Table 1: MK-1654 PN001 Interim PK NCA Summary for Adults

Panel	Dose (mg)	Route	T_{last} (day)	C_{max} (µg/mL)	$AUC_{0-\infty}$ (day*µg/mL)	AUC_{0-90d} (day*µg/mL)	T_{max} (day)	$t_{½}$ (day)
A	100	IM	150	11.1 (18.1)	1,170 (16.3)	644 (12.3)	6.00 (2.00 - 13.0)	77.6 (16.4)
B	300	IM	150	31.2 (11.6)	3,670 (18.6)	1,910 (12.8)	9.50 (4.00 - 27.0)	82.4 (22.5)
C	300	IV	120	107 (12.3)	5,190 (19.2)	2,750 (13.2)	0.167 (0.104 - 0.167)	85.1 (25.8)
D	1000	IV	90	326 (18.7)	14400 (49.8)	8,080 (29.0)	0.167 (0.104 - 0.333)	76.8 (53.7)
E	3000	IV	90	1050 (15.8)	42,100 (29.0)	25,500 (22.0)	0.167 (0.104 - 0.167)	69.5 (20.0)

Disclosures. **B. Maas**, Merck: Employee and Shareholder, Salary and stock options. **A. Aliprantis**, Merck: Employee and Shareholder, Salary and stock options. **D. Wolford**, Merck: Employee and Shareholder, Salary and stock options. **G. Fayad**, Merck: Employee and Shareholder, Salary and stock options. **K. Vora**, Merck: Employee, Salary. **D. Geng**, Merck: Employee and Shareholder, Salary and stock options. **H. Ma**, Merck: Employee and Shareholder, Salary and stock options. **L. Caro**, Merck: Employee and Shareholder, Salary and stock options.

1385. Efficacy of Ceftazidime–Avibactam in Combination with Aztreonam (COMBINE): Solutions for Metallo-β-Lactamase Producing-Enterobacteriaceae (MBL)

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Background. Novel antibiotics will not be available to combat the threat of MBLs until 2021. One strategy to overcome MBLs is to combine CAZ-AVI + ATM. ATM is not hydrolysed by MBLs and AVI offers protection for ATM and CAZ vs. ESBLs and AmpCs. The combination also offers a theoretical advantage to inactivating multiple PBPs by using dual β-lactam therapy. Our objective was to define optimal dosing profiles for clinical use of ATM to add to CAZ-AVI in the hollow fiber infection model (HFIM).

Methods. *E. coli* ARLG-1013 (bla_{NDM-1}, bla_{CTX-M}, bla_{CMY}, bla_{TEM}) and *K. pneumoniae* ARLG-1002 (bla_{NDM-1}, $bla_{CTXM-15}$, bla_{DHA}, bla_{SHV}, bla_{TEM}) were studied at a 7.5 $\log_{10}$ CFU/mL in the HFIM. Human dosing regimens of CAZ-AVI 2 g/0.5 g q8h (2 hours infusion) and ATM 2 g q8h (2 hours infusion) were simulated in alone and in combination. Continuous infusion (CI) regimens of CAZ-AVI 6 g/1.5 g per day CI + ATM 6 g/day CI and q8h regimens were given simultaneously and sequentially (ATM given 2 hours after CAZ-AVI). Resistant subpopulations were profiled on single (ATM), double (CAZ/AVI) and triple (ATM/CAZ/AVI) drug plates containing 2/2/4, 8/8/4, or 32/32/4 mg/L over 7 days.

Results. Against *E. coli* ARLG-1013, ATM alone mirrored growth control (+3.14 at 168 hours) (All units Log_{10} CFU/mL change vs. baseline). CAZ-AVI alone showed some intrinsic activity (+1.19 at 168 hours). CAZ-AVI 2g/0.5g q8h (2 hours infusion) + ATM 2g q8h (2 hours infusion) given sequentially resulted regrowth and stasis (+0.34 at 168 hours) vs. the simultaneous combination resulted initial bactericidal activity (-3.53 killing within 28 hours) which regrew at (–0.90 at 168 hours). All CI regimens were effective. CAZ-AVI 6g/1.5g per day CI + ATM 6 g/day CI resulted in dramatic killing (up to -5.78 killing within 50 hours) which was sustained (up to -3.90 killing at 168 hours). Comparing the infusion time of CAZ/AVI + ATM on bacterial killing: CI + CI > 2 hours + 2 hours > 30 minutes + 30 minutes. CI + CI resulted in complete suppression of resistance over 7 days. Against *K. pneumoniae* ARLG-1002, CAZ/AVI (CI) + ATM (CI) resulted in early synergy (>5.0 log killing within 24 hours) and suppression of resistance for more than 168 hours.

Conclusion. The combination of CAZ-AVI + ATM was highly synergistic and suppressed resistance against MBL Enterobacteriaceae in HFIM. ATM efficacy in combination was driven by %*T* > MIC. A Phase I study will assess safety to provide patients a critically important solution against "untreatable" Gram negatives.

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1386. Efficacy of Repeat Dosing of Oral Fosfomycin in a Dynamic Bladder Infection *In Vitro* Model

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Background. Oral fosfomycin is indicated for uncomplicated urinary tract infections with activity against MDR-uropathogens. Despite off-label use of giving three doses every 2–3 days, limited supporting data are available. We performed pharmacodynamic profiling using a dynamic bladder infection *in vitro* model to assess adequacy of repeat doses of fosfomycin.

Methods. A bladder infection *in vitro* model simulating urinary fosfomycin concentrations after 3 g (equiv.) oral doses was used with Mueller–Hinton broth (MHB) with 25 mg/L glucose-6-phosphate. Fosfomycin exposures were validated by LC–MS/MS measurements. Pharmacodynamic response of 16 clinical Enterobacteriaceae isolates were examined (eight *E. coli*, four *E. cloacae*, four *K. pneumoniae*; agar dilution MIC 0.25–64 mg/L) following three doses of fosfomycin given every 72, 48 or 24 hours, compared with single dose therapy. Pathogen kill and resistance was assessed by quantitative cultures on drug-free and fosfomycin-containing Mueller–Hinton agar (MHA +64 mg/L, +512 mg/L).

Results. Fosfomycin exposure following single and multiple doses were accurately reproduced (mean deviation from target 5.0 ± 3.4%, max 11.8%) with minimal variability (mean relative SD 2.7 ± 1.7%, max 8.8%). Fosfomycin high-level heteroresistance was detected prior to drug exposure in 8/16 isolates (proportion 0.00002–0.001% of total population). All isolates with high-level heteroresistance regrew following single dose fosfomycin. Following three doses given every 72 hours, one additional *K. pneumoniae* isolate was killed. All other isolates regrew with amplification of HLR subpopulation (median proportion: 71.4%, IQR 57.5–100%). Despite dosing 48 and 24 hourly, the same isolates regrew, although HLR subpopulation amplification was reduced (48 hours dosing: 32.0%, IQR 0.005–83.3%; 24 hours dosing: 0.3%, IQR 0.0004–81.3%).

Conclusion. Dynamic *in vitro* modeling of multiple doses of oral fosfomycin fails to additionally suppress regrowth in the majority of isolates compared with single dose therapy. Baseline high-level heteroresistance is an important predictor for regrowth. These results suggest that giving multiple doses of fosfomycin is not necessarily better than standard single dose therapy. Earlier timing of repeat doses may help suppress the emergence of resistance.

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1387. Phase I Study to Evaluate the Safety and Pharmacokinetics (PK) of Single and Multiple Ascending Doses (SAD/MAD) of Intravenous (IV) Minocycline in Healthy Adult Subjects

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Background. Carbapenem-resistant *Acinetobacter baumannii* infections are defined by the WHO as a critical threat. IV minocycline is approved in the United States for treatment of *Acinetobacter* infections at doses up to 200 mg BID. This study investigated safety and PK of single and multiple doses of IV minocycline, including doses higher than approved in the United States.

Methods. This was a randomized, double blind, placebo-controlled, SAD/MAD study of 6 doses (100–600 mg) of IV minocycline. Healthy adult subjects received a single dose of minocycline or placebo on Day 1, and 15 doses BID starting on Day 4. Safety was assessed throughout the study. Serial blood and urine samples were collected for PK assessment.

Results. Sixty-nine healthy subjects were randomized, 49 were included in the PK analysis. No serious adverse events (AEs) occurred; 55 subjects (79.9%) reported study drug-related AEs; dizziness 40 (58.0%) and nausea 34 (49.3%) were the most common. All related AEs were mild except for seven subjects with moderate nausea and/or dizziness. Dosing in the 400 mg cohort was discontinued due to AEs, therefore MAD escalation was stopped. Subsequent cohorts were escalated for SAD and loading dose only.

SAD Mean (SD) PK Parameters

Dose (mg)	100	200	300	400	500	600
N	8	8	8	8	8	9
Cmax (mg/L)	0.99 (0.2)	1.89 (0.4)	3.35 (1.2)	4.93 (1.8)	4.36 (0.9)	7.03 (2.4)
$T_{1/2}$ (h)	11.05 (2.1)	13.70 (2.3)	16.62 (3.9)	17.55 (2.1)	14.44 (2.7)	17.27 (3.6)
$AUC_{0-\infty}$(mg*h/L)	9.73 (1.4)	25.90 (6.9)	39.16 (13.8)	63.64 (18.2)	53.76 (20.3)	83.00 (29.4)
Cl (L/h)	10.48 (1.8)	8.21 (2.2)	8.28 (2.1)	6.71 (1.7)	10.25 (3.0)	8.07 (2.8)
Vss (L)	156 (36.7)	148 (36.6)	158 (45.4)	142 (38.0)	179 (46.5)	153 (52.8)

AUC, area under the drug concentration–time curve; Cmax, maximum observed drug concentration; $T_{1/2}$, half-life; Cl, plasma clearance; Vss, volume of distribution at steady state. *N*, number of subjects.

Conclusion. Single IV doses of minocycline up to 600 mg were tolerated reasonably well, but the maximum tolerated multi-dose was 300 mg BID. Most common AEs were mild nausea and dizziness with evidence of increasing incidence but not increasing severity with increasing dose. Exposure increased in a dose proportional fashion with exception of the 500 mg dose. The dosage regimen selected for further studies will be a 600 mg loading dose followed by 300 mg BID.

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