is median observed APOL1. Yellow region shows the model 90% confidence interval for the median APOL1

- The model identified a clear dose dependent APOL1 protein reduction after repeated dosing.
- Exposure from a single dose appeared too short to provide clear APOL1 reduction and hence the model is mostly informed by the 6 weeks QW data in the MAD study.
- Reductions of 36 and 64% are predicted for 50 and 150mg once weekly opemalirsen doses in the MAD study.
- The model predicts additional APOL1 reduction for longer treatment duration compared to the 6 weeks treatment in the MAD study.

Figure 3. Model predicted APOL1 protein reduction for QW dosing



Solid line with area indicating 90% CI is for 6 weeks QW dosing in the MAD study. Dashed line is the projected time course for 16 weeks or longer following QW dosing.

Conclusions

- A KPD model for APOL1 was built on SAD and MAD data.
- The model predicts dose-dependent plasma APOL1 reductions with 36 and 64% predicted for 6 weeks once weekly dosing of 50 and 150mg, respectively
- The modelling presented here provided key data for selection of doses for the ongoing Ph2b study.

References

1. NCT04269031
2. NCT05351047
3. Geary RS. Antisense oligonucleotide pharmacokinetics and pharmacodynamics in animals and man. British Journal of Clinical Pharmacology. 2009;68(4):427–447
4. Dayneka NL, Garg V, Jusko WJ. Comparison of four basic models of indirect pharmacodynamic responses. J Pharmacokinet Biopharm. 1993;21(4):457–478

Supported by AstraZeneca

Presented at the PAGE conference, June 2026