**RESULTS**

- Addition of ETX2514 to SUL at these optimized dosing regimens shifts the SUL MIC₉₀ from a resistant value of 128 mg/L to 4 mg/L, restoring SUL sensitivity against ABC (Figure 2).
- Similar results were predicted using ELF exposures (data not shown).

**METHODS**

- A published SUL PKP model was leveraged for the present analyses, with qualification performed using all Phase 1 and Phase 2 plasma data (3).
- Two-compartment disposition: linear elimination through renal (CL) and nonrenal (CLₚ) clearance components.
- IV estimated for all structural parameters.
- Renal function is a significant covariate for SUL CL.

**OBJECTIVES**

- To construct a PK model for plasma ETX2514 disposition data using from Phase 1 single/multiple-ascending dose (SAD/MAD) and renal impairment (RI) studies.
- To qualify the developed model using data from a Phase 1 lungen penetration (ELF) study and a Phase 2 study in patients with complicated urinary tract infections (CUT).
- To conduct joint PK-PD TA analyses of SUL combined with ETX2514 in support of phase 3 dose regimens in patients with varying renal function.

**RESULTS**

- Joint ETX2514 SUL TA was determined as the combination of achieving the SUL MIC₉₀ for the nominal SUL MIC or ETX2514 targets at the potentiated SUL MIC.
- A free-drug 24-hour AUC:MIC (unbound fraction, 0.62), using the nominal or potentiated SUL MIC (2).
- ETX2514 free-drug 24-hour AUC:MIC ratio targets of 10 (stasis) and 30 (1-log₁₀ kill) were employed (unbound fraction, 0.90) using the SUL MIC resulting from concentration with a constant 4 mg/L of ETX2514 (potentiated SUL MIC) (4, 5).
- A 50% increase in ETX2514 SUL dose is required in cases of augmented renal clearance.
- Similar results were observed for Phase 1 studies (data not shown).

**CONCLUSIONS**

- The developed ETX2514 and literature SUL PKP models provide accurate description of observed plasma PK data.
- Joint PK-PD TA for ETX2514/SUL was excellent, shifting the SUL MIC₉₀ for ABC from 128 mg/L to 4 mg/L (proposed susceptibility breakpoint).
- Planned Phase 3 ETX2514 SUL dosing regimens for treatment of ABC infections maximize PK-PD TA across a broad range of renal function, including augmented renal clearance.