Final Results of the Phase 1 Study in Healthy Volunteers of AB928, a Dual Antagonist of the $A_{2a}R$ and $A_{2b}R$ Adenosine Receptors Being Studied as an Activator of Anti-Tumor Immune Response

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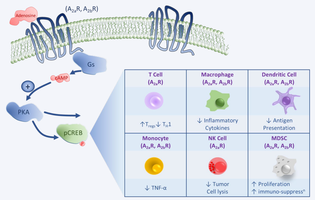
INTRODUCTION

In many tumors, extracellular adenosine contributes to an immunosuppressed tumor micro-environment (TME) via activation of the A_{2a} receptor ($A_{2a}R$), expressed on lymphocytes and the A_{2b} receptor ($A_{2b}R$), highly expressed on myeloid cells. Relative to other tissues like the brain, adenosine concentrations in the TME are much higher. Also unlike the brain, tumors contain high levels of albumin, to which many small molecule drugs bind non-specifically. AB928 is a novel and selective dual $A_{2a}R/A_{2b}R$ antagonist designed to potently block the immunosuppressive effects of adenosine in the TME.

A placebo-controlled (3:1) study of AB928 was conducted in healthy volunteers to study the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of the drug. This poster describes the final unblinded safety and PK/PD ($A_{2a}R$ coverage in blood T cells) data from this study.

Adenosine Receptor Mediated pCREB Signaling

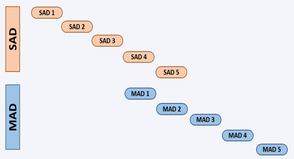


METHODS

Phase 1 Healthy Volunteer Study: This Phase 1 healthy volunteer study consisted of single ascending dose (SAD) and multiple ascending dose (MAD) arms. In the SAD arm, we evaluated single doses of 10, 25, 75, and 150 mg, and two doses of 100 mg, 12 hours apart. In the MAD arm, we evaluated single daily doses of 10, 25, 75, 150 and 200 mg administered for 4 consecutive days. The study enrolled 85 participants (randomized 3:1, active:placebo) 40 each in the SAD and MAD arms, plus 5 in a food-effect assessment cohort.

Multi-color Phospho-flow Cytometry: Monoclonal antibodies to cell type specific markers including fluorochrome labelled anti-pCREB (Cyclic AMP Response Element Binding Protein) antibody were used to quantify CREB phosphorylation in placebo and dosed subjects.

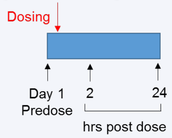
Clinical Study Design



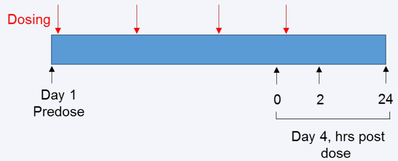
Group	SAD	MAD
1	10 mg once	10 mg daily X 4
2	25 mg once	25 mg daily X 4
3	75 mg once	75 mg daily X 4
4	150 mg once	150 mg daily X 4
5	100 mg twice	200 mg daily X 4

Schedule of PD Assessments

Single Ascending Dose (SAD)



Multiple Ascending Dose (MAD)

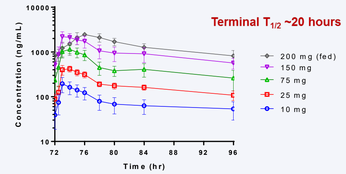


Bioanalytical / PK analysis: Plasma samples were prepared by a protein precipitation extract procedure. The analyte, AB928, and internal standard, AB928-d_6, were extracted from plasma with acetonitrile/methanol (90/10, v/v). Concentrations of AB928 were determined by LC-MS/MS. Descriptive PK parameters were obtained by a standard non-compartmental analysis from the plasma concentration-time curves using Phoenix WinNonlin v6.3 or higher (Certara, Princeton, NJ).

pCREB in Human Whole Blood: The inhibition of $A_{2a}R$-mediated effects by AB928 was determined in blood samples from the Phase 1 study by the decreased phosphorylation of CREB following stimulation *ex vivo* with the adenosine receptor agonist NECA (5'-N-ethylcarboxamidoadenosine). At each PD time point, levels of pCREB were assessed by flow cytometry both in the absence and following *ex vivo* stimulation with 1, 5 and 10 µM NECA.

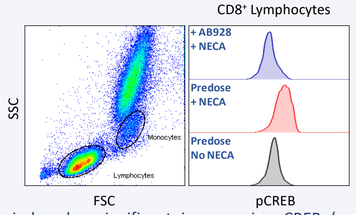
RESULTS

AB928 PK Profile at Steady State Supports Once Daily Dosing



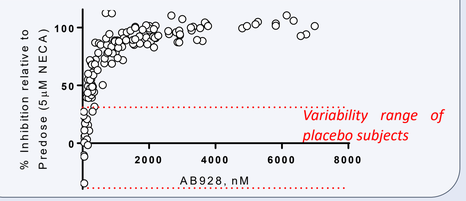
A high-fat meal decreased the rate of AB928 absorption (C_{max}) but had no effect on the extent of AB928 absorption (AUC).

NECA-Induced pCREB Increases in Peripheral Immune Cells Are Blocked by AB928



NECA induced a significant increase in pCREB (grey vs. red histograms) in peripheral blood $CD8^+$ cells. This increase, in response to 5 µM NECA, is still inhibited at trough plasma levels following 4 once daily doses with 150 mg AB928 (blue histograms). Prior to dosing, NECA-induced pCREB elevations were observed in $CD8^+$ T cells in all subjects evaluated to date. The increase in pCREB signal was consistently strongest in blood $CD8^+$ T cells across all subjects evaluated.

PK/PD Correlation in AB928 Dosed Subjects Measured by pCREB Inhibition of 5 µM NECA Effects on $CD8^+$ T cells



Relationship Between Mean AB928 Plasma Levels and PD Endpoints

MAD Cohort	2-hr Post-Dose		24-hr Post-Dose	
	AB928 Plasma Conc. (ng/mL)	% Inhibition of 5 µM NECA	AB928 Plasma Conc. (ng/mL)	% Inhibition of 5 µM NECA
10 mg qd (Day 4)	163	51 %	53	(12 %) *
25 mg qd (Day 4)	420	82 %	108	51 %
75 mg qd (Day 4)	1148	100 %	261	76 %
150 mg qd (Day 4)	2113	100 %	566	≥ 90%
200 mg qd fed (Day 4)	1517	≥ 90%	819	≥ 90%

[a] Some or all dosed subjects were within the range of variation observed in placebo subjects (-39 to 30%).
[b] Data collected 12 hours following the second daily dose.

AB928 Was Well Tolerated at Single and Multiple Oral Doses

The current trial was enrolled from 13th of October, 2017 to the 5th of March 2018. The final data was available on the 12th of June 2018. Across the SAD and MAD cohorts the subjects ranged in age from 26-33. There was a slightly higher percentage of females enrolled across the entire study (62%).

SAD SAFETY RESULTS

Subjects with	Placebo (N=10) n (%)	AB928 Treatment (mg), n (%)					
		10 (N=6)	25 N=6)	75 (N=6)	150 (N=6)	100 q12h (N=6)	Total (N=30)
Any AE	6 (60)	3 (50)	1 (7)	4 (67)	6 (100)	4 (67)	18 (60)
Related AE	4 (40)	2 (33)	1 (17)	3 (50)	6 (100)	4 (67)	16 (53)
Grade 1 AE[a]	4 (40)	2 (33)	1 (17)	3 (50)	5 (83)	3 (50)	14 (47)
Grade 2 AE[b]	2 (20)	1 (17)	0	1 (17)	1 (17)	1 (17)	4 (13)
Related Grade 1 AE	3 (30)	1 (17)	1 (17)	3 (50)	5 (83)	3 (50)	13 (43)
Related Grade 2 AE	1 (10)	1 (17)	0	0	1 (17)	1 (17)	3 (10)

[a] All resolved except for fatigue and vessel puncture site pain in 1 subject each in the 100 mg q12h group.
[b] All resolved.

MAD SAFETY RESULTS

Subjects with	Placebo (N=10) n (%)	AB928 Treatment (mg, qd), n (%)					
		10 (N=6)	25 N=6)	75 (N=6)	150 (N=6)	200 fed (N=6)	Total (N=30)
Any AE	8 (80)	3 (50)	6 (100)	6 (100)	6 (100)	6 (100)	27 (90)
Related AE	5 (50)	1 (17)	4 (67)	4 (67)	3 (50)	3 (50)	15 (50)
Grade 1 AE[a]	8 (80)	3 (50)	6 (100)	6 (100)	5 (83)	4 (67)	24 (80)
Grade 2 AE[b]	0	0	0	0	1 (17)	2 (33)	3 (10)
Related Grade 1 AE	5 (50)	1 (17)	4 (67)	4 (67)	3 (50)	2 (33)	14 (47)
Related Grade 2 AE	0	0	0	0	0	1 (17)	1 (3)

[a] All resolved, except for vessel puncture site bruise, contusion, and headache in 1 subject and vessel puncture site bruise in another subject in the 25 mg qd group, fatigue and nasopharyngitis in 1 subject each in the 200 mg qd fed group, and headache and medical device site irritation in 1 subject each in the placebo group.
[b] All resolved.

There were no deaths or serious adverse events in the study. All other clinical safety assessments, including vital signs, physical examinations, ECGs and laboratory evaluations were unremarkable across all SAD and MAD groups. This includes heart rate, PR, QT and QTc intervals, and QRS duration.

CONCLUSIONS

- AB928 has demonstrated an excellent oral PK profile in human subjects, consistent with once-daily dosing.
- AB928 was well tolerated in this study. No stopping rules were met and dose escalation continued until highest dose (200 mg) and maximal PD effects were observed at 150 mg (one dose level below the maximum dose).
- There was no evidence of the physiological effects associated with other adenosine receptor antagonists tested in humans.
- Assessing pCREB levels on whole blood $CD8^+$ T cells following *ex vivo* stimulation with 5 µM NECA provides an excellent measure of the PD effects of AB928 in dosed subjects. In all dose groups, significant inhibition at peak plasma concentrations was observed. Significant inhibition was also observed 24 hours post-dose in the higher dose groups.
- Consistent with previously generated *in vitro* data, AB928 plasma levels ≥ 1 µM are associated with ≥ 90% adenosine receptor inhibition.
- This study supported a starting dose of 75 mg AB928 in our dose-escalation trials for AB928 in patients. Four dose-escalation trials evaluating AB928 in combination with chemotherapy and / or PD-1 therapy have been initiated.

AB928 Combination Studies in Oncology Have Been Initiated in Australia and the US

Study number	Combination (Dose Escalation)	Tumor Type
AB928CSP0002	AB928 + PLD (SOC)	TNBC or Ovarian
AB928CSP0003	AB928 + mFOLFOX (SOC)	GEC or CRC
AB928CSP0004	AB122 monotherapy (240 mg Q2W) AB928+ carbo/pem + pembro (SOC) AB928+ carbo/pem	NSCLC
AB928CSP0005	AB928 + AB122 (240mg Q2W)	Solid Tumors

In the dose-escalation portion of these clinical studies, AB928 will be evaluated at doses of 75, 150 and 200 mg.

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