

Determination of antisense oligonucleotide tissue half-life

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Background

Antisense oligonucleotide (ASO) PK is largely sequence-independent and characterized by rapid (hours) distribution to tissue and slow (weeks) terminal half-life due to re-distribution from tissue [1]. Therefore, one expects accumulation of drug in tissue for standard dosing intervals (e.g. once monthly). The half-life determines tissue accumulation upon chronic dosing and is pivotal in the human dose-response prediction if target is situated in tissue and of general interest to interpret safety aspects. Monkey is a good animal model for human PK prediction using body-weight based allometric scaling [2].

Objective

To estimate the tissue half-life of an ASO accurately and precisely, by properly designing and analysing a cynomolgus monkey study.

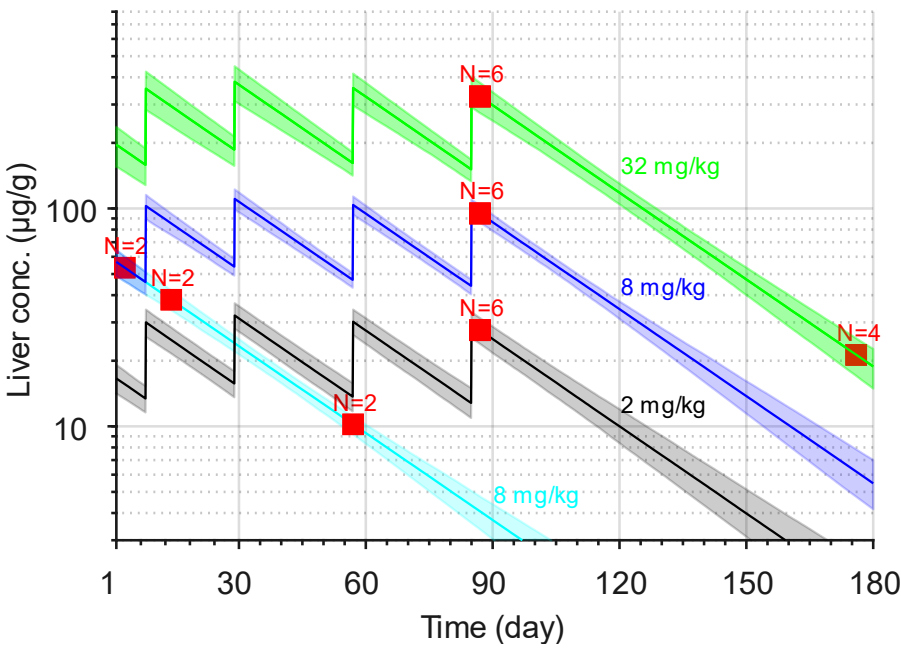
Methods

The liver PK of an ASO was to be measured in 28 cynomolgus monkeys using four monthly subcutaneous (SC) injections (2, 8 or 32 mg/kg) plus one extra loading dose after one week. To investigate toxicology aspects of the ASO, 6 monkeys per dose group (18 in total) were to be terminated two days after the last dose. We sought a suitable termination schedule for the remaining 10 monkeys to estimate tissue half-life from the complete data set of all 28 animals.

We used Yu et al.'s cynomolgus monkey population model describing plasma and liver PK of an ASO [3]. The model contains three compartments, representing plasma, liver and all other tissues.

We considered a space of 20 experimentally plausible designs, plus one rich design with >100 monkeys to serve as baseline. The search space is hence not exhaustive but represent designs that could realistically be achieved in practice. For each design we simulated 1000 studies (IIV on V_{plasma} with CV=19% [3], and additive noise on samples with CV=22% estimated from [3]).

A one-compartment model with dose-dependent volume of distribution was simultaneously fitted to data from all dose groups in each simulated study. The non-linearity represents saturated liver uptake at high doses, and a similar non-linearity was used by Yu et al. The absorption rate was fixed to 1 d⁻¹. The secondary parameter t_{half} and its precision and its bias with respect to the estimate of the rich design was calculated for each design.



The design that was selected for the monkey study

Red squares indicate sampling points. Solid lines and shaded areas represent the medians and the 5th-95th percentile intervals of the inferred models for each arm.

To investigate toxicology aspects of the ASO, 6 monkeys per dose group (18 in total) were to be terminated two days after the last dose (day 87). For the remaining 10 monkeys a satellite single dose group (8 mg/kg) was observed in time-series during days 3 to 57 (N=6), and another satellite group (32 mg/kg) was observed during washout 3 months after the last dose (N=4).

Conclusions

Modelling and reasoning were used to design a cynomolgus monkey study to determine the tissue half-life of an ASO with predicted bias <20% and good precision. From the resulting data, the tissue half-life could be inferred as 17.6 (15, 21; 5th and 95th percentiles) days.

Results

The two best proposed designs (bias 4-11%; 90% confidence of t_{half} within 14-17% of point estimate) included one satellite group (either 2 or 8 mg/kg) that was observed during washout 3 months after the last dose (N=4) and the remaining 6 animals assigned to the other two dose groups, three to each.

The two following best proposed designs (bias 10-29%; 90% confidence of t_{half} within 17-24% of point estimate) included a satellite single dose group (2 or 8 mg/kg) that was observed in time-series during days 3 to 57 (N=6), and another satellite group (32 mg/kg) was observed during washout 3 months after the last dose (N=4).

For robustness, it was decided to go for the latter designs to ensure that the half-life could be determined without a modelling approach in case the tested ASO would exhibit significantly different PK from the ASO considered in Yu et al.

Repeating the analysis with a linear PK model gave qualitatively similar results.

The design with a dose of 8 mg/kg, and not 2 mg/kg, of the first satellite group was selected to reduce the risk of obtaining data below the limit of quantification. From the resulting in vivo data, the liver exposure half-life was estimated to 17.6 (15, 21; 5th and 95th percentiles) days based on mathematical modelling taking all liver exposure data simultaneously into account.

Learnings

1. ASO toxicology studies in cynomolgus monkey can inform the human dose-response prediction.
2. The best designs sample the majority of animals at steady state, and a few animals in time-series.
3. Robustness of the tissue half-life estimate may increase by sampling a larger fraction of the animals in time-series, to avoid non-conclusive data in case accumulation turns out to be negligible.
4. The lowest dose is often of greatest interest from an efficacy point of view but carefully consider the risk of obtaining data below the limit of quantification.
5. If longitudinal target engagement biomarker data are available, consider dose-response-time modelling to infer the tissue half-life [4]. Naturally, robustness increases if several approaches are combined.

References

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