Opemalirsen antisense oligonucleotide targeting the APOL1 mRNA does not prolong the QTc interval

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Introduction

- All drugs with systemic bioavailability need assessment of the QT interval by ECG in clinical trials to rule out risk of QT prolongation and Torsade de Pointes [1]
- Oligonucleotide therapeutics have low risk of QT prolongation [2]; However, the Health Authorities highlight that the clinical experience remains limited, and it is currently insufficient to conclude the proarrhythmic risk of specific oligonucleotide classes [3].
- Opemalirsen (previously known as AZD2373) is an antisense oligonucleotide (ASO) targeting the APOL1 mRNA. The aim of this work was to assess the risk of QT-interval prolongation with opemalirsen using concentration-QTc (C-QTc) modelling, with the aim to contribute to the growing body of evidence that ASOs are unlikely to cause QT prolongation.

Methods

- Two randomized, placebo-controlled Phase 1 trials in healthy male volunteers were included in the assessment [4,5]. The studies were pooled to increase the sample size for the C-QTc modelling. Summary of the studies are shown in Table 1.
- Digital ECG (dECG) recordings were taken at scheduled timepoints preceding PK sampling, and time-matched opemalirsen concentrations were obtained across all arms

Table 1 Summary of clinical trials included in the analysis

Study	Drug dose and administration	Sampling design
NCT04269031 (SAD)	Placebo (n=9), 10 (n=6), 30 (n=5), 75 (n=6) and 150 (n=5) mg subcutaneous dose administration	11 time-matched PK and dECG samples per participant: Pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48h post-dose.
NCT05351047 (MAD)	Placebo (n=6), 20, 50, and 150 mg once weekly subcutaneous dose administration (n=6 per dose)	25 time-matched PK and dECG samples per participant: Day 1: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 h post-dose. Days 8, 15, 22, 29: pre-dose Day 36: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 and 48 h post-dose

- A prespecified linear mixed-effects model [6] was applied with ΔQTcF (change from baseline QTcF) as the dependent variable, time-matched opemalirsen concentration as the independent variable, and baseline QTcF, nominal time, and treatment arm as factors (Equation 1).
- Model adequacy was evaluated via goodness-of-fit plots.
- Heterogeneity was assessed (since data were pooled from multiple studies) by comparing model-derived standardized residuals between the two studies included in the analysis.

Results

Prespecified model assumptions were assessed and confirmed:

- No significant impact of opemalirsen on heart rate was observed (Figure 1)
- Fridericia correction method (QTcF) was deemed appropriate for the analysis
- No evidence of hysteresis was found in the data, supporting the assumption of a direct relationship between drug concentration and QTcF effect
- No indication of non-linearity was observed in the data, supporting the use of linear model

Equation 1 Prespecified linear mixed-effects model [6], adapted for the pooled analysis

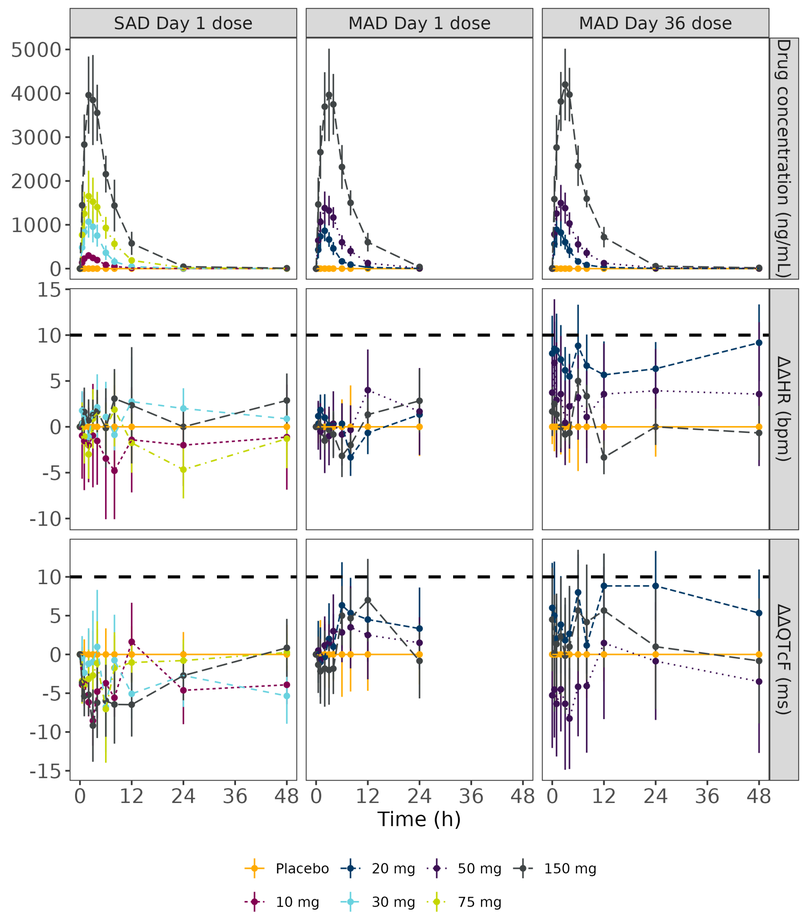
$$\Delta QTc_{ijkl} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + (\theta_2 + \eta_{2,i})C_{ijkl} + \theta_3 STUDYDAY_k + \theta_4 TIME_l + \theta_5 \left(QTc_{ijkl=0} - \overline{QTc_0}\right)$$

ΔQTcijk: change from baseline in QTc for participant i in treatment j at (nominal) at study day k (e.g. SAD , MAD day 1, MAD day 36) and time l; θ0: population mean intercept in the absence of a treatment effect; η0,i: random effect associated with the intercept term θ0; θ1: fixed effect associated with treatment j (0 = placebo,1 = active drug); θ2: population mean slope of the assumed linear association between concentration and ΔQTcijk; η2,i: random effect associated with the slope θ2; Cijk: concentration for participant i in treatment j at study day k and time l; θ3: fixed effect associated with study day; θ4: fixed effect associated with time; θ5: fixed effect associated with baseline QTci,j,kl=0; QTc_0: overall mean of QTcijk0

Prespecified model

Prespecified linear mixed effect model was successfully fitted to the data. A concentration-ΔQTcF relationship was estimated with a slope of -0.0009 ms/ng/mL (95% CI: -0.0019, 0.0000). The slope was not statistically significant.

Figure 1. Time-course of opemalirsen plasma concentration and baseline-adjusted and placebo corrected QTcF (ΔΔQTcF) for SAD and MAD studies.



Assessment of Heterogeneity

No clear differences were observed in the distribution of residuals with no indication of bias between SAD and MAD studies (Figure 2).

Figure 2 Diagnostic plots for the prespecified model
Distribution of standardized residuals in SAD and MAD studies

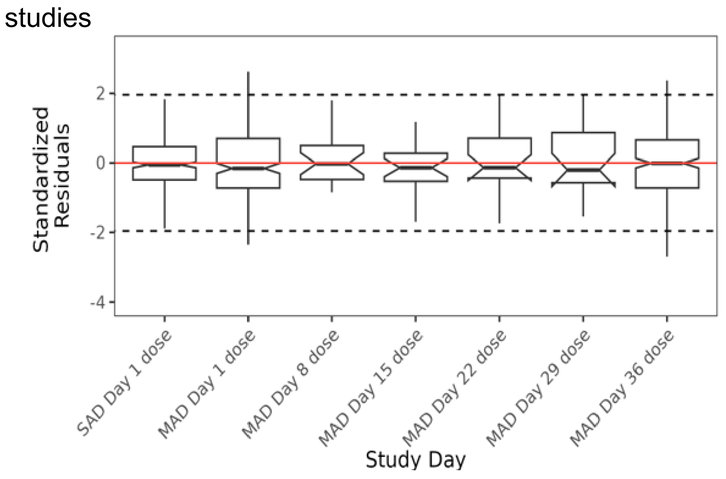
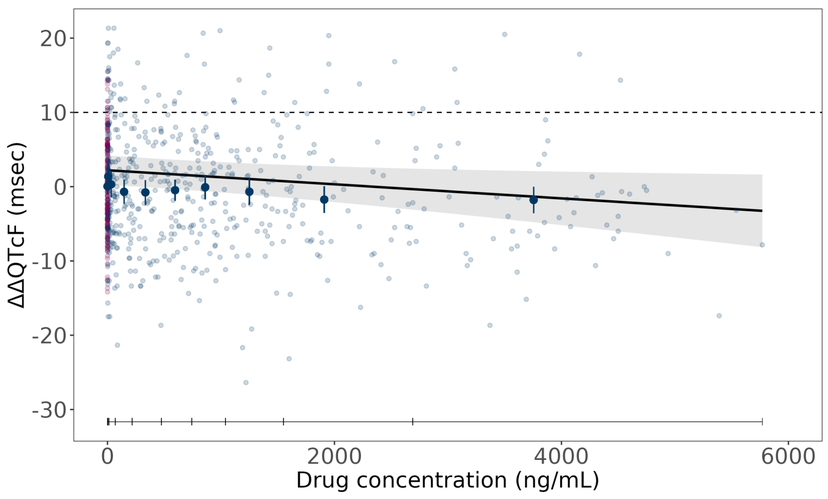


Figure 3. Model-derived ΔΔQTcF versus opemalirsen concentration (calculated for the entire observed concentration range).



Black line with shaded area denotes mean model estimates with 90% CI; If relevant, purple line represents the drug concentration for which the upper 90% CI around ΔΔQTcF crosses the threshold of 10 msec; ΔΔQTcF: baseline-adjusted and placebo-corrected QT.

Estimation of ΔΔQTcF at Clinically Relevant Concentrations

Model-estimated mean of ΔΔQTcF and 90% confidence interval at the geometric mean peak opemalirsen are presented in Table 2 and for the entire observed concentration range are illustrated in Figure 3. The model-derived upper 90% confidence interval CI around mean ΔΔQTcF was below 10 msec (threshold level of regulatory concern) for the entire concentration range.

Table 2. Model-derived ΔΔQTcF estimations at geometric mean peak opemalirsen concentrations.

Study	Dose, mg	Geomean Cmax, ng/mL	ΔΔQTcF (90% CI), ms
NCT04269031 (SAD)	10	291.20	1.94 (-0.02 to 3.9)
	30	1,043.99	1.23 (-0.82 to 3.27)
	75	1,623.50	0.68 (-1.56 to 2.91)
	150	4,095.08	-1.66 (-5.33 to 2.01)
NCT05351047 (MAD)	20	897.06	1.37 (-0.65 to 3.38)
	50	1,471.04	0.82 (-1.35 to 3)
	150	4,274.77	-1.83 (-5.63 to 1.96)

Conclusions

- No clinically relevant QTcF prolongation was observed within the studied exposure range of opemalirsen.
- ASOs are currently held to the same regulatory standards as small molecules for evaluating QT effects, despite their low proarrhythmic risk [3] and this assessment contributes to the growing body of evidence that ASOs are unlikely to cause QT prolongation.
- The modelling presented here provides a practical example on how to conduct C-QTc modelling assessment for pooled studies.

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