PKPD MODELLING OF EYP001A, A NOVEL FXR AGONIST IN HEALTHY VOLUNTEERS AND HEPATITIS B PATIENTS

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INTRODUCTION

EYP001a is an non bile salt, carboxylic acid agonist of the nuclear farnesoid X receptor (FXR) which binds bile acids. FXR agonists, originally discovered for a therapy of non-alcoholic steato-hepatitis, primary biliary cholangitis and metabolic syndrome, were found to have anti-viral activity on Hepatitis B virus (HBV) [1]

The objective of this analysis was to develop a population PK-PD model using FGF19 data (intestinal protein involved in bile acid synthesis) to assess the influence of EYP001 on FXR pathway in both healthy volunteers and HBV infected patients

PATIENTS AND METHODS

Data/study description (Table 1)

Data from 3 phase 1 studies conducted in healthy volunteers and HBV-infected patients were included in this analysis (including single and repeated doses)

Methods, model development

A covariate analysis, using a stepwise approach, was performed to assess the impact of food effect, age, sex, weight-derived covariates and also to investigate the potential differences between healthy volunteers and HBV infected patients

Limits of quantification

The limit of quanitifcation for EYP001 concentrations was set to 10ng.mL^{-1} but data between 1 and 10ng.mL^{-1} were available (1ng.mL^{-1} being considered as the limit of detection)

All data for FGF19 concentrations were above the limit of quantification (24.7 pg.mL^{-1})

Simulations

Simulations of the PKPD model were performed in order to investigate FGF19 behavior.

Model development, model diagnostics and model simulations were performed using NONMEM 7.3 and PsN 4.6.0

Table 1: Studies' characteristics

	Study C01	Study 102	Study 104
Population	European Healthy Volunteers	European HBV patients	Australian Healthy Volunteers
Number of individuals	71	11	8 (preliminary results)
Type of study	Single and multiple dose	4-arm cross-over	Drug drug interaction
Dose	From 30 to 800mg + placebo	300mg	300mg + placebo

RESULTS

Model development description

PK model

Plasma PK of EYP001 was best described with:

- 2-compartment disposition model
- 5 transit compartments for the absorption phase

Covariate analysis revealed:

- relative bioavailability appeared to decrease after repeated administrations and to decrease as dose increases
- lower clearance in HBV patients (~25%)
- administration under fed condition decreases k_{tr} by a 2-fold factor
- administration in the evening decreases k_{tr}

PD model

FGF19 time-course was modelled using:

- a turn-over model
- a K-PD approach [2] was used to describe the increase of FGF19 production induced by meal intake
- an effect compartment and a sigmoidal function stimulating FGF19 production for EYP001 drug effect

Schematic of the models and parameter estimates are provided in **Figure 1** and in **Table 2**, respectively

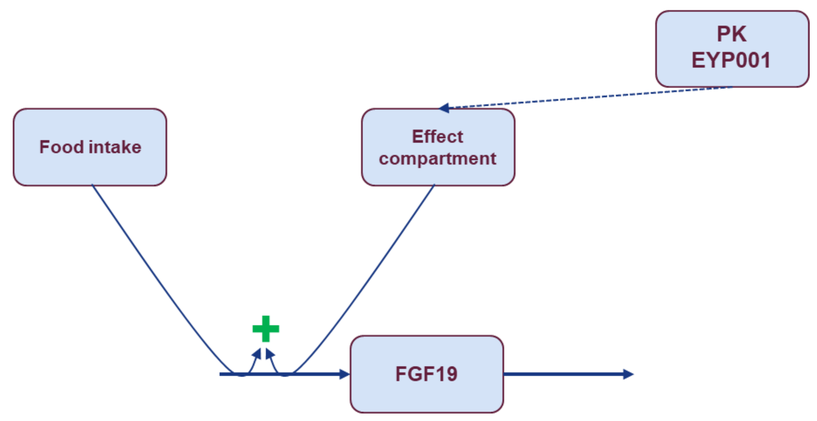

Figure 1: Schematic of the PKPD model linking EYP001 PK to FGF19 concentrations

Table 2: Estimated parameters for the PKPD model

Parameter	Unit	Estimate (RSE%)	IIV in CV % (RSE%)	Parameter	Unit	Estimate (RSE%)	IIV in CV % (RSE%)
PK part				**FGF19 part**			
F1	-	1 fix	19.7 (27.6)	Base	pg.mL^{-1}	125 (3.9)	28.9 (21.4)
Ktr	h^{-1}	3.73 (4.0)	33.2 (16.9)	Kout	h^{-1}	0.696 (18.9)	-
CL	L.h^{-1}	46.4 (3.1)	10.8 (27.5)	SLP meal	h^{-1}	2.77 (38.2)	-
Vc	L	114 (3.5)	-	Kmeal	h^{-1}	0.811 (36.1)	-
Q	L.h^{-1}	2.79 (5.2)	-	Keo	h^{-1}	0.822 (23.0)	-
Vp	L	46.6 (5.2)	-	Emax		3.51 (12.9)	-
BoxCox on Ktr	-	-0.538 (56.7)	-	EC_{50}	ng.mL^{-1}	450 (17.6)	54.3 (35.5)
F1 for 800mg	-	-0.28 (31.4)	-	Gam	-	2.19 (22.9)	-
Base F1 after MD (300mg)	-	0.497 (3.4)	-	F for dinner snack	-	0.10 (132.3)	-
F1 MD (dose effect)*	-	-0.23 (14.9)	-	Base Stud 104	-	-0.23 (36.4)	-
Evening on Ktr	-	-0.25 (10.1)	-	Add Res Err	%	47.7 (2.4)	-
Food on Ktr	-	+0.55 (3.3)	-				
Population on CL	-	+0.23 18.0)	-				
Add Res Err	%	43.6 (5.4)	44.3 (19.0)				
Add Res Err	%	53.3 (5.6)					

IIV: Inter-individual variability; CV: coefficient of variation;
RSE: Relative Standard Error
RSE computed from Sampling Importance Resampling process [3]
*power model

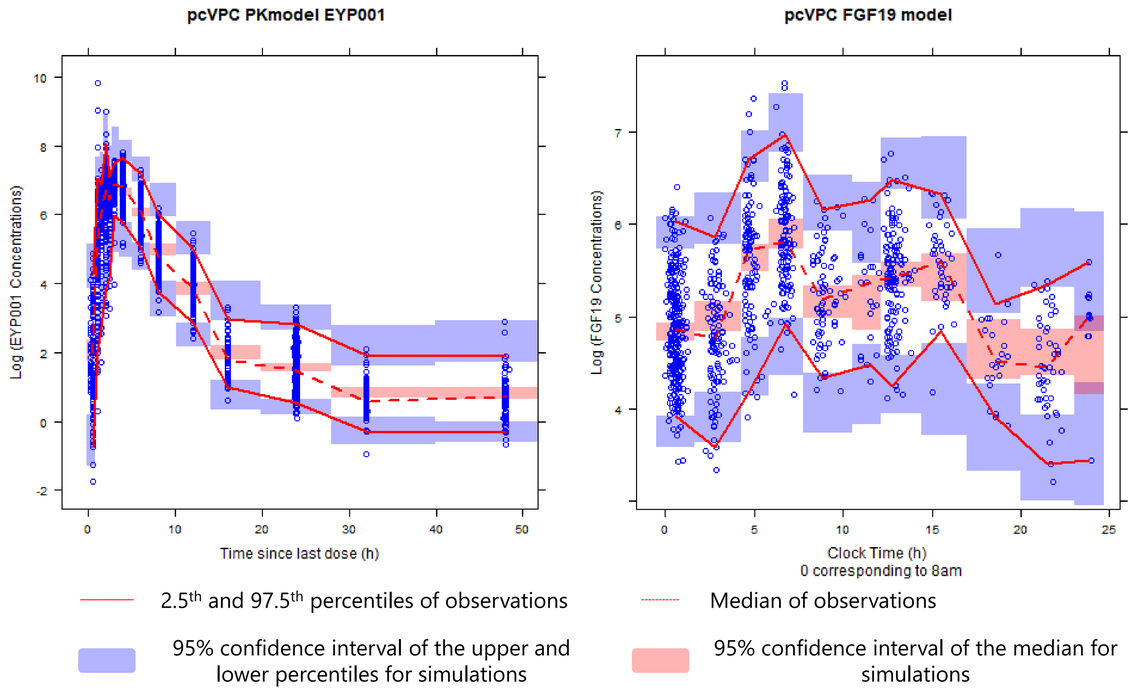

Figure 2: pcVPCs for the PK (left) and the FGF19 (right) models

Simulations of FGF19 model after administration of EYP001

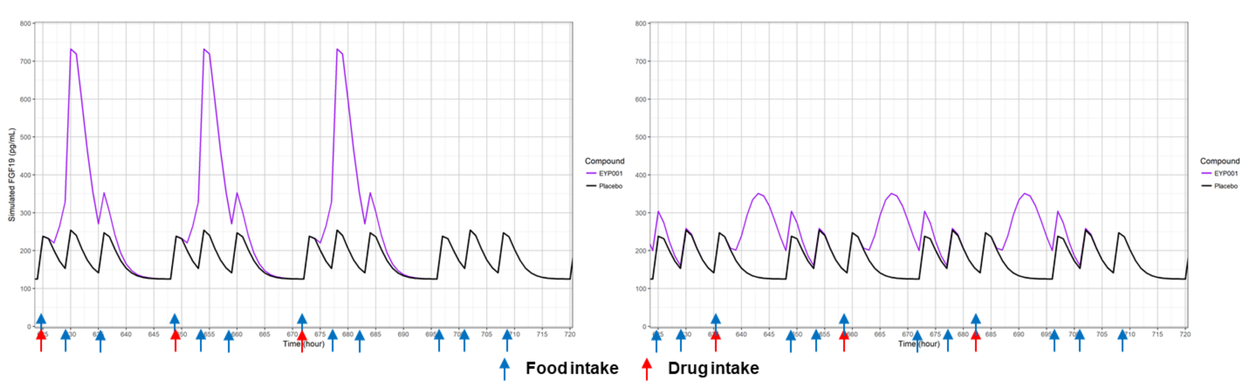

Figure 3: Simulations of the PK-FGF19 model in HV after 4 weeks of administration Administration of 400mg QD in the morning (left) or in the evening (right)

CONCLUSION

EYP001 and FGF19 concentrations were adequately described by the proposed approach and confirm the impact of EYP001a on FXR pathway. The model will be expanded to other biomarkers, such as C4 concentrations

References:

[1] Radreau, P et al, FASEB J. 30, 2016 Sep;30(9):3146-54.
[2] Jacqmin, P et al, JPKPD. 2007; 34(1):57-85
[3] Dosne, AG et al, JPKPD. 2016; 43(6):583-596