Population Pharmacokinetics and Pharmacodynamics of Etrumadenant (AB928) in Healthy Volunteers and Cancer Patients

PRESENTER:
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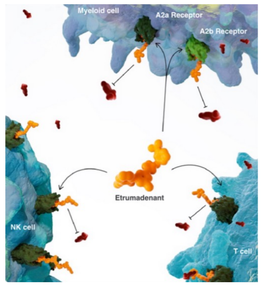
BACKGROUND



- Etrumadenant (AB928), an orally bioavailable, small-molecule, selective dual adenosine receptor (A2a and A2b) antagonist, reverses the immunosuppressive effects caused by high concentrations of adenosine in the tumor microenvironment.
- It is being evaluated in several clinical trials across multiple oncology indications.

OBJECTIVES

- Characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of etrumadenant
- Inform dose selection for Phase 2 studies

METHODS

Study	Summary of Design	Number of Patients	Number of Samples
AB928CSP 0001	A Phase 1 dose escalation study of etruma in healthy adults	65 (PK) 71 (PD)	1046 (PK) 250 (PD)
AB928CSP 0002	A Phase 1/1b dose escalation study of etruma + PLD or etruma + PLD + IPI in breast or gynecologic cancer patients	28 (PK) 6 (PD)	479 (PK) 45 (PD)
AB928CSP 0003	A Phase 1/1b dose escalation study of etruma + mFOLFOX in gastrointestinal cancer patients	43 (PK) 7 (PD)	628 (PK) 46 (PD)
AB928CSP 0004	A Phase 1/1b dose escalation study of etruma + Carbo/Pem + Pembro or etruma + Carbo/Pem + AB122 in lung cancer patients	10 (PK) 6 (PD)	129 (PK) 41 (PD)
AB928CSP 0005	A Phase 1/1b dose escalation study of etruma + AB122 in advanced cancer patients	32 (PK) 12 (PD)	402 (PK) 117 (PD)

etruma: etrumadenant; PLD: pegylated liposomal doxorubicin; IPI: IPI-549; Carbo: carboplatin; Pem: pemetrexed; Pembro: Pembrolizumab; AB122: Zimberelimab.

- Data (AB928 capsule was used in all the studies)
  - PK: plasma concentrations of etrumadenant (PK/PD model) and its glucuronide metabolite (PK model only)
  - PD: percent inhibition of phosphorylated cAMP Response Element Binding protein (pCREB) levels in $CD8^+$ T cells
- Population PK/PD analysis was performed using NONMEM (version 7.4, ICON, Hanover, MD, USA) and 1st-order conditional estimation method with interaction.
- Clinical simulations were conducted to predict etrumadenant PK and %pCREB inhibition at various dose levels.

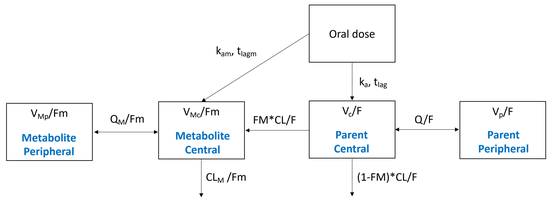
CONCLUSIONS

- The PK of etrumadenant was adequately described by a 2-compartment model with delayed first-order absorption from the gastrointestinal tract and first-order elimination from the central compartment
  - Slower absorption with unchanged oral bioavailability when given with food
  - Insignificant reduction in exposure when given with ARAs which may be further validated with more PK data
  - No other clinically relevant PK covariates
- A direct effect PD model with complete inhibition at high concentrations of etrumadenant adequately described the inhibition of pCREB after etrumadenant treatment
  - IC50 = 88.4 ng/mL, IC90 = 455 ng/mL
  - No significant PD covariates
- At the selected Phase 2 dose of 150 mg once daily (QD), the majority of patients are projected to achieve the target PD response (90% pCREB inhibition)

The preliminary PKPD analysis shown here supported the choice of 150 mg QD capsules as the etrumadenant dose in Phase 2 studies in patients with advanced malignancies. The preliminary PKPD analysis suggested etrumadenant capsule can be administered with concomitant ARAs and food.

RESULTS: PK

PK Model Structure



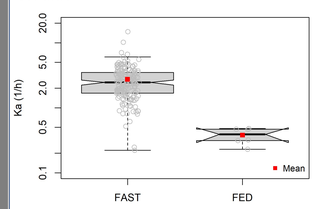
CL/F: apparent clearance for AB928; CL_m/F_m: apparent clearance for AB928 glucuronide; FM: fraction of AB928 metabolized to AB928 glucuronide which was fixed to 1 in the model; K_a: absorption rate constant for AB928; K_{am}: absorption rate constant for AB928 glucuronide, accounting for the presystemic formation of AB928 glucuronide; Q/F: apparent inter-compartmental clearance for AB928; Q_m/F_m: apparent inter-compartmental clearance for AB928 glucuronide; t_{lag}: lag time for AB928 absorption after oral administration of AB928; V_c/F: apparent volume of distribution in the central compartment for AB928; V_{cm}/F_m: apparent volume of distribution in the central compartment for AB928 glucuronide; V_p/F: apparent volume of distribution in the peripheral compartment for AB928; V_{pm}/F_m: apparent volume of distribution in the peripheral compartment for AB928 glucuronide.

PK Parameter Estimates

Parameter	Estimate	Estimate RSE (%)	IIV (CV%)	IIV RSE (%)	Shrinkage (%)
CL/F (L/h)	5.93	2.7	32.8	5.9	7.3
V_c/F (L), 70-kg body weight	57.8	4.3	22.9	13.4	25.0
Weight on V_c/F [a]	1.06	10.4	NA	NA	NA
Q/F (L/h)	11.9	5.3	NA	NA	NA
V_p/F (L)	104	5.2	57.0	11.2	15.9
K_a (1/h) (FAST)	2.6	15.2	76.0 (FAST) 37.1 (FED)	14.8 (FAST) 43.6 (FED)	46.4 (FAST) 76.9 (FED)
FED on K_a (ratio)	0.134	17.5	NA	NA	NA
t_{lag} for group 1 (h)	0.361	11.9	NA	NA	NA
t_{lag} for group 2 (h)	0.489	0.9	NA	NA	NA
Proportion of subjects in group 1 (ratio)	0.544	14.2	NA	NA	NA
CL_m/F_m (L/h)	2.69	3.9	42.1	8.4	18.5
V_{cm}/F_m (L)	2.30	39.8	106	19.9	37.1
Q_m/F_m (L/h)	6.37	15.4	NA	NA	NA
V_{pm}/F_m (L)	6.37	9.7	NA	NA	NA
K_{am} (1/h) (FAST)	0.03	71.3	132	27.6	40.6
FED on K_{am} (ratio)	0.213	62.0	NA	NA	NA
Proportional ERR (%CV) for AB928	25.1 (HV) 31.3 (CP)	4.7 (HV) 3.0 (CP)	NA	NA	11.6 (HV) 9.3 (CP)
Proportional ERR (%CV) for AB928 glucuronide	28.6 (HV) 26.9 (CP)	8.9 (HV) 3.0 (CP)	NA	NA	6.0 (HV) 10.6 (CP)
AB928 elimination half-life (h)	23.2	NA	NA	NA	NA
AB928 distribution half-life (h)	1.8	NA	NA	NA	NA

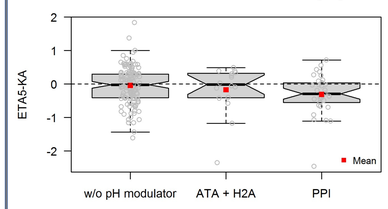
RSE: relative standard error; IIV: interindividual variability shown as %CV; CV: coefficient of variation; CP: cancer patients; HV: healthy volunteers; ERR: residual error. Group 1 and group 2 are two subpopulations with different values of lag time estimated using $MIXTURE subroutine in NONMEM.

Absorption Rate Constant vs. Fasting Condition



K_a: absorption rate constant for AB928; FAST: fasting condition; FED: fed condition.

Inter-Individual Random Effects for Absorption Rate Constant vs. Concomitant Use of Acid-Reducing Agents

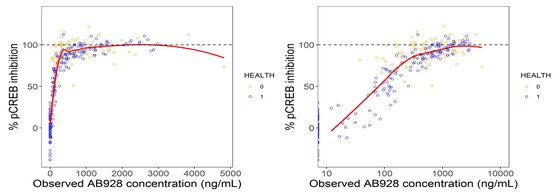


ETA_Ka: inter-individual random effects for AB928 absorption rate constant; ATA: antacids; H2A: H2 antagonists; PPI: proton pump inhibitors.

- Covariate analysis indicated slower absorption but unchanged oral bioavailability of etrumadenant when given with food.
- Administration of etrumadenant with ARAs resulted in a small but insignificant reduction in etrumadenant exposure.
- None of the other investigated covariates (age, gender, body weight, study population, concomitant acid-reducing agents [ARAs], hepatic and renal function) have a clinically relevant impact on etrumadenant PK.

RESULTS: PD

Observed Percent pCREB Inhibition vs. Observed AB928 Concentration in Healthy Volunteers and Cancer Patients



pCREB: phosphorylated cAMP Response Element Binding protein; HEALTH: 0=cancer patients; 1=healthy volunteers. The x-axis is on linear scale in the left plot and on log scale in the right plot.

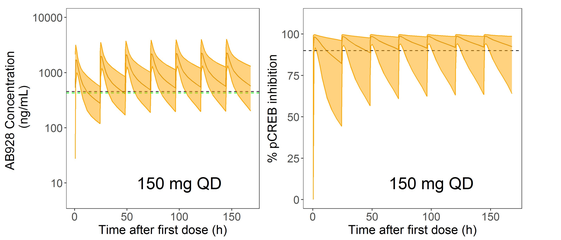
PD Parameter Estimates

Parameter	Estimate	Estimate RSE (%)	IIV (CV%)	IIV RSE (%)	Shrinkage (%)
I_{max} (%)	100 FIX	NA	NA	NA	NA
IC_{50} (ng/mL)	88.4	9.4	51.4	12.4	26
HILL	1.34	5.8	NA	NA	NA
Additive Error (%)					
HV, Placebo	14.1	13.0			0
HV, AB928	5.3	8.1			12
Patient, AB928	13.2	9.4			3
IC_{90} (ng/mL)	455	NA	NA	NA	NA

IC_{50}: concentration corresponding to 50% of maximum effect; IC_{90}: concentration corresponding to 90% of maximum effect; I_{max}: Maximum effect; HILL: Hill coefficient; HV: healthy volunteers; IIV: interindividual variability; NA: not applicable; RSE: relative standard error.

RESULTS: Clinical Simulation

Projected PK/PD Profiles of AB928 Following 150 mg QD



QD: once daily dosing; pCREB: phosphorylated cAMP Response Element Binding protein; NECA: 5'-N-Ethylcarboxamidoadenosine. The dashed lines represent the model estimated IC_{90} (455 ng/mL) (black) and NECA EC90 (1uM or 426.5 ng/mL) (green) in PK plot and 90% pCREB inhibition in PD plot. The solid lines represent the median and 2.5th and 97.5th percentiles.

- Clinical PK and PD simulations showed that a majority of subjects are projected to achieve the target etrumadenant response (90% pCREB inhibition) at the dose of 150 mg QD being evaluated in Phase 2 studies in cancer patients.

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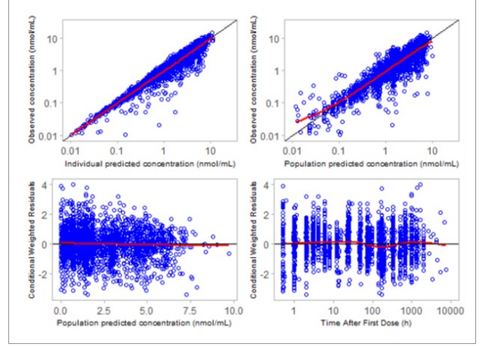
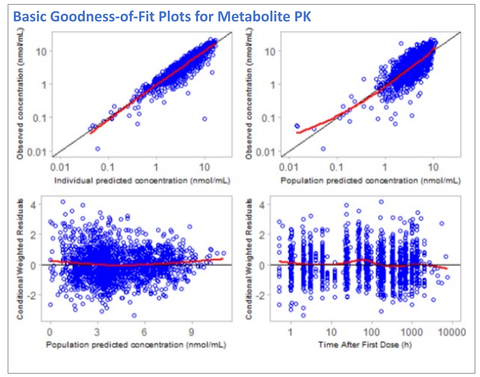
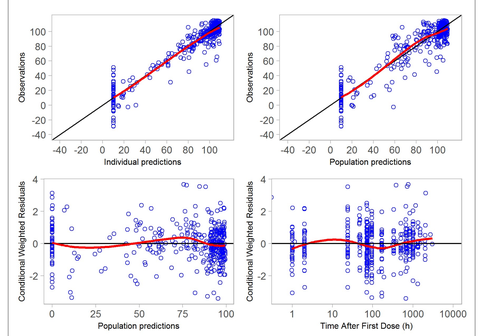
Basic Goodness-of-Fit Plots for Parent Drug PK



Basic Goodness-of-Fit Plots for Metabolite PK



Basic Goodness-of-Fit Plots for PD



PD observations: percent inhibition of pCREB; pCREB: phosphorylated cAMP Response Element Binding protein.

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