

## Abstract 3155

ARX517, a next generation anti-PSMA antibody drug conjugate (ADC), demonstrates notable stability and pharmacokinetic (PK) profile in the ARX517 phase 1 clinical trial (APEX-01)

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## Background

ARX517 is a next-generation, anti-PSMA, ADC conjugated to AS269 (pAF-269; a potent tubulin inhibitor), at a drug-to-antibody ratio (DAR) of two. ARX517 was designed to address the instability issues encountered by previous PSMA-targeted ADCs with three key components: a non-cleavable PEG linker, a non-cell permeable payload, and stable oxime conjugation chemistry. The site-specific conjugation of AS269 to the mAb is enabled using proprietary synthetic amino acid incorporation. This ADC design minimizes premature payload release and off-target toxicity.

## Methods

21 patients received ARX517 at doses ranging from 0.32 to 2.4 mg/kg across 7 cohorts. ARX517 was administered by intravenous infusion q3w. Patient serum samples were collected at fixed time points and evaluated in validated Total Antibody (TA; sum of deconjugated antibody and conjugated antibody), ADC (conjugated antibody with a DAR of 1 or 2), and payload pAF-AS269 assays. The lower limit of quantitation for the TA, ADC, and pAF-AS269 assays were 62.5 ng/mL, 7.8 ng/mL, and 0.02 ng/mL, respectively. PK parameters were determined using noncompartmental analysis based on serum concentrations of TA, ADC, and pAF-AS269.

## Results

ARX517 exhibited virtually overlapping TA and ADC PK concentration-time curves at all dose levels tested, indicating strong stability of the ADC with minimal premature payload release. A long ADC terminal half-life of ~6–10 days was observed at doses  $\geq$  1.4 mg/kg, thereby maximizing drug exposure over a dosing cycle of 3 weeks. Low concentrations of pAF-AS269 (approximately 0.02–0.2 ng/mL) were observed at all dose levels and appeared slowly in the circulation, with C<sub>max</sub> observed approximately 7 days after administration. This is in contrast to other ADCs that typically exhibit payload C<sub>max</sub> hours to days after dosing.

## Conclusions

ARX517 is the first anti-PSMA ADC tested in the clinic to demonstrate notable stability and a long terminal half-life. These attributes enable continuous drug delivery throughout the dosing cycle to potentially improve efficacy and minimize toxicity due to premature payload release, indicating a clear and favorable therapeutic index.

## Clinical trial identification

NCT04662580

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