Comparison of Pharmacokinetics of DSTA4637S, a novel THIOMAB™ Antibody-Antibiotic Conjugate, in Patients with *Staphylococcus aureus* Bacteremia Receiving Standard-of-Care Antibiotics with Pharmacokinetics in Healthy Volunteers

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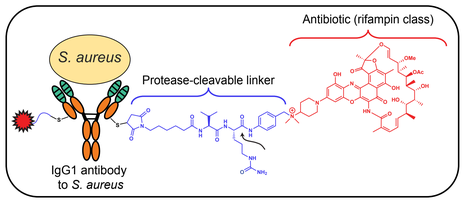
Introduction

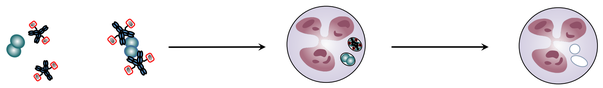
***Staphylococcus aureus* bacteremia** is challenging to cure with standard-of-care antibiotics, leading to complications such as osteomyelitis and endocarditis. One proposed mechanism by which *S. aureus* escapes antibiotic treatment is the ability to survive within host phagocytic cells.

DSTA4637S (TAC)

- A novel THIOMAB™ Antibody-Antibiotic Conjugate designed to kill intracellular *S. aureus*



- Mechanism of Action



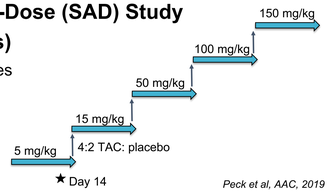
1 TAC binds free *S. aureus*

2 Phagocytosis into lysosome, linker cleavage

3 Free antibiotic kills intracellular *S. aureus*

Phase 1 Single Ascending-Dose (SAD) Study in Healthy Volunteers (HVs)

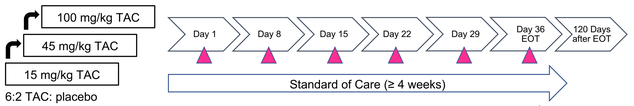
- Single-center trial in United States
- Objectives: Safety and PK
- N = 30 (20 TAC: 10 placebo)



Peck et al, AAC, 2019

Phase 1 Multiple Ascending-Dose (MAD) Study in Patients with complicated *S. aureus* Bacteremia

- Global multi-center trial in United States, Spain, and South Korea (17 sites)
- Objectives: Safety and PK
- N = 25 (19 TAC: 6 Placebo)



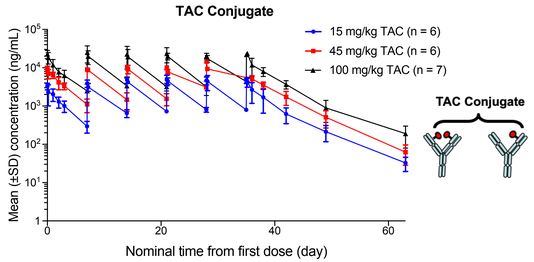
TAC Dose (mg/kg)	Number of Patients Receiving Dose					
	D1	D8	D15	D22	D29	D36
100	7	6	5	4	2	1
45	6	4	3	3	1	0
15	6	4	3	3	2	2

Results

Pharmacokinetics of TAC in patients with *S. aureus* bacteremia (SAB)

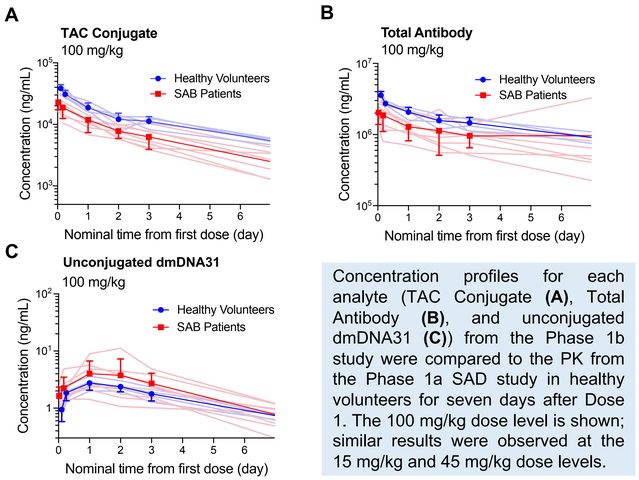
A

Analyte	Analyte Measurement Details
TAC Conjugate (as antibody-conjugated dmDNA31)	Total concentration of dmDNA31 conjugated to the antibody
Total Antibody	Total concentration of anti-*S. aureus* antibody, including all drug-to-antibody ratios
Unconjugated dmDNA31	Concentration of dmDNA31 not conjugated to anti-*S. aureus* antibody



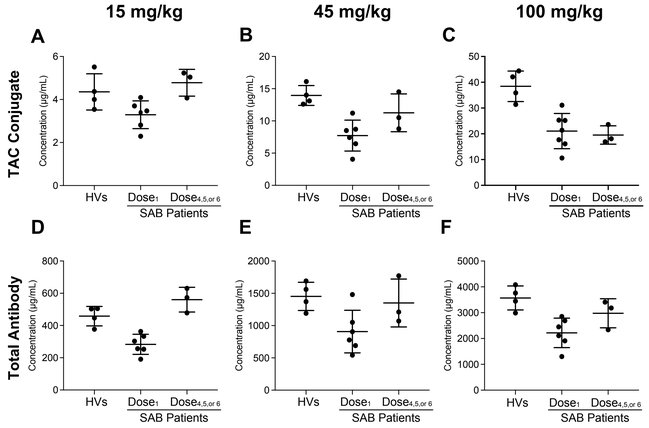
Patients with SAB received 1–6 doses of TAC in addition to standard-of-care antibiotics. Systemic exposure was characterized for three analytes **(A):** TAC Conjugate **(B)**, TAC Total Antibody **(C)**, and unconjugated dmDNA31 **(D)** for 155 days.

PK of TAC Conjugate and Total Antibody is reduced immediately post-TAC administration in SAB patients



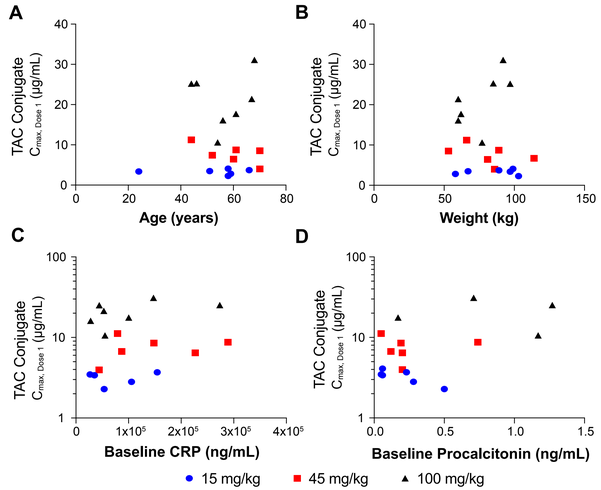
Concentration profiles for each analyte (TAC Conjugate **(A)**, Total Antibody **(B)**, and unconjugated dmDNA31 **(C)**) from the Phase 1b study were compared to the PK from the Phase 1a SAD study in healthy volunteers for seven days after Dose 1. The 100 mg/kg dose level is shown; similar results were observed at the 15 mg/kg and 45 mg/kg dose levels.

The C_{max} of TAC Conjugate and Total Antibody is reduced in SAB patients throughout study duration



C_{max} values of TAC Conjugate **(A-C)** and Total Antibody **(D-F)** were compared after Dose 1 in the SAD study in healthy volunteers and in patients with SAB, and from the last dose from patients with SAB who received 4-6 doses of 15 mg/kg **(A, D)**, 45 mg/kg **(B, E)**, and 100 mg/kg **(C, F)** TAC.

Drivers of reduced TAC exposure in patients with SAB remain unclear



TAC Conjugate (the analyte expected to correlate with efficacy) was plotted against demographic factors (age, weight, sex), clinical status (infection site), adverse events (infusion-related reactions), and exploratory biomarkers (CRP, procalcitonin, inflammatory cytokines (IL-8, IL-10, MCP-1)). Similar conclusions were observed for Cmax, Dose 1 and AUC0-7. Correlations between Cmax, Dose 1 and age **(A)**, weight **(B)**, CRP **(C)**, and procalcitonin **(D)**.

Conclusions

- TAC Conjugate and Total Antibody systemic exposures were lower in patients with *S. aureus* bacteremia compared to healthy volunteers, where C_{max} was reduced 27%–51% and $AUC_{0\text{-}7}$ was reduced 38%–62%
- Unconjugated dmDNA31 concentration levels were low systemically and did not differ between healthy volunteers and patients
- Clearance and volume of distribution may contribute to lower systemic exposures in patients and warrant further exploration
- Additional future studies will explore other factors leading to reduced exposures in patients, including non-specific organ uptake and target-mediated clearance

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