Population Pharmacokinetic Analysis of Compound A and Its Metabolite in Healthy Subjects and Patients with Diabetic Nephropathy

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Introduction

Compound A is a potent and highly selective non-steroidal mineralocorticoid receptor (MR) antagonist being developed for the treatment of diabetic nephropathy and other potential indications. Richly sampled PK data collected in phase 1 studies exhibited complex PK profiles for Compound A (secondary and tertiary peaks as well as prolonged absorption profiles following initial peak concentrations in conjunction with dose-dependent reductions in exposure with increasing doses) and its major metabolite (Metabolite B; slow formation and elimination).

Objectives

The objectives of the analyses were to develop population pharmacokinetic models that describe these characteristics of Compound A and Metabolite B.

Methods

The population PK (popPK) analyses included data pooled from 4 densely-sampled and 2 sparsely-sampled phase 1 studies conducted in healthy subjects and 3 sparsely-sampled phase 2a studies conducted in patients with type 2 diabetic nephropathy. The doses of Compound A tested in these studies ranged from 2.5 mg to 640 mg. A summary of subject demographic characteristics included in the popPK analysis are shown in Table 1.

Table 1. Summary of Subject Demographic Characteristics

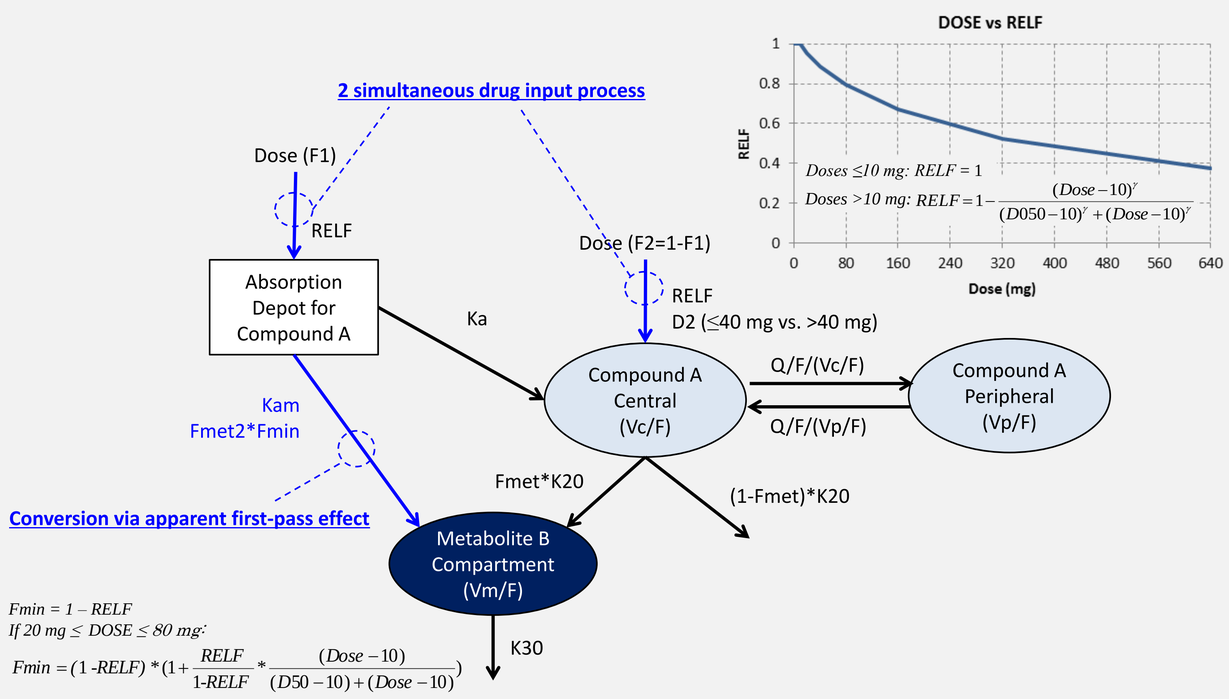
Characteristics	Median (range) or n (%)	Characteristics	Median (range) or n (%)
Age (y)	40.0 (19-80)	TBIL (mg/dL)	0.6 (0.2-1.9)
Weight (kg)	78.80 (50.6-144.0)	Albumin (g/dL)	4.600 (3.50-5.38)
BMI (kg/m^2)	25.50 (18.6-44.8)	AST (U/L)	21.0 (10-93)
GGT (U/L)	20.0 (8-543)	ALT (U/L)	21.0 (5-105)
ALP (U/L)	67.0 (20-402)	eGFR (mL/min/1.73m^2)	88.43 (27.4-185.0)
RACE		SEX	
White	275 (79.3)	Male	310 (89.3)
Japanese	57 (16.4)	Female	37 (10.7)
African American	15 (4.3)		

BMI: Body mass index, GGT: Gamma glutamyl transpeptidase, ALP: Alkaline phosphate, TBIL: Total bilirubin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, eGFR: Estimated glomerular filtration rate

Plasma concentrations of Compound A and Metabolite B were sequentially fit by popPK models using nonlinear mixed effects modeling implemented in NONMEM 7.1.2. Various compartmental models with dose-dependent relative bioavailability (RELF) and more complex absorption processes were evaluated to best capture the dose dependencies and the combination of rapid and prolonged absorption for Compound A. A covariate analysis was also performed. Models were qualified through prediction-corrected Visual Predictive Checks (VPC) with 1000 replicates of the analysis dataset.

Results

Figure 1. PopPK Model Scheme of Compound A and Metabolite B



F1, fraction of dose absorbed via Ka; Ka, first-order absorption rate constant; D2, duration of zero-order absorption; RELF, relative bioavailability; Vc/F, apparent central volume of distribution for Compound A; Vp/F, apparent peripheral volume of distribution for Compound A; Q/F, apparent inter compartmental clearance; Kam, first-order absorption rate constant for Metabolite B; K20, first-order elimination rate constant; Fmet, fraction of Compound A transformed to Metabolite B; Fmet2, fraction of Compound A converted to Metabolite B during absorption; Fmin, fraction of Compound A lost to apparent first-pass effect; Vm/F, apparent volume of distribution of Metabolite B; K30, first-order elimination rate constant for Metabolite B; D050, dose at which 50% of maximum relative bioavailability occurs; γ: gamma term for Hill function for RELF, D50, dose at which 50% of Fmin occurs for doses from 20 mg to 80 mg

Compound A concentration-time profiles were best described by a 2-compartment model with 2 parallel absorption inputs (a first-order process to describe initial peaks and a zero-order process to describe prolonged absorption), dose-dependent relative bioavailability (described by a sigmoid Hill function), and first-order elimination. Several covariates influencing the PK of Compound A were identified, but there was no substantial evidence to indicate that any covariate effect would independently contribute to a clinically significant alteration in Compound A exposure (Figure 3).

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Table 2. Parameter Estimates for Compound A

	Final Parameter Estimate		IIV/RV	
Parameter	Typical Value	RSE (%)	Magnitude	RSE (%)
Ka (1/h)	0.552	8.51	69.8 %CV	18.8
CL/F (L/h)	0.207	3.07	25.8 %CV	7.53
Vc/F (L)	67.7	3.45	24.0 %CV	5.50
Vp/F (L)	11.7	5.83	-	-
Q/F (L/h)	0.0825	10.5	-	-
D2 (dose≤40mg) (h)	3.22	3.54	-	-
D2 (dose>40mg) (h)	33.7	4.65	-	-
D050 (mg)	355	10.7	28.3 %CV	49.0
F1	0.665	2.88	-	-
GAMMA	0.848	7.59	-	-
FED on RELF for dose ≥ 80 mg	0.200	11.2	-	-
Non-tablet shift on RELF	-0.206	9.36	-	-
BMI on Vc/F [exp]	0.0658	5.58	-	-
Formulation (tablet) on Ka [add]	2.49	32.5	-	-
Food effect on Ka [prop]	-0.567	6.82	-	-
Weight on CL/F [exp]	0.00737	15.8	-	-
Age on Vc/F [exp]	0.00661	19.7	-	-
Albumin on CL/F [pow]	-0.928	22.0	-	-
RV for full profile (Phase 1)	0.156	0.823	0.395 SD	-
RV for sparse profile (Phase 1)	0.00549	2.06	0.0741 SD	-
RV for Phase 2a	0.0253	2.70	0.159 SD	-

IIV, inter-individual variability; RSE (%), standard error of the mean expressed as a percentage; RV, residual variability; SD, standard deviation; %CV, coefficient of variation expressed as a percentage; CL/F, apparent clearance

Figure 2. Prediction-corrected VPC for Compound A Concentration

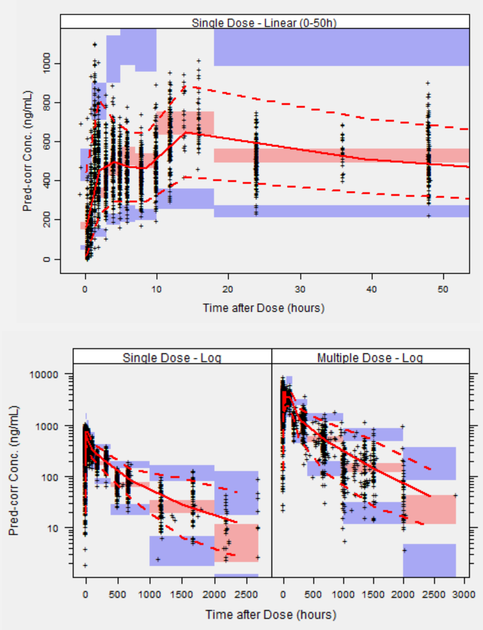
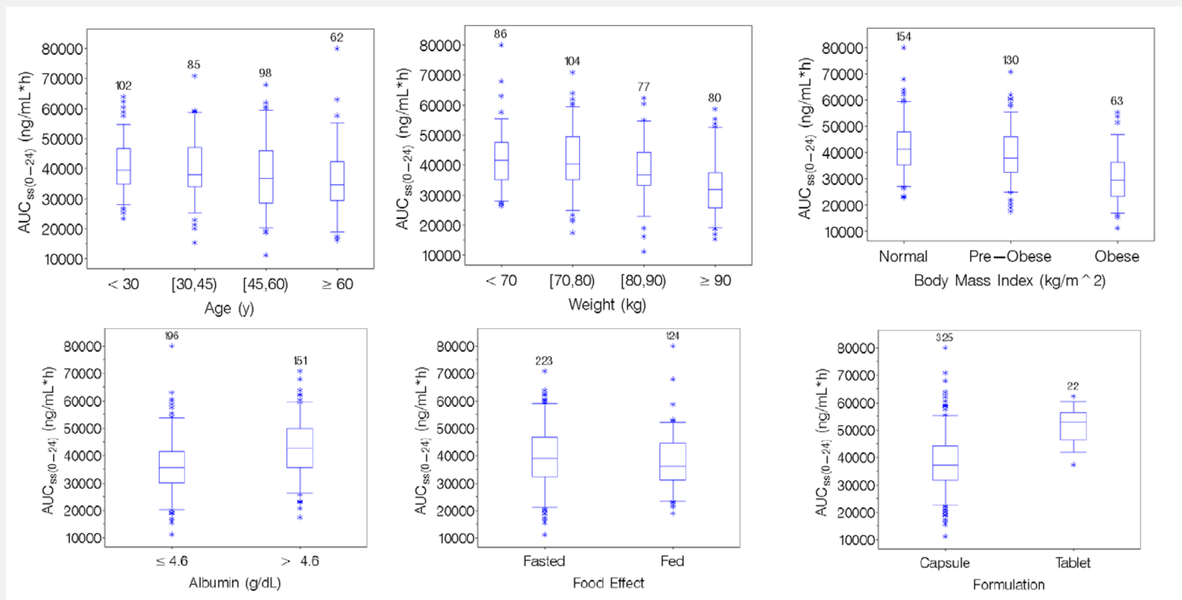


Figure 3. Effect of Covariates on Model-Predicted $AUC_{ss(0-24)}$ for Compound A



Hypothetical 10 mg Compound A Daily Dosing
$AUC_{ss(0-24)}$, area under the concentration-time curve from time 0 to 24 hours at steady-state; Normal BMI: 18.5 to 24.99 kg/m^2, Pre-Obese BMI: 25 to 29.99 kg/m^2, Obese BMI: > 30 kg/m^2; The number of subjects is above each box.

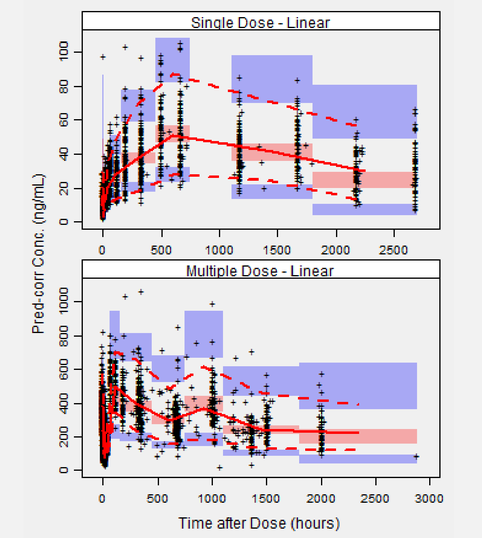
Metabolite B concentration-time profiles were best described by a 1-compartment model with linear elimination. The formation of metabolite was characterized by 2 input processes, with 1 formation pathway described as a fraction of the systemic elimination of Compound A, and the second formation pathway described as a proportion of Compound A converted via apparent first-pass effect. Model-predicted steady-state exposures indicate that the overall impact of the statistically significant covariates on Metabolite B PK are not expected to be clinically meaningful given the considerable overlap in metabolite exposures across the range of covariate values in the study population (data not shown).

Table 3. Parameter Estimates for Metabolite B

	Final Parameter Estimate		IIV/RV	
Parameter	Typical Value	RSE (%)	Magnitude	RSE (%)
Vm/F (L)	67.7	FIXED	-	-
CLm/F (L/h)	0.0510	4.18	36.3 %CV	13.4
CLm/F for 2 Phase 2a (L/hr)	0.0413	9.27	36.3 %CV	13.4
FMET	0.0947	3.48	0.400 SD	9.67
FMET for 2 Phase 2a	0.0621	7.72	0.400 SD	9.67
FMET2	0.09	FIXED	-	-
Kam (1/hr)	0.0197	7.50	64.3 %CV	16.3
$D50_{(20-80)}$ (mg)	12.2	21.4	-	-
BMI on Fmet [pow]	-1.90	10.6	-	-
Age on Fmet [exp]	-0.0109	17.5	-	-
BMI on CLm [exp]	-0.0523	18.3	-	-
eGFR on CLm [pow]	0.468	23.5	-	-
GGT on Fmet [pow]	-0.210	20.9	-	-
Food effect on Fmet [prop]	-0.153	13.9	-	-
ALT on Kam [exp]	-0.0258	28.4	-	-
Japanese race on CLm/F [prop]	-0.213	32.7	-	-
RV for Phase 1 studies	0.0216	1.27	0.147 SD	-
RV for Phase 2a studies	0.0258	1.93	0.161 SD	-

CLm/F, apparent metabolite clearance; $D50_{(20-80)}$, dose at which 50% of Fmin occurs for doses from 20 mg to 80 mg

Figure 4. Prediction-corrected VPC for Metabolite B Concentration



Conclusion

The atypical PK profiles observed in these data were adequately described by modeling the absorption of Compound A via parallel input processes as well as modeling the formation of Metabolite B as a function of both first-pass and systemic parent drug elimination.