AVA6103 is a FAP-enabled pre|CISION® Peptide Drug Conjugate Delivering Sustained Release of Exatecan in the Tumor Microenvironment with Potent Antitumor Activity

Curtis Rink[1], Tom Clough[2], Ellen Watts[2], Folake Orafidiya[2], Marine Houée[2], Ruairidh Edwards[1], Sophie Brown[2], Victoria Juskaite[2], Vidicha Chunilal[2], Iva Zlatareva[2], Gezim Lahu[3], Karen Campbell[1], Dave Liebowitz[1], David Jones[2], Michelle Morrow[2], Francis Wilson[2]

[1]Avacta Therapeutics, Clinical Development, White City Imperial College Campus, London, W12 7RZ, [2]Avacta Therapeutics, Discovery, White City Imperial College Campus, London, W12 7RZ, [3]Quantitative Clinical Pharmacology, thinkQ2 AG, Baar, Switzerland

Abstract #5846

Introduction

- The **pre|CISION®** compound **AVA6103** is a **peptide drug conjugate** (PDC) comprising a peptide bound to the TOPI inhibitor **exatecan** by a linker that is specifically **cleaved by fibroblast activation protein-α (FAP)**, which is overexpressed by cancer associated **fibroblasts (CAFs)** in the TME of many solid tumors
- As FAP is selectively expressed by CAFs within tumors, with limited normal tissue expression, **exatecan is released in the TME**, minimizing exposure to healthy tissues, **improving the therapeutic window** and **maximizing efficacy** whilst **reducing adverse effects** compared to treatment with exatecan alone

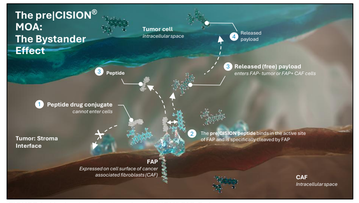


FIGURE 1. Mechanism of action of pre|CISION® FAP-Exd

pre|CISION® peptide drug conjugates offer key advantages over conventional ADC approaches:

1 Optimized Dosing of Exatecan
The maximum tolerated dose of FAP-EXd is significantly higher than that of conventional exatecan allowing greater tumor concentration

2 FAP-EXd is inert in the absence of FAP
FAP-EXd is completely inert unless FAP+ CAFs are present to cleave the peptide and release exatecan

3 FAP-EXd optimizes sustained tumor release
We observe high tumor levels of both PDC and released exatecan over five days, whereas conventional exatecan disappears from circulation and the tumor within hours

FIGURE 2. The sustained release mechanism of pre|CISION® FAP-Exd

Traditional ADC CHALLENGES	pre|CISION® PDC OPPORTUNITIES
Payload release: Non-specific protease cleavable linkers result in **organ toxicity** (e.g. pneumonitis, hepatitis)	**Tumor-specific release** by FAP with no organ toxicity (e.g. no cardiac toxicity, no pneumonitis or hepatitis)
Tumor penetration: **Slow uptake kinetics** (>24 hours) into tumor cells for payload to be released intracellularly	**Payload release observed in minutes** with T_{max} in the tumor less than 1 hour
Bystander effect: **Complex bystander effect** requires antibody intracellular payload release with CAFs as a resistance mechanism	PDC have **simple extracellular release** resulting in kill of FAP+ and FAP- cells
Addressable market opportunity: Market opportunity for each ADC is limited by **single antigen expression levels**	**FAP expression in 90% of all solid tumors** with the bystander effect active and release demonstrated in levels to 1+ by IHC

FIGURE 3. The common challenges with traditional ADCs, and the key opportunities when using pre|CISION® PDCs

The pre|CISION® Bystander Effect is Mediated by the Spatial Organization of FAP Expression in Tumors

See the other Avacta poster at this meeting:

Characterization and translational development of novel pre|CISION® technology compounds delivering complementary dual payloads to the tumor microenvironment following FAP cleavage

(Abstract #5656, Section 10, Board 26)
Tuesday, April 21, 2026, 2-5pm

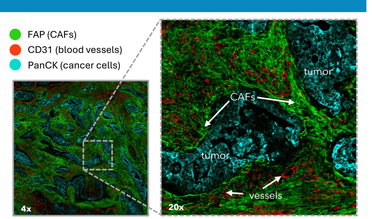


FIGURE 4. The bystander effect of the pre|CISION® platform warhead delivery: The close proximity of **blood vessels** (●), FAP+ **CAFs** (●), and **cancer cells** (●), allows pre|CISION® compounds to be readily delivered, cleaved, and taken up by neighboring cancer cells

AVA6103 is Uniquely Cleaved by FAP to Release the Cytotoxic Warhead Exatecan

- AVA6103 leverages pre|CISION® technology to **extend the half-life** of released exatecan to cover the entire cell cycle
- **Increase tumor exposure to exatecan** by adjusting the release kinetics via modification of the **capping group and linker** (alter the k_{cat}/K_M of the conjugate)
- Slower exatecan release and extended plasma PK of the conjugate will result in a **sustained release mechanism**, lower plasma levels of exatecan and **reduced systemic exposure**

Capping group
Designed to hold the PDC in the tumor (vs. plasma) via potent binding in the FAP active site

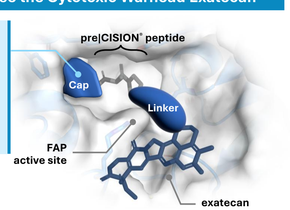


Figure 5: Schematic showing AVA6103 docked into the FAP active site, containing a capping group, *D*-Ala-Pro pre|CISION® dipeptide unit, self-immolative linker and exatecan. After cleavage of the pre|CISION® dipeptide by FAP, the linker undergoes self-immolation and free exatecan is released. AVA6103 docked into the FAP active site

AVA6103 Demonstrates FAP Enzymatic Selectivity Across a Panel of DASH Subfamily Members and PREP

- AVA6103 was incubated with a **panel of DASH** (dipeptidyl peptidase IV activity and/or structure homologous) **subfamily enzymes** (dipeptidyl peptidase 2 [DPP2], DPP4, DPP8, DPP9) and prolyl endopeptidase **(PREP)**
- **Increased levels of exatecan were observed only in the presence of FAP**, whereas PREP and all tested DPP enzymes showed exatecan levels comparable to the no-enzyme controls
- These data demonstrate that the D-Ala–L-Pro dipeptide in **AVA6103 is highly selective for FAP over other post-proline peptidases**

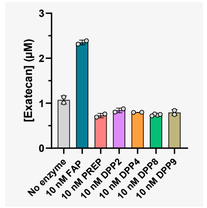
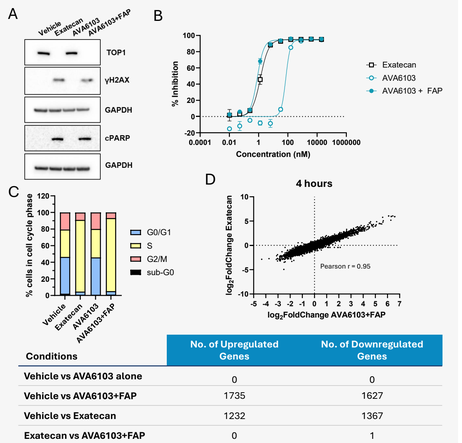


FIGURE 6; Table 1. Exatecan concentrations were measured following 30 min incubation of AVA6103 ±10nM of each enzyme. The amount of exatecan present in each sample after incubation was determined by LC-MS. Data expressed as mean ± SD performed in duplicates or quadruplicate for DPP8.

Conditions	Released Exatecan Concentration (μM)
No Enzyme	1.07
FAP	2.35
PREP	0.73
DPP2	0.84
DPP4	0.80
DPP8	0.79
DPP9	0.74

AVA6103 Demonstrates Expected TOP1i Mechanism of Action only in the Presence of FAP

- To validate the **mechanism of action of AVA6103**, **DU145 prostate cancer** cells were treated with AVA6103 in the presence or absence of recombinant FAP, or with free exatecan
- AVA6103 alone had minimal effect on TOP1, DNA-damage (γH2AX) and apoptosis (cleaved PARP) markers. **In the presence of FAP**, however, **AVA6103 decreased TOP1 levels** and induced robust **increases in γH2AX and cleaved PARP**, identical to the effects observed with free exatecan
- Flow cytometry analysis showed AVA6103 induced **FAP-dependent S-phase arrest** and **tumor cell killing**
- In **NCI-H82 SCLC** cells, changes in **transcriptional signatures** following AVA6103 treatment **aligned with those seen with exatecan treatment**
- These FAP-dependent changes are consistent with activation of **Topoisomerase I inhibitor–mediated DNA damage response** (DDR) and **programmed cell death** pathways



Conditions	No. of Upregulated Genes	No. of Downregulated Genes
Vehicle vs AVA6103 alone	0	0
Vehicle vs AVA6103+FAP	1735	1627
Vehicle vs Exatecan	1232	1367
Exatecan vs AVA6103+FAP	0	1

FIGURE 7. A). Western blot analysis after treatment of DU145 cell line with 300nM AVA6103 (±10nM hFAP) or 300nM free Exatecan for 24hr. **B).** DU145 cells were treated for 72h with varying concentrations of AVA6103 (±10nM hFAP) and Exatecan. Cell death was measured by CTG as % luminescence reduction vs. vehicle control. **C).** Cell cycle analysis after treatment of DU145 cell line with 5nM AVA6103 (±10nM hFAP) or 5nM free Exatecan for 24hr. **D).** Scatter plot comparing log2 fold changes of shared differentially expressed genes (relative to vehicle) when NCI-H82 cells were treated with 100nM AVA6103 (±10nM hFAP) or 100nM exatecan for 4 hours. Each point represents a gene. The strong correlation (Pearson *r* = 0.95) indicates highly similar transcriptional responses between the two treatments. **TABLE 2.** Number of significantly differentially expressed genes ($p < 0.05$) for the comparisons shown.

AVA6103 Demonstrates Tumor Growth Inhibition and Complete Regressions Superior to Exatecan in Multiple Efficacy Studies

- In a series of **efficacy studies**, mice were dosed subcutaneously with **AVA6103 or exatecan** at maximum tolerated dose (MTD) for all studies
- All PDX here have previously shown FAP **expression on murine stromal fibroblasts**
- **Gastric #1** – 3/4 mice exhibited complete responses
- **Gastric #2** – 3/3 mice exhibited stable disease
- **Colorectal #1** – 3/3 mice exhibited partial responses
- **Colorectal #2** – 3/3 mice exhibited partial responses
- **Pancreatic #1** – 2/3 mice exhibited complete responses
- **Pancreatic #2** – 3/3 mice exhibited partial responses
- **SCLC** – 3/3 mice exhibited complete responses
- AVA6103 demonstrated superior efficacy to exatecan with greater TGI and sustained tumor regressions even after treatment cessation. Greater reduction in tumor volumes were also noted with AVA6103, some of which were >90%. In these studies, AVA6103 was well tolerated, where any minimal weight loss recovered to normal levels following treatment cessation

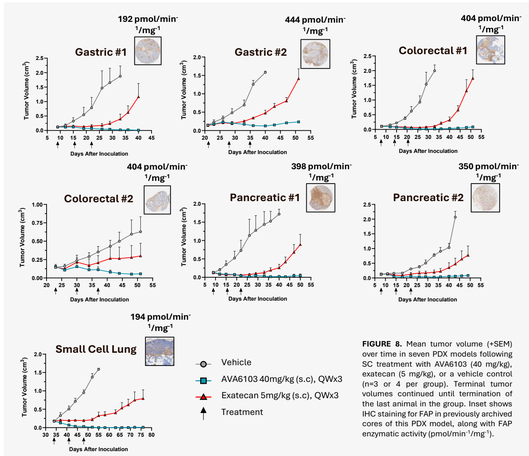


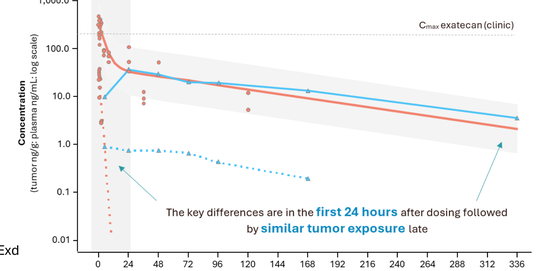
FIGURE 8. Mean tumor volume (+SEM) over time in seven PDX models following SC treatment with AVA6103 (40 mg/kg), exatecan (5 mg/kg), or a vehicle control (n=3 or 4 per group). Terminal tumor volumes continued until termination of the last animal in the group. Inset shows IHC staining for FAP in previously archived cores of this PDX model, along with FAP enzymatic activity (pmol/min⁻¹/mg⁻¹).

pre|CISION® Delivery Demonstrates Significantly Higher Tumor Selectivity Index vs. Cleavable ADC (T-Dxd, Enhertu®)

- **Tumor Selectivity Index (TSI)** Ratio of the $AUC_{0.083h\text{-}14d}$ of released payload in the tumor vs. plasma
- TSI is a straightforward, quantitative measure of how **payload preferentially distributes to tumor tissue** relative to systemic circulation
- **pre|CISION® exatecan** delivery is associated with **significantly higher TSI compared to Enhertu®** in antigen-high models

TSI_{max}: $AUC_{0.083h\text{-}14d}$ [tumor/plasma]

Enhertu | **47** vs. **126** | FAP-Exd



Rapid Tumor Penetration
TUMOR T_{max}: MINUTES vs. DAY
The **tumor C_{max}** with pre|CISION® occurs **within minutes of dosing** vs. the Enhertu tumor C_{max} occurs at **24 hours**[6]
CAFs begin releasing exatecan on contact

C_{max} of Free Payload in Tumor
TUMOR C_{max}: >ONE LOG HIGHER
The C_{max} of pre|CISION®-released exatecan in the tumor is **more than 11x higher** than the C_{max} of Enhertu-released deruxtecan (822 vs. 74.2 nmol/L)[6,9]

Tumor Selectivity Index (TSI)*
TSI: NEARLY 3X INCREASE
The **TSI is nearly 3x increased** with pre|CISION® exatecan vs. ADC (Enhertu®) deruxtecan[6] (126 vs. 47)
The **TME functions as a payload reservoir** as plasma exposure declines

FIGURE 9 (Above). Shaded ribbons represent the ± 0.9 SD (≈68%); Reference lines: user-defined thresholds of relative concentrations based on internal data or published data. C_{max} of exatecan in humans in *Esteva, et al. (2003) A Phase II Study of Intravenous Exatecan Mesylate (DX-8951f) Administered Daily for 5 Days Every 3 Weeks to Patients with Metastatic Breast Carcinoma. Cancer 98(5):900-7.* Modelled nonclinical data taken from *Vasalou C, et al. Quantitative evaluation of trastuzumab deruxtecan pharmacokinetics and pharmacodynamics in mouse models of varying degrees of HER2 expression. CPT Pharmacometrics Syst Pharmacol. 2024 (6):994*1005. *doi: 10.1002/psp4.13133.*
FIGURE 10 (Left). Payload Delivery with pre|CISION® vs. cleavable ADC (T-Dxd, Enhertu®).
TSI is defined as the ratio of tumor to plasma exposure ($AUC_{0.083h\text{-}14d}$[tumor/plasma]), and provides a straightforward, quantitative measure of how preferentially a compound distributes to tumor tissue relative to systemic circulation.

Tempus AI's LENS Database Identifies a FAP-SLFN11 Correlation Ahead of Clinical Dosing of AVA6103

- To evaluate the translational relevance of **SLFN11 in the context of FAP-targeted delivery**, RNA expression data were extracted from the **Tempus LENS database** across multiple solid tumor types
- **FAP+ / SLFN11^{High} (teal)** expression identifies patient populations with an **enhanced likelihood of responding to AVA6103** and other pre|CISION® enabled DNA damage agents, **improving the probability of clinical benefit**
- Additionally, **FAP or SLFN11 expression does not significantly change** between pre- and post- TOP1i treated samples, supporting the use of **pre|CISION® medicines as second- or third-line therapy** in pretreated patients
- A total of **six indications** were selected in which to conduct a **first-in-human (FIH), Phase 1** open-label, multicenter **dose escalation study investigating AVA6103,** which **began treating patients in March 2026**

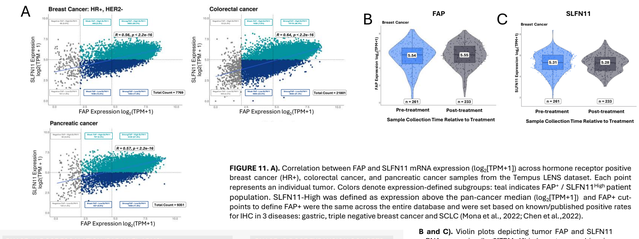
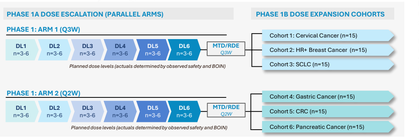


FIGURE 11. A). Correlation between FAP and SLFN11 mRNA expression (log_2[TPM+1]) across hormone receptor positive breast cancer (HR+), colorectal cancer, and pancreatic cancer samples from the Tempus LENS dataset. Each point represents an individual tumor. Colors denote expression-defined subgroups: teal indicates FAP$^+$ / SLFN11^{High} patient population. SLFN11-High was defined as expression above the pan-cancer median (log_2[TPM+1]) and FAP+ cut-points to define FAP+ were the same across the entire database and were set based on known/published positive rates for IHC in 3 diseases: gastric, triple negative breast cancer and SCLC (Mona et al., 2022; Chen et al.,2022).



PHASE 1 DOSE ESCALATION:

Patient population
FAP-positive cancers:
- SCLC
- Pancreatic (PDAC)
- Gastric (GC/GEJ)
- Cervical and Vulvar
- Colorectal (CRC)
- HR+ Br Cancer

Ph Ia Statistics implement the BOIN algorithm design to **identify optimal dose** (MTD/RDE)

Using the Tempus database, expression of **FAP and SLFN11** were observed for multiple tumor types

Primary Endpoints
- Safety
- Selection of RDE

Project Optimus
Cohort backfill to optimize patient numbers with biopsies to study tumor and plasma exposure

Secondary Endpoints
- Efficacy (ORR, PFS, OS, DCR, DoR)
- Efficacy by FAP level in tumor
- PK in plasma and tumor of released exatecan and PDC (FAP-Exd)

CONCLUSIONS

- **AVA6103 is the second pre|CISION® clinical candidate** and is based on the novel sustained release mechanism that provides for **prolonged release of payload directly in the tumor**, minimizing systemic exposure via a **specific cleavage of the peptide by Fibroblast Activation Protein-α (FAP)**
- AVA6103 shows **robust and durable complete responses** in a number of PDX models with expression of **FAP only on invading murine fibroblasts** of varying levels of expression
- Topo I payload delivery studies comparing exatecan delivery from AVA6103 and deruxtecan delivery from Enhertu® demonstrate **three key differences in the PK** of the payload: **1). more rapid tumor penetration** and payload release with AVA6103; **2). tumor Cmax of more than one log higher with AVA6103 v Enhertu®**; and **3). TSI of 3X higher with AVA6103 v Enhertu®**
- These preclinical data suggest the sustained release mechanism has **optimized payload delivery** with a **high intratumoral concentration** and prolonged exposure of released payload in the tumor, coupled with **limited systemic exposure** of the released payload
- **The pre|CISION® peptide is cleaved only in the presence of membrane-bound FAP** expressed on the cell surface of cancer associated fibroblasts (CAFs), and active exatecan is released in the extracellular space. This mechanism **masks the toxic effects** of a payload in healthy tissues and **mediates specific delivery of exatecan to the tumor**
- AVA6103 is being evaluated in the **FOCUS-01 Phase 1 trial** (FAP-Exd in Oncologic Cancers with Unmet needS), with **first dosing in March 2026**. The trial is being conducted in six indications, including SCLC, PDAC, Gastric/GEJ, Cervical and Vulvar, CRC, and HR+ BrCa

References

1) Tsvetkova et al. A Phase I trial of AVA6000, a fibroblast Activation Protein (FAP)-released, tumor microenvironment (TME)-targeted doxorubicin peptide drug conjugate (PDC) in patients with FAP-positive solid tumors. The European Society of Medical Oncology Annual Meeting 2024.
2) Banerji et al. A Phase I trial of AVA6000, a Fibroblast Activation Protein (FAP)-released and tumor microenvironment (TME)-targeted doxorubicin peptide drug conjugate in patients with FAP-positive solid tumors. The American Association for Cancer Research Annual Meeting 2024.
3) Tap et al. A Phase I trial of FAP-Dox (AVA6000, a fibroblast activation protein(FAP)-released and tumor microenvironment (TME)-targeted doxorubicin peptide drug conjugate in patients with FAP-positive solid tumors. The European Society of Medical Oncology Annual Meeting 2025.
4) Rink et al. The novel peptide drug conjugate AVA6103 is a FAP-enabled pre|CISION® medicine which targets exatecan, a topoisomerase I inhibitor, to the tumor microenvironment following FAP cleavage. The American Association for Cancer Research Annual Meeting 2025
5) Esteva et al. A Phase II study of intravenous exatecan mesylate (DX-8951f) administered daily for 5 days every 3 weeks to patients with metastatic breast carcinoma. Cancer. 2003 Sep 1;98(5):900-7. doi: 10.1002/cncr.11587.
6) Vasalou et al. Quantitative evaluation of trastuzumab deruxtecan pharmacokinetics and pharmacodynamics in mouse models of varying degrees of HER2 expression. CPT Pharmacometrics Syst Pharmacol. 2024 (6):994*1005. doi: 10.1002/psp4.13133.
7) Chen et al. Expression of fibroblast activation protein in lung cancer and its correlation with tumor glucose metabolism and histopathology. Eur J Nucl Med Mol Imaging 49, 2938–2948 (2022). doi.org/10.1007/s00259-022-05754-4
8) Mona et al. Correlation of 68Ga-FAPI-46 PET Biodistribution with FAP Expression by Immunohistochemistry in Patients with Solid Cancers: Interim Analysis of a Prospective Translational Exploratory Study. J Nucl Med. 2022 Jul;63(7):1021-1026. doi: 10.2967/jnumed.121.262426.
9) Bussing et al. Quantitative Evaluation of the Effect of Antigen Expression Level on Antibody-Drug Conjugate Exposure in Solid Tumor. AAPSJ. 2021 Apr 15;23(3):56.doi: 10.1208/s12248-021-00584-y

Acknowledgements

The investigators and the team at Avacta would like to thank the patients and their families for participating in the trial; Synthesis MedChem who performed chemical synthesis; Sygnature Discovery who performed chemical synthesis, kinetics assays, bioanalysis and computational modelling; GENEWIZ who performed the RNAseq; Concept Life Sciences who performed multiplex-immunofluorescence; Experimental Pharmacology & Oncology Berlin who performed tumor uptake, in vivo efficacy studies and provided archive PDX data.

Presented at the American Association for Cancer Research Annual Meeting, April 2026 San Diego, CA USA