A Phase Ia/Ib Trial of FAP-Dox (AVA6000), a Fibroblast Activation Protein (FAP)-released and Tumor Microenvironment (TME)-targeted Doxorubicin Peptide Drug Conjugate in Patients with Salivary Gland Cancers

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Avacta THERAPEUTICS

Abstract: e15113

BACKGROUND

pre|CISION® peptide drug conjugates comprise a peptide moiety bound to an active payload by a linker that is specifically cleaved by FAP

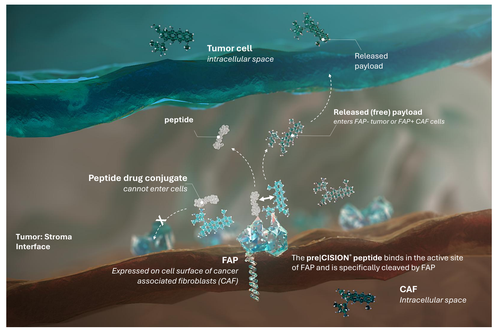
FAP is a protease selectively overexpressed in the tumor microenvironment (TME) of many solid tumors on cancer-associated fibroblasts

The pre|CISION® peptide prevents cellular entry of the conjugate unless cleaved by FAP, enabling targeted delivery of released payload directly to tumors

This targeted release mechanism has been validated in both preclinical animal models and clinical biopsy data, demonstrating that the payload is predominantly activated and released in the FAP-rich tumor environment

- Doxorubicin is an effective anthracycline, however, its clinical utility is significantly limited by dose-dependent, cumulative cardiotoxicity and bone marrow toxicity
- Encouraging safety and preliminary efficacy data from the Phase 1 trial with faridoxorubicin have been presented previously (Tap et al. ESMO 2025, Lahu et al AACR 2025, Banerji, AACR 2024, Twelves, ESMO 2024)
- It is hypothesized that the tumor-specific release mechanism of pre|CISION® medicines reduces the initial "first pass" normal tissue exposure to released doxorubicin (e.g. cardiac and bone marrow)

FIGURE 1. The pre|CISION® Bystander Effect



Patient Population and Trial Methods

The faridoxorubicin (AVA6000) Phase 1a dose escalation enrolled patients with a diagnosis of cancers frequently noted as FAP-positive, including sarcoma, pancreatic cancer, colorectal cancer, head and neck cancers (n=63)

Specific indications were selected for Phase 1b expansions (n=48). Cardiac safety and PK data are presented with preliminary efficacy in SGC in Ph 1a and 1b. FAP expression was tested retrospectively. The data cutoff presented is 15 May 2026

- **Prior therapy with any anthracycline was limited to total cumulative dose of less than 350 mg/m².** The lifetime cumulative maximum exposure was limited to 550 mg/m² in the AVA6000 trial based on favorable safety data until Amendment to remove lifetime maximum based on favorable cardiac safety and Health Authority interaction. A subset of patients were treated to a lifetime maximum of 550 mg/m²
- **Trial analyzed for safety (primary endpoint) and efficacy.** Safety is analyzed in all patients receiving at least one dose of AVA6000 (n=63, Ph 1a and n=48 Ph 1b, N=111 total). Efficacy in patients with a diagnosis of salivary gland cancers treated at the dose of 250 mg/m² and above are presented across doses ranging from 250 mg/m² to 385 mg/m² (n=11) or in Ph Ib at 310 mg/m² at least 1 post-therapy scan completed to assess response (n=27). Among pts with SGC, there is a median of 1 prior line of therapy in the metastatic setting
- **Full plasma and tumor pharmacokinetics were completed.** Plasma samples were obtained at the same time as tumor biopsy samples (24 hours post first dose). Plasma samples were obtained and analyzed for AVA600, released doxorubicin, doxorubicinol and the released pre|CISION peptide

FIGURE 2.

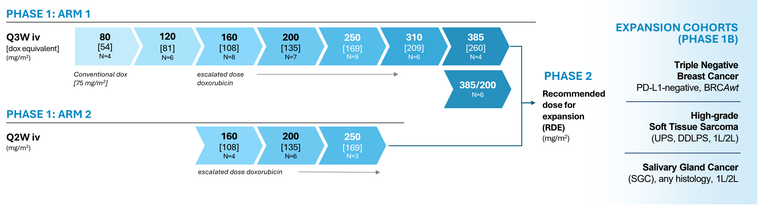


TABLE 1. Patient Demographics in All Enrolled Patients and Phase 1b SGC Cohort

	Phase 1a and 1b N=111 All dose levels	Phase 1b n=48 310 mg/m²
Age, median (range)	59 (25 - 81)	55.5 (25 - 81)
Sex, Male (%) / Female (%)	56 (51) / 55 (49)	20 (42) / 28 (58)
Ethnicity		
Hispanic, n (%)	2 (2)	2 (4)
Not Hispanic, n (%)	104 (94)	45 (94)
Unknown or Not Reported, n (%)	5 (4.5)	1 (2)
Race		
Caucasian, n (%)	88 (79)	37 (77)
Asian, n (%)	10 (9)	4 (8)
Black, n (%)	8 (7)	6 (13)
Not Reported, n (%)	5 (5)	1 (2)
ECOG Score at Baseline (0, 1)		
ECOG 0 (%) / ECOG 1 (%)	54 (49) / 57 (51)	29 (60) / 19 (40)

Data cut off 15 MAY 2026.

SAFETY

TABLE 2. Grade 3/4 Treatment-Related Adverse Events Reported in More than 1 Patient

	Phase 1a and 1b N=111 All dose levels	Phase 1b n=48 310 mg/m²
Adverse Event[1]		
Neutropenia, n (%)	27 (24.3)	14 (29.2)
Leukopenia, n (%)	13 (11.7)	7 (14.6)
Lymphopenia, n (%)	8 (7.2)	4 (8.3)
Anemia, n (%)	7 (6.3)	3 (6.3)
Fatigue, n (%)	7 (6.3)	5 (10.4)
Thrombocytopenia, n (%)	4 (3.6)	1 (2.1)
Dyspnea, n (%)[2]	2 (1.8)	1 (2.1)

Data cut off 15 MAY 2026.
[1] Adverse event and lab findings were merged programmatically. These include low neutrophils merged into neutropenia, low WBC count into leukopenia, low lymphocytes into lymphopenia, low hemoglobin in anemia and low platelet count into thrombocytopenia.
[2] Two Gr 3 cases of dyspnea include 1 patient with co-existing COVID-19 infection and 1 patient with ARDS , pleural/pericardial effusions. No cases of pneumonitis reported in the 111 patients treated in the trial.

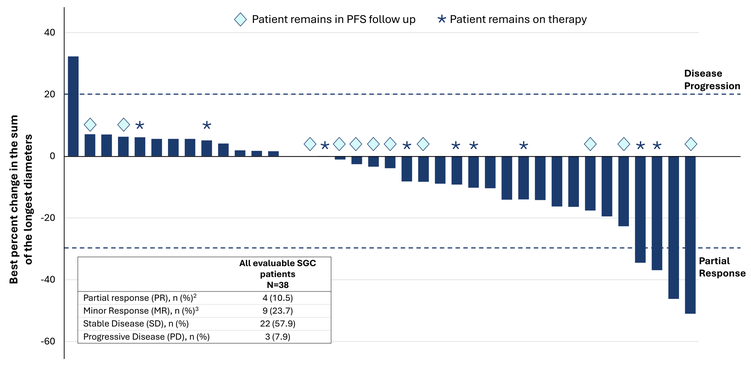
TABLE 3. Clinically Significant Reductions in LVEF

	450 mg/m² or lower cumulative exposure[1]	450-550 mg/m² cumulative exposure[1]	All patients N=111
Reduction in LVEF[1]			
LVEF remains >LLN, decreased >20% from baseline	n=0	n=1	1 (0.9%)
LVEF below LLN, decreased >10% from baseline	n=2	n=1	3 (2.7%)
All LVEF changes	n=2	n=2	4 (3.6%)

Data cut off 15 MAY 2026.
[1]Criteria for LVEF analysis based on criteria in the doxorubicin and liposomal doxorubicin labels.

EFFICACY

FIGURE 3. Waterfall Plot of Best Response from Baseline In Patients with SGC[1]

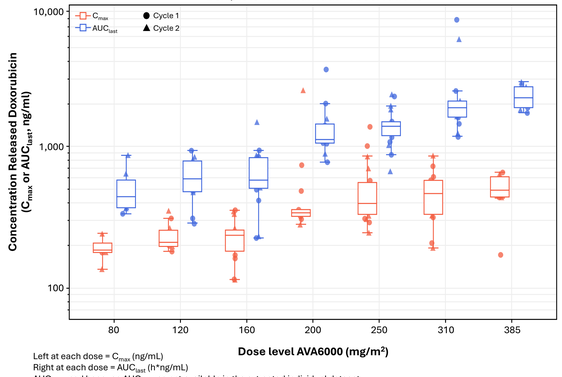


	All evaluable SGC patients N=38
Partial response (PR), n (%)[2]	4 (10.5)
Minor Response (MR), n (%)[3]	9 (23.7)
Stable Disease (SD), n (%)	22 (57.9)
Progressive Disease (PD), n (%)	3 (7.9)

Data cut off 15 MAY 2026.
[1]Patients with the diagnosis of salivary gland cancer were treated with at least 250 mg/m² (Phase 1a) or at 310 mg/m² (Phase 1b). Patients eligible for efficacy include those in both cohorts with at least 1 on-treatment scan to assess response.
[2] One pt with unconfirmed response (PR), this patients remains on therapy.
[3] Minor response is 10-29% shrinkage in SLD.

FIGURE 4. Dose Proportionality of Released Doxorubicin

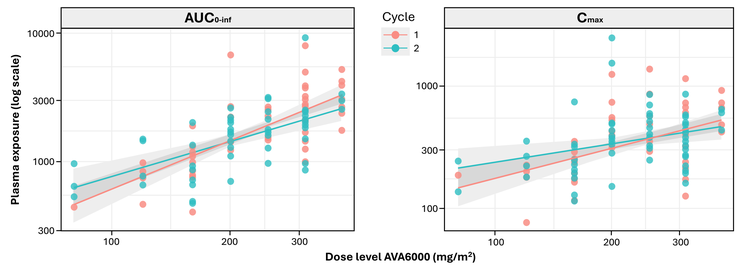
Doxorubicin: C_{max} and AUC_{last} on a common y-axis
Box plots with individual observations



Left at each dose = C_{max} (ng/mL)
Right at each dose = AUC_{last} (h*ng/mL)
AUC_{last} used because AUC_{inf} was not available in the extracted individual dataset.

- **Measurable concentrations of released doxorubicin were observed in the trial across all doses and cycles.** The PK profiles were characterized by a rapid distribution phase followed by slower elimination phase, consistent with the known pattern of disposition of conventional doxorubicin
- **Exposure increased approximately dose-proportionally over the range of doses tested,** as reflected here in the Geometric means of AUC and C_{max}. C_{max} concentrations remained suppressed as compared to C_{max} with dosing of conventional doxorubicin
- **Median T_{max} (not shown) indicates that systemic peak concentrations of released doxorubicin occurred shortly after the end of infusion,** confirming the rapid appearance of released doxorubicin in plasma
- **Elimination half-life values were broadly comparable across dose levels and cycles** suggesting linear clearance and time-independent pharmacokinetics

FIGURE 5. Dose Proportionality of Released Doxorubicin by Cycle



Regression analyses demonstrate that systemic exposure to released doxorubicin increased

- The slopes of the log-log regressions for AUC and C_{max} were close to unity and the 95 percent confidence intervals overlapped between cycles, confirming linear and time-independent pharmacokinetics
- No cycle-dependent accumulation or non-linearity was observed
- These data together indicate that AVA6000 provides a consistent and predictable release of doxorubicin after repeat administration

Preliminary Population PK Analysis compared with recent doxorubicin analysis demonstrates rationale for limited cardiac toxicity in the ongoing trial

- Higher clearance and the larger central volume of distribution for released doxorubicin following AVA6000 demonstrates that the active drug enters plasma gradually following FAP-mediated cleavage in the TME
- Slow appearance of released doxorubicin in the periphery eliminates the sharp systemic peaks typical of conventional i.v. dosing, resulting in markedly low cardiac exposure (Tables 2 and 3, Villalobos 2020)
- Combination of rapid elimination and extensive distribution volume produces lower plasma concentrations even following dosing of AVA6000 at a dose level ~4x the MTD of conventional doxorubicin (conventional doxorubicin Population PK model published [Kontny 2013])
- Consistent with this profile, essentially no cardiac toxicity is observed and minimal changes in LVEF following dosing are reported (Tables 2 and 3)

TABLE 4.
Preliminary Population PK Model Compared to Conventional Doxorubicin

	Released doxorubicin (from AVA6000) All dose levels	Conventional doxorubicin (75 mg/m²)	Fold Difference
Parameter[1]			
Clearance (L per hr)	157	47-56	~3x higher
Central Volume (L)	141	17-19	~7-8x higher
Peripheral Volume (L)	1170	672-2124	Comparable

FIGURE 6. Exposure Response Analysis of LVEF Changes with Released Doxorubicin in Quartile Distribution

Cumulative doxorubicin exposure by quartile analysis was compared to the maximum changes in the LVEF over the course of treatment

In this analysis, a clear relationship between increasing total exposure (cumulative AUC, panel A) to released doxorubicin and negative changes in LVEF was NOT observed

- Similarly, higher early exposure (AUC last Cycle 1, panel B) and maximum plasma concentration (C_{max}, Cycle 1, panel C) failed to demonstrate a trend in higher exposure/concentration and LVEF decreases
- Together, these data do not indicate a consistent exposure-response relationship for either cumulative exposure, early systemic exposure or peak exposure with respect to LVEF changes within the range evaluated

Methods:

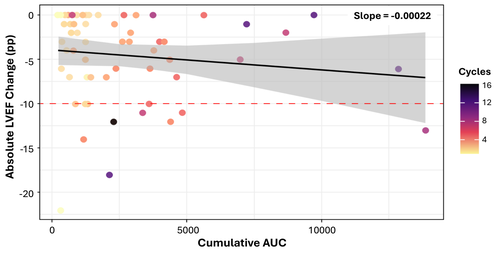
- Patients with complete PK exposure metrics and full LVEF analysis post-dosing were included in the integrated exposure response analysis (n=63) with a data cutoff of 28 Oct 2025. No imputation was applied to preserve analytical integrity
- Exposure-response analysis focused on linking cumulative total exposure, exposure per Cycle and peak concentration versus baseline-adjusted LVEF changes

FIGURE 7. Regression Analysis of LVEF Change Versus Cumulative AUC

The linear regression analysis using cumulative AUC as the predictor and absolute LVEF change as the continuous outcome did not indicate a statistically meaningful association

In this analysis, the modeled slope estimate was near zero and the explained variance was low, suggesting that cumulative doxorubicin exposure did not predict the magnitude of LVEF change within the evaluated exposure range (patients received up to the equivalent exposure of 550 mg/m² doxorubicin)

- Together, the regression analyses over the exposure range do not support the presence of an exposure-response relationship between cumulative doxorubicin exposure and LVEF reductions



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CONCLUSIONS

Faridoxorubicin (AVA6000) is safe and well-tolerated in both the Q3W and Q2W dosing regimens, with preliminary evidence of efficacy in patients with salivary gland cancers (SGC) with multiple confirmed responses observed in Ph Ia and Ib and patients still with ongoing treatment

- **Following faridoxorubicin (AVA6000) dosing, active doxorubicin is enzymatically released by FAP cleavage in the tumor microenvironment, and only a fraction of the active drug subsequently enters the systemic circulation, reaching other organs—including the heart—at delayed and lower concentrations. This is in direct contrast to conventional intravenous administration, which is known to deliver high concentrations of doxorubicin systemically from the outset**
- **Minimal LVEF changes and no severe cardiac toxicities were noted in the N=111 patients dosed to date with a subset of patients reaching the protocol-defined lifetime maximum exposure of 550 mg/m² and less than 4% of patients with clinically significant LVEF changes and no events of cardiomyopathy (of any grade) were observed**
- **The initial Population PK modeling demonstrates higher clearance and larger central volume of distribution for released doxorubicin with faridoxorubicin vs. conventional doxorubicin, demonstrating released doxorubicin enters plasma gradually following FAP-mediated cleavage in the TME, eliminating the sharp systemic peaks typical of conventional dosing**
- **Exposure-Response analysis found that there was not a meaningful relationship between the LVEF changes and released doxorubicin exposure, suggesting that the cardiac toxicity observed with conventional dosing of doxorubicin is not observed with released doxorubicin from faridoxorubicin and supporting removal of the lifetime maximum limit of dosing**