DEVELOPMENT OF A PHARMACOKINETIC (PK) MODEL AND ASSESSMENT OF PATIENT (PT) COVARIATE EFFECTS ON DOSE-DEPENDENT PK FOLLOWING DIFFERENT DOSING SCHEDULES IN TWO PHASE I TRIALS OF AP23573 (AP), AN mTOR INHIBITOR

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Background

AP23573 is a novel non-prodrug rapamycin analog that potently inhibits mTOR (through bivalent binding to FKBP and mTOR), a downstream effector of PI3K/Akt and nutrient-sensing pathways. A PK model was developed to characterize the blood concentration-time profile of AP23573 and evaluate patient covariate effects following different dosing schedules.

Phase I Objectives

- Determine safety, tolerability and MTD of single-agent AP23573 in pts with refractory or recurrent malignancies that are advanced or metastatic, and not amenable to standard therapy or surgery
- To develop a compartmental PK model that can adequately characterize the pharmacokinetics of AP23573 and provide reasonable estimates of PK parameters, resulting in the ability to apply the PK model to future clinical trials; and
- To examine the effect of patient covariates on AP23573 PK parameters; AUC, CL, and V_{SS}.

Trial Designs

- Two phase I trials: open label, sequential, accelerated titration
- Flat-fixed dosing of AP23573 as a 30-minute IV infusion without premedication
- One trial examining AP23573 administered once weekly starting at 6.25 mg
- One trial examining AP23573 administered QDx5 (Daily) every other week (two courses of 5 days of dosing followed by a 9 day rest per cycle) starting at 3 mg

Phase I Trials – Patient Population

Common Tumor types	101 (N=46)	102 (N = 33)
• Colorectal carcinoma	8	1
• Renal cell carcinoma	8	7
• Lung (NSCLC*)	12	5
– NSCLC, large cell, Bronchoalveolar carcinoma		
– Mesothelioma		
• Soft tissue sarcoma	6	5
– Malignant mixed mullerian, liposarcoma leiomyosarcoma, GIST		
• Other sarcoma	--	3
– Ewing's tumor, Osteosarcoma		
• Breast	--	2
• Head and neck	--	2
• Other **	12	8

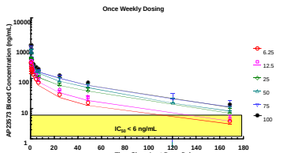
*NSCLC = non small cell lung cancer
**Other tumor types included:
Trial 101 – Adenocarcinoma (2), cholangiocarcinoma, esophageal adenocarcinoma, medually thryoid, melanoma, ovarian, periampullary, prostate, small bowel carcinoma, squamous cell carcinoma, transitional cell bladder cancer.
Trial 102 - Hepatocellular, hurtle cell thyroid, large cell lymphoma, melanoma, pancreatic, prostate, uterine cancer, neuroendocrine

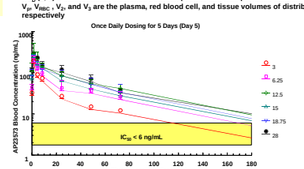
Trial 101 – 31M/15F, median age 61.5 yrs
- Maximum Tolerated Dose (MTD) = 75 mg
- Dose Limiting Toxicity: Two (2) occurrences of Grade 2/3 mucositis at 100 mg

Trial 102 – 17M/16F, median age 51.0 yrs
- Maximum Tolerated Dose (MTD) = 18.75 mg
- Dose Limiting Toxicity: Two (2) occurrences of Grade 3 mucositis at 28 mg

Methods and Results

- Whole blood AP23573 samples were analyzed using LC/MS/MS
- Using a two-stage population PK approach, each individual's AP23573 blood concentrations were best fit to a 3-compartment model using WinNonlin. Model characteristics include separate compartments for highly- and less-perfused tissues
- Compartmental modeling best captured the tri-exponential decline of AP23573 blood concentrations over time, thus providing reasonable PK parameter estimates of $T_{1/2}$, V_{SS}, CL, and AUC
- Linear and nonlinear regression methods were utilized to evaluate patient covariate effects on dose-dependent AP23573 PK parameters; AUC, CL, and V_{SS}
  - Patient factors include sex, age, baseline RBC, body weight, and BSA
  - Significance was determined at $\alpha = 0.05$





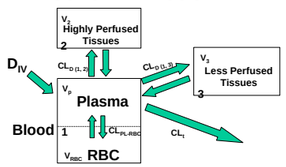
- At therapeutic doses of 50 mg QW and 12.5 mg QD x 5 (TD = 62.5 mg), AP23573 blood concentrations exceed the IC_{50} of various tumor types for > 180 hr

Mean Predicted Blood PK Parameters of AP23573

Trial	Dose (mg) (N)	C_{max} (ng/mL)	AUC $_{0\text{-}\infty}$ or $_{0\text{-}24}$ (µg*hr/mL)	$T_{1/2}$ (hr)	CL (L/hr)	V_{ss} (L)[b]
Single Dose (Trial101: Single N = 42*)	6.25 (1)	329	3.1	57.3	2.0	148
	12.5 (3)	394 ± 56	4.6 ± 1.5	52.6 ± 13.9	3.0 ± 1.1	167 ± 30
	25 (4)	570 ± 56	7.6 ± 1.7	44.8 ± 6.7	3.4 ± 0.7	188 ± 20
	50 (15)	982 ± 194	10.0 ± 2.6	57.6 ± 27.6	5.4 ± 1.5	322 ± 72
	75 (15)	1195 ± 279	11.8 ± 3.6	58.2 ± 16.6	7.0 ± 2.2	429 ± 89
	100 (4)	1255 ± 97	11.9 ± 2.4	50.9 ± 4.0	8.7 ± 1.9	523 ± 83
Multiple Dose (Trial102: Day 5) N = 29*	3 (1)	263[a]	2.0	55.7	1.5	59.2
	6.25 (2)	321 ± 57[a]	2.8	65.1	2.4	137
	12.5 (2)	618 ± 212[a]	4.7	73.5	2.7	171
	15 (6)	576 ± 89[a]	4.4 ± 0.8	59.5 ± 11.6	3.5 ± 0.5	150 ± 33
	18.75 (12)	611 ± 178[a]	4.4 ± 1.0	61.7 ± 12.4	4.4 ± 0.9	206 ± 45
	28 (6)	774 ± 232[a]	6.0 ± 2.4	70.7 ± 26.8	5.4 ± 2.3	248 ± 87

Mean predicted blood PK parameters for AP23573. * represents the PK evaluable population.
[a] Observed C_{max} is on Day 1, [b] V_{ss} - steady-state volume of distribution

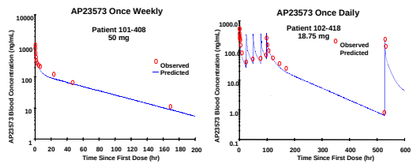
AP23573 PK Model



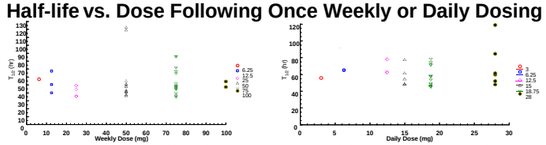
D_{IV} = IV infusion of AP23573
CL_L = apparent total body clearance
CL_D (1, 2) = distributional clearance between plasma and highly perfused tissues
CL_D (1, 3) = distributional clearance between plasma and less perfused tissues
V_p, V_{RBC}, V_2, and V_3 are the plasma, red blood cell, and tissue volumes of distribution, respectively

PK Modeling of AP23573 – Once Weekly and Daily Dosing

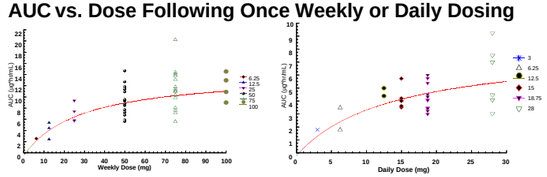
Representative model-fitted and observed AP23573 concentration-time profiles for patients in the once weekly or daily dosing trials



Half-life vs. Dose Following Once Weekly or Daily Dosing

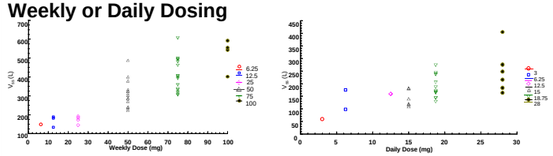


AUC vs. Dose Following Once Weekly or Daily Dosing



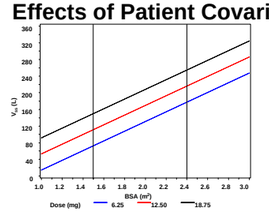
Red line represents model fit.

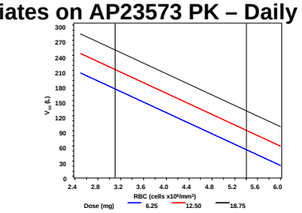
Steady State Volume of Distribution vs. Dose Following Once Weekly or Daily Dosing



- AP23573 displays nonlinear pharmacokinetics
  - C_{max} and AUC increase disproportionately with dose
  - Both V_{ss} and CL increase with dose
    - $T_{1/2}$ remains constant due to increases in both V_{ss} and CL with dose
- These findings suggest that the dose nonlinearity has to be accounted for prior to assessment of patient covariate effects on AP23573 PK parameters

Effects of Patient Covariates on AP23573 PK – Daily



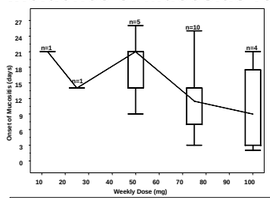


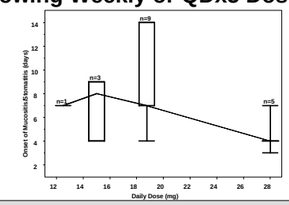
- Vertical lines represent the data range on which the model was developed. In Trial 102, BSA ranged from 1.5-2.4 m^2 and RBC ranged from 3.1-5.4 cells $x10^6/mm^3$

Trial 102 (Daily)
- AUC increases disproportionately with dose
- CL increases with dose, but is inversely related to RBC
- V_{ss} increases with dose and BSA, but is inversely related to RBC

Trial 101 (Weekly)
- AUC increases disproportionately with dose
- CL increases with dose and in females
- V_{ss} increases with dose, but is inversely related to RBC

Incidence of Mucositis following Weekly or QDx5 Dosing





- Severity and time to onset of mucositis related to dose
- No relationship observed between C_{max} and onset date of mucositis

Summary and Conclusions

- AP23573 PK are nonlinearly related with dose
- Interpatient variability of model-predicted PK parameters was modest within each cohort
- Dose, BSA, and RBC are significant patient factors that describe the interpatient variability in V_{ss} and CL
- The relationship between dose and AUC, V_{ss}, and CL could be attributed to saturation of distibution sites, such as RBC, allowing for deeper penetration of AP23573 to other tissues
- Based on a dose-toxicity relationship, onset of mucositis is faster with once daily dosing regimen of AP23573, which may be attributed to sustained blood levels above a threshold concentration indicative of triggering a DLT
- Both QW and QD x 5 regimens provide therapeutic AP23573 concentrations that exceed the IC_{50}, thus providing support for utility of both regimens in Phase 2 trials currently ongoing
- AP23573 has a reproducible and predictable pharmacokinetic profile with limited interpatient variability. These features are supportive of its use in combination chemotherapy regimens where precise pharmacokinetic behavior is crucial.

References

- Raymond E, et al. J. Clin. Oncol. 22: 2336-2347, 2004.
- Ferron G, et al. Clin. Pharmacol. Ther. 61: 416-428, 1997.
- AP23573 Investigator's Brochure

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