Characterizing exposure of apalutamide and its active metabolite, N-desmethyl-apalutamide, in healthy and castration-resistant prostate cancer subjects

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INTRODUCTION

Apalutamide (APA) is a next-generation androgen receptor (AR) inhibitor that binds directly to the ligand-binding domain of the AR and prevents AR nuclear translocation and inhibits DNA binding and AR-mediated transcription.[1] APA (Erleada™), is approved in the USA and EU for the treatment of non-metastatic castration-resistant prostate cancer (NM-CRPC) at the recommended dose of 240 mg once daily, based on the pivotal Phase 3 clinical study SPARTAN.[2]

N-desmethyl-apalutamide (N-APA), the main metabolite of APA, is pharmacologically active with one-third of the pharmacological activity observed for APA. APA and N-APA are predominantly eliminated by metabolic clearance, with the formation of N-APA mediated by CYP2C8 and CYP3A4 following repeat-dose administration.

OBJECTIVE To characterize the exposure of APA and its active metabolite N-APA following single and repeat oral dosing and evaluate relevant covariates

DATA

Plasma concentration data of APA and N-APA from 1092 subjects (117 healthy subjects and 975 subjects with CRPC) from 7 studies were pooled. An overview of the different studies is provided in Table 1.

Table 1: Overview Data

Study	N	Design	Dose (mg)
ARN-509-001 (NCT01171898)	126	Phase 1/2 safety, PK and proof of concept study in subjects with CRPC	30-480
56021927PCR1008 (NCT02162836)	6	Phase 1 in subjects with metastatic CRPC	240
56021927PCR1011 (NCT02160756)	75	Relative bioavailability study of 3 tablet formulations in healthy volunteers	240
56021927PCR1018 (NCT02524717)	24	Phase 1, single-dose hepatic impairment study in healthy volunteers	240
56021927PCR1019 (NCT02578797)	45	Phase 1, single-dose QT/QTc study in healthy volunteers	240
56021927PCR1021 (NCT02835508)	18	Phase 1, single-dose study in healthy male Japanese participants	60, 120 and 240
ARN-509-003 (NCT01946204)	798	Phase 3, multicenter, randomized, double-blind, placebo-controlled in men with NM-CRPC	240

PK MODEL

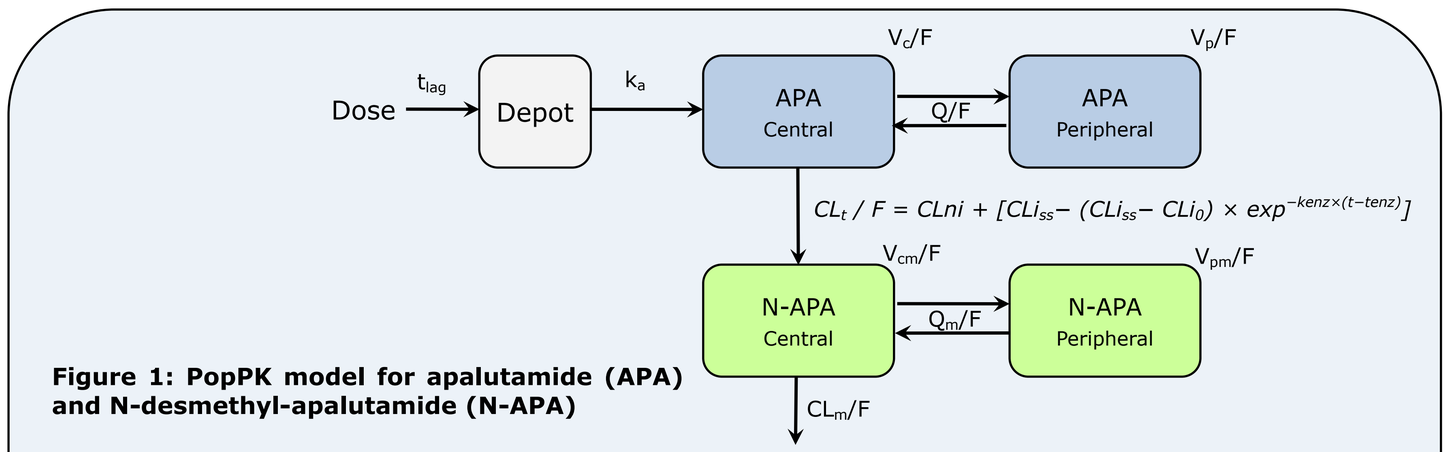


Figure 1: PopPK model for apalutamide (APA) and N-desmethyl-apalutamide (N-APA)

t_{lag} (h) is the lag-time absorption APA; k_a (1/h) is the APA first-order absorption rate constant; V_c/F and V_p/F (L) are the APA apparent volumes of distribution from central and peripheral compartment, respectively; CL_t/F (L/h) is the total apparent clearance of APA, the sum of not inducible (time -independent) clearance (CL_{ni}), and an inducible (time-dependent) clearance with CL_{i0} the inducible clearance at baseline and CL_{iss} the induced clearance at steady state; k_{enz} (1/h) the first order turnover rate of the inducible enzymes and t_{enz} (h) is the lag time for induction; Q/F (L/h) is the APA apparent inter-compartmental clearance; CL_m/F (L/h) is the N-APA apparent clearance; Q_m/F (L/h) is the N-APA apparent inter-compartmental clearance; V_{cm}/F and V_{pm}/F (L) are the central and peripheral volume of distribution of N-APA respectively.

Model development and evaluation was done using NONMEM® version 7.2.0 or higher (Icon Development Solutions, USA) and R version 3.2.3 or higher (http://cran.r-project.org/). A standard stepwise approach (forward inclusion/backward elimination) was used to evaluate the covariate effects

RESULTS

PK of APA and N-APA

APA pharmacokinetics were adequately described with an open linear two-compartment disposition model with a time-dependent apparent clearance and lagged first-order absorption, as shown in the prediction corrected visual predictive check (pcVPC, Figure 2). The resulting parameters are presented in Table 2. The formation of the metabolite N-APA was assumed to be equal to apalutamide elimination. N-APA pharmacokinetics were described with an open linear two-compartment disposition model with linear elimination. At steady-state, the elimination half-life of APA and N-APA was 4.2 and 4.6 days, respectively. At 240 mg of apalutamide per day, APA and N-APA exposure exhibited a 5.3 and 85.2-fold accumulation in plasma, respectively. After 4 weeks of treatment, more than 95% of steady state exposure of APA and N-APA is reached.

Covariate Effects

Within the range of covariate values evaluated only health status (healthy vs. CRPC subjects), body weight and albumin concentration were statistically associated with the exposure of APA or N-APA and the effect was small, as illustrated in Figure 3. The difference between healthy vs. CRPC subjects may be confounded by a difference in study design (single dose in healthy subjects vs multiple dose in CRPC). In addition, age (18-94 y), race (Black, non-Japanese Asian, Japanese), renal function (mild to moderate), hepatic function (mild, based on NCI), total bilirubin (TB), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), total protein (TP) and estimated glomerular filtration rate (eGFR), CYP3A4-inducing and CYP2C8-inhibiting co-medication had no clinically relevant impact on the PK parameters of APA and N-APA.

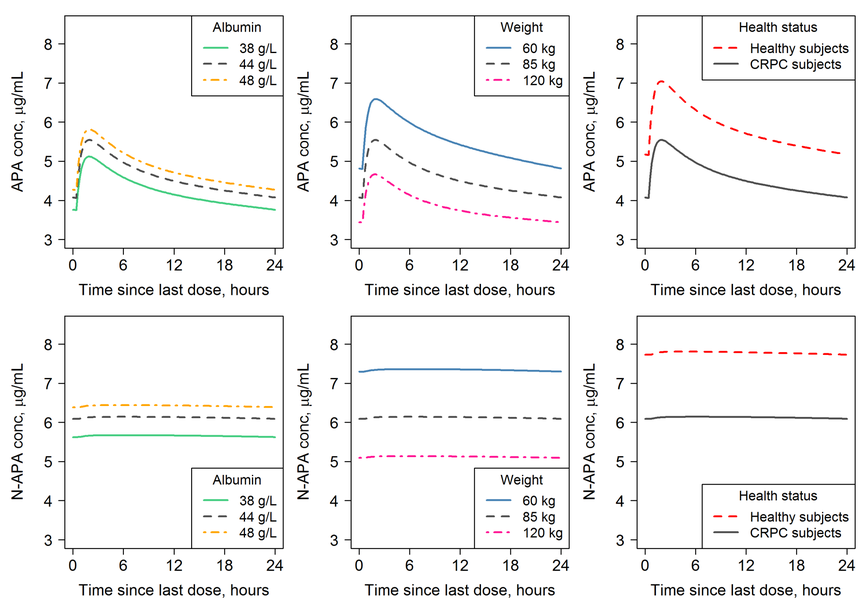
Table 2: PopPK Model Parameters

Structural Model Parameters		Inter-individual Variability (IIV; CV %)	
Parameters[a]	Estimate (RSE %)	Parameter	Estimate (RSE %)
Apalutamide (APA)			
t_{lag} (h)	0.418 (0.3)		
$k_{a\ tablet}$ (1/h)	0.216 (6.7)	IIV k_a	60.7 (11.8)
$\theta_{capsule}$[b]	0.851 (8.6)		
V_c/F (L)	14.5 (9.7)	IIV V_c/F	230.1 (14.9)
CL_{ni}/F (L/h)	1.17 (4.4)	IIV CL/F	19.1 (4.8)
CL_{i0}/F (L/h)	0.141 (35.2)		
CL_{iss}/F (L/h)	0.869 (6.0)		
k_{enz} (1/h)	0.0016 (4.0)		
t_{enz} (h)	57.7 (fixed)		
V_p/F (L)	261 (4.3)	IIV V_p/F	46.1 (8.1)
θ_{weight}[c]	0.882 (12.7)		
Q/F (L/h)	22.6 (3.5)	IIV Q/F	34.6 (17.0)
F_{CRPC}	1 (fixed)	IIV F	15.0 (4.6)
θ_{weight}[d]	-0.519 (5.2)		
$\theta_{albumin}$[d]	0.545 (13.0)		
$\theta_{healthy\ subjects}$[d]	0.27 (10.6)		
N-desmethyl-apalutamide (N-APA)			
V_{cm}/F (L)	26.3 (6.9)	IIV V_{cm}/F	56.8 (25.3)
CL_m/F (L/h)	1.53 (0.8)	IIV CL_m/F	7.3 (16.2)
V_{pm}/F (L)	212 (4.6)	IIV V_{pm}/F	47.3 (10.9)
$Q_{m,CRPC}/F$ (L/h)	67.3 (4.8)	IIV Q_m/F	22.6 (29.2)
$\theta_{healthy\ subjects}$[e]	-0.355 (10.7)		
		Residual variability (CV %)	
		APA	22.6 (0.3)
		N-APA	15.0 (0.2)

RSE: relative standard error; CV: coefficient of variation; CRPC: castrate resistant prostate cancer subjects. [a]Typical PK parameters reported are apparent [b]$k_{a,capsule} = k_{a,tablet} \times \Theta_{capsule}$; [c]$V_p/F = \Theta_{VP/F} \times (weight/75)^{\theta weight}$; [d]$F = 1 \times (AGE/75)^{\theta WT} \times (weight/75)^{\theta weight} \times (ALB/44)^{\theta albumin} \times (1 + \Theta_{healthy\ subjects})$; [e]$Q_m/F = \Theta_{Qm/F} \times (1 + \Theta_{healthy\ subjects})$

Figure 2: pcVPC of the final PK model for APA and N-APA following single and multiple doses

Figure 3 Deterministic simulations of 24h concentration-time profile at steady state of APA and N-APA for different covariates



CONCLUSION

The popPK analysis adequately characterized the PK of APA and N-APA. Health status, body weight and serum albumin were statistically associated with APA or N-APA PK parameters. Nevertheless, the magnitude of the effect of body weight and serum albumin concentration on the APA and N-APA PK parameters in CRPC subjects is low (<25%). In addition, within the range of covariate values evaluated, age, race, renal function, hepatic function, TB, AST, ALT, ALP, TP, eGFR, CYP3A4-inducing and CYP2C8-inhibiting co-medication had no discernable impact on the PK parameters. Consequently, APA dose adjustment based on these covariates is not warranted.

REFERENCES:

[1] Clegg NJ, Wongvipat J, Joseph JD, Tran C, Ouk S, Dilhas A, et al. ARN-509: a novel antiandrogen for prostate cancer treatment. Cancer Res. 2012;72(6): 1494-503.

[2] ERLEADA™ (apalutamide) prescribing information. 2018. https://ww.accessdata.fda.gov/drugsatfda_docs/label/2018/210951s000lbl.pdf. Accessed 11 January 2019.