Introduction

One example of targeted therapy is the development of antisense oligonucleotides (ASOs) against a variety of mRNA coding for proteins involved in the pathogenesis of many diseases (e.g. diabetes, cancer...). Using ASOs to inhibit the expression of these proteins may stop or slow down the disease process. The knowledge gathered to date shows that the pharmacokinetic properties of second generation ASOs (of similar length) is well conserved across the platform and scale well across species (using body weight). Hence a modeling approach at the ASOs platform level will likely be very informative for the development of new ASOs.

Objectives

- To develop a Phase I clinical trial design for ASO B & C.
- To inform the first human dose clinical trials design for ASO B and C.
- To select the dosing regimen for phase II for ASOs B & C.
- To inform the first human dose clinical trials design for ASO B and C.
- To update the PK/PD model as the phase I clinical data (for ASO B and C) become available.

Purpose of the model

- To help elucidate key questions such as:
  - Drug response at the site of action (tissue level)
  - Tissue concentrations greater than the EC50 (leading to greater than 50% target inhibition) leads to in vivo efficacy in preclinical model for ASO B and ASO C.

- To select the dosing regimen for phase II for ASO B & C.

Data & Method

PK/PD

Modelling strategy

Second generation ASOs:

Clinical plasma – tissue integrated PK model

Assuming similar PK/PD relationship in mouse and human tissue

ASO B – ASO C

Prediction of target inhibition in human

Discussion - Conclusion