Modelling Pharmacokinetic and Pharmacodynamic Properties of Second generation Antisense-Oligonucleotides (ASOs)

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Introduction & objectives

Introduction

One example of targeted therapy is the development of antiseense oligonucleotides (ASO(s)) 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 plasma-tissue PK model using ASO A data to predict the clinical PK of ASOs B & C (prior Phase I clinical trials) .

•To develop of an integrated plasma-tissue PK/PD model for ASOs B and C to predict the mRNA (B and C) and protein (B and C) down regulation.

•To update the PK/PD model as the phase I clinical data (for ASO B and C) are available.

Purpose of the model

• I - To inform the first human dose clinical trials design for ASOs B and C.

• II - To help elucidate key questions such as :

- **Drug exposure at the site of action (tissue level)**
- **Drug response (protein inhibition) versus drug exposure in tissue**
- **Level of protein inhibition required for clinical efficacy**
  - 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.

• III - To select the dosing regimen for phase II for ASOs B & C.

Data & Method

PK
Plasma / Tissue

Model building data set – ASO A

ASO A preclinical PK data (213 plasma PK obs – 18 tissue PK obs)
N = 12 - Group 1 : X mg/kg 1h infusion q2d*4
N = 6 Group 2 : X mg/kg 1h infusion q2d*4 + q4d*21 (starting day 11)
ASO A clinical PK data (272 plasma PK obs)
N=9 (3 per dose levels)
Single dose over 1 h infusion
0.67*X mg.kg 1.33*X mg/kg 2*X mg/kg

Validation data set – ASO B & C

ASO B clinical PK data (206 plasma PK obs)
N = 15 : 5 dose levels (Y mg, 2*Y, 4*Y, 6*Y,7.5*Y)
Regimen 3 hours infusions day 1 day 2 day 3 then q1w starting day 8
ASO B and C preclinical PK data (103 plasma PK obs per ASOs)
N = 6 : 5*X mg/kg/day 72h infusion then 1.33*X mg/kg q2w 3h infusion

PK/PD
In tissue

ASO B and C
preclinical in vitro and in vivo mRNA and protein inhibition data and in vivo efficacy data

ASO B
estimated EC50 from in vitro preclinical experiment

ASO C mice PK/PD studies
Z mg/kg & 4*Z mg/kg SD
4*Z mg/kg (SD & MD q2d*3, *4,*5,*6)
2*Z mg/kg (SD & MD q2d*4)

simulation of clinical response : protein B and C inhibition following different dosing regimen
Assumption: same PD parameters in mouse and human

NONMEM version V was used for modelling and simulation
N = number of individuals

PK/PD modelling strategy

ASO A
Monkey plasma and tissue PK data
+ Clinical PK data

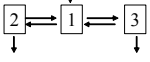
Allometric scaling based on body weight
CL=a*WGT^b
V=c*WGT^d
CL; clearance. V; Volume of distribution

"Second generation ASOs"
Clinical plasma – tissue integrated PK model
Validation with ASO B and ASO C clinical plasma PK data

Assuming similar PK/PD relationship in mouse and human tissue

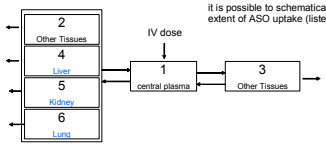
ASO B – ASO C
Prediction of target inhibition in human

PK Model 1 : empirical model



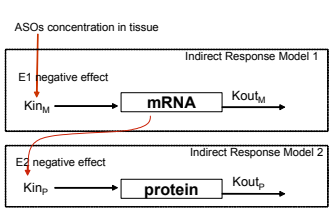
Allometric scaling based on body weight
CL=a*WGT^b
V=c*WGT^d
CL; clearances. V; Volumes of distribution

PK Model 2 : Semi-physiologic model



it is possible to schematically categorize tissues into five categories with respect to the extent of ASO uptake (listed from very high (a) to very low (e) uptake):
a - Kidney and liver (used as surrogate for high uptake tissue PK)
b - Spleen
c - Testes, ovaries, pancreas, skin, lymph nodes, bone marrow, prostate
d - Lung (used as surrogate for low uptake tissue PK), colon heart, jejunum
e - Muscle, brain

PK/PD Model



$$\frac{dmRNA}{dt} = KINM * E1 - KOUM * [mRNA]$$

$$\frac{dPROT}{dt} = KINP * E2 - KOUP * [PROT]$$

E1 = effect ASO concentration
E1 = 1-(1*ASO$^{\beta}$)/(ASO$^{\beta}$+ASO$_{50}^{\beta}$)
E2 = effect mRNA on protein
E2 = 1-(1*(1-mRNA)$^{\beta}$/((1-mRNA)$^{\beta}$+mRNA$_{50}^{\beta}$)

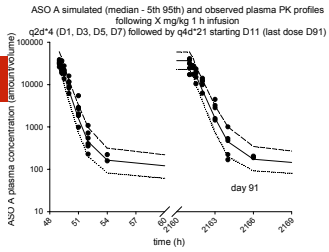
- KINM=KOUM & KINP=KOUP
- Absence of drug E1 = E2 = 1
- ASO$_{50}$=ASO tissue concentration leading to 50 % decrease in mRNA expression
-mRNA$_{50}$ = % decrease in mRNA % expression from baseline leading to 50 % decrease in protein expression

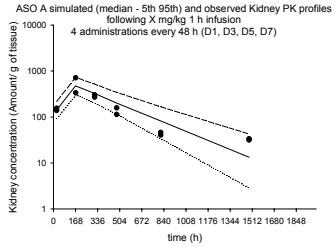
Results

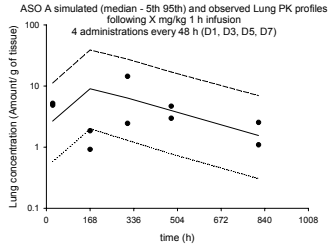
Parameter Description	Model 1 ASO A - Allometric scaling Monkey – Human Data Used : Plasma PK Data: Population mean (%SEE)		Model 1 ASO A - Allometric scaling Monkey – Human Data Used : Plasma PK Data: IIV (%) (%SEE)		Model 2 ASO A - integrated preclinical plasma- Tissue PK model: Population mean Estimate (%SEE)		Model 2 ASO A - integrated preclinical plasma- Tissue PK model: IIV Estimate (%) (%SEE)	
CL (L/h/kg)	1.90	(10.6)	45.5	(45.2)	na			
CL other tissue (L/h/kg)	na				0.24	Calculated = Kel*(V2+V3)		
CL liver (g/h/kg)	na				0.031	Calculated = Kel*(V liver)		
CL Kidney (g/h/kg)	na				0.013	Calculated = Kel*(V Kidney)		
CL lung (g/h/kg)	na				0.68	Calculated = Kel*(V lung)		
V Liver (g/kg)	na				11.2	(17.7)		
V Kidney (g/kg)	na				4.81	(11.7)		
V lung (g/kg)	na				249	(28.8)		
V1 (L/kg)	0.0422	(13.1)			0.0403	(3.37)		
Q2 (L/h/kg)	0.0772	(5.85)			0.0151	(3.05)	11.3	(36.5)
V2 (L/kg)	451	(8.47)			85.3	Calculated = Q2/K21		
Q3 (L/h/kg)	0.00217	(10.4)			0.00477	(22.6)	19.3	(126)
V3 (L/kg)	0.00942	(15.9)			1.04	Calculated = Q3/K31		
Scaling Coefficient on clearance terms	0.922	(2.23)			na			
Scaling Coefficient on Volume terms	1.19	(3.36)			na			
K12 (1/h)	1.83	Calculated Q2/V1			0.375	Calculated = Q2/V1		
K21 (1/h)	0.000171	Calculated Q2/V2			0.000177	fixed		
K13 (1/h)	0.0514	Calculated Q3/V1			0.118	Calculated = Q3/V1		
K31 (1/h)	0.23	Calculated Q3/V3			0.0458	(26.6)		
K elimination (1/h)	0.004213	Calculated CL/(V2+V3)			0.00273	(13.0)	20.0	(45.6)
Residual Error plasma % (SEE %)		37.9 % (11.5)				28.5 % (19.1)		
Residual Error liver % (SEE %)						40.1 % (37.8)		
Residual Error Kidney % (SEE %)						25.5 % (63.6)		
Residual Error lung % (SEE %)						90.2 % (39.7)		

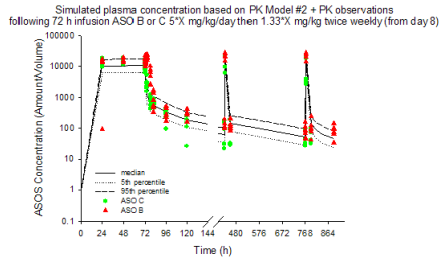
SEE = Standard ERROR on the Estimates (%); IIV = inter-individual variability (%); na = non applicable

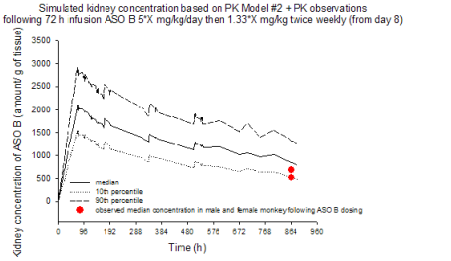
Posterior Predictive check and ASO B and C simulated PK profile using model 2 scaled to human







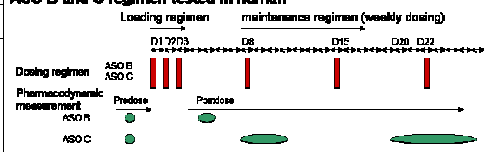


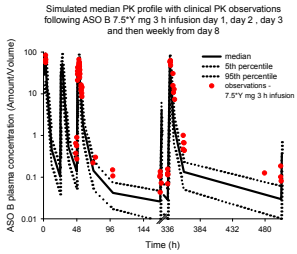


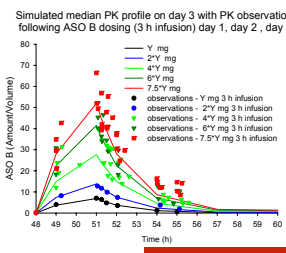
Pharmacodymamic Parameters

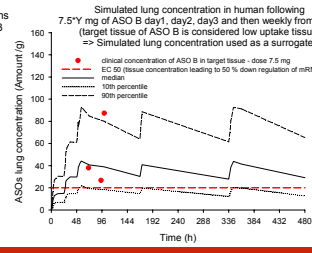
ASO B Preclinical observations	Assumed PK/PD parameters for ASO B	ASO C PK/PD preclinical model : PD parameters
ASO B Cmax ss in low uptake tissues are in the range of 10 to 20 µg/g following efficacious dosing regimen in preclinical efficacy model.	EC50, the tissue concentration leading to 50% down regulation of mRNA B is assumed to be 20 µg/g.	EC50 = 101 µg/g (SEE 7.63 %)
EC50 predicted range: 2 to 21.6 µg/g (in vitro target inhibition data + protein binding data).	50% target inhibition is required for efficacy.	mRNA C half-life 6.5 h (SEE 7.63 %)
Following single dose of ASO B, peak tissue concentration and maximum effect occurs at approximately the same time (24 h).	Protein B and mRNA B half lives are short and assumed to be 30 min and 2 h, respectively.	Protein C half-life 4.1 days (SEE 16.1 %)

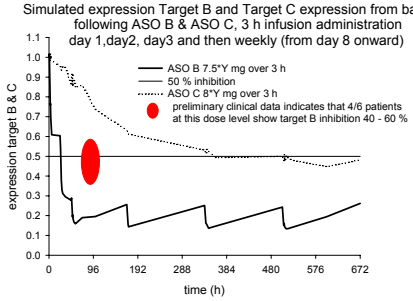
ASO B and C regimen tested in human











Discussion - Conclusion

• The PK model built using ASO A data was adequately predictive of ASO B and C preclinical PK data and ASO B clinical data

• Using preclinical data on ASO B & C, PD parameters were derived to develop a PK/PD model in tissue for ASO B and C. This model allowed to simulate the protein (B and C) inhibition

• Next step - To update the PK/PD model as the phase I clinical data (for ASO B and C) become available.

• I - The PK model supports that the loading and maintenance dosing paradigm (qd*3 then weekly from day 8) implemented in first human dose clinical trials for ASOs B and C adequately delivers and maintains constant ASOs tissues concentrations.

• II – **The model helps elucidate key questions :**

- The PK model allows to simulate ASOs concentration at the site of action (either low or high uptake target tissue).
- The PK/PD model allows to simulate response (target inhibition).

• III - **The model support selection of the dosing regimen for phase II for ASO B and C:**

- The model predicts an efficacious dose range (7.5*Y mg or greater) for ASO B. Preliminary clinical data showed evidence of target down inhibition at this dose range. The model appears to over-estimate the response based on the preliminary data available
- The model predicts an efficacious dose range for ASO C (8*Y mg or greater). Clinical data are not yet available.

Lilly Answers That Matter