Cefiderocol Compared with Imipenem/Cilastatin in the Treatment of Adults with Complicated Urinary Tract Infections with or without Pyelonephritis or Acute Uncomplicated Pyelonephritis: Results from a Multicenter, Double-blind, Randomized Study (APEKS-cUTI)

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Disclosures

Shionogi & Co., Ltd	Shionogi Inc.	Medical Consultant
Mitsuaki Machida Mari Ariyasu Tsutae “Den” Nagata	Simon Portsmouth David van Veenhuyzen Juan Camillo Arjona Ferreira	Roger Echols

Anti-Microbial Resistance

WHO Priority Pathogen List For R&D of New Antibiotics

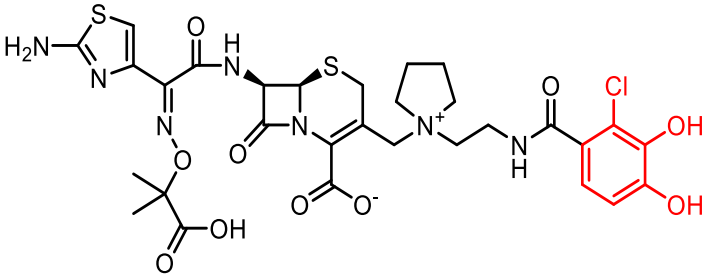
[Priority 1: Critical]

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant

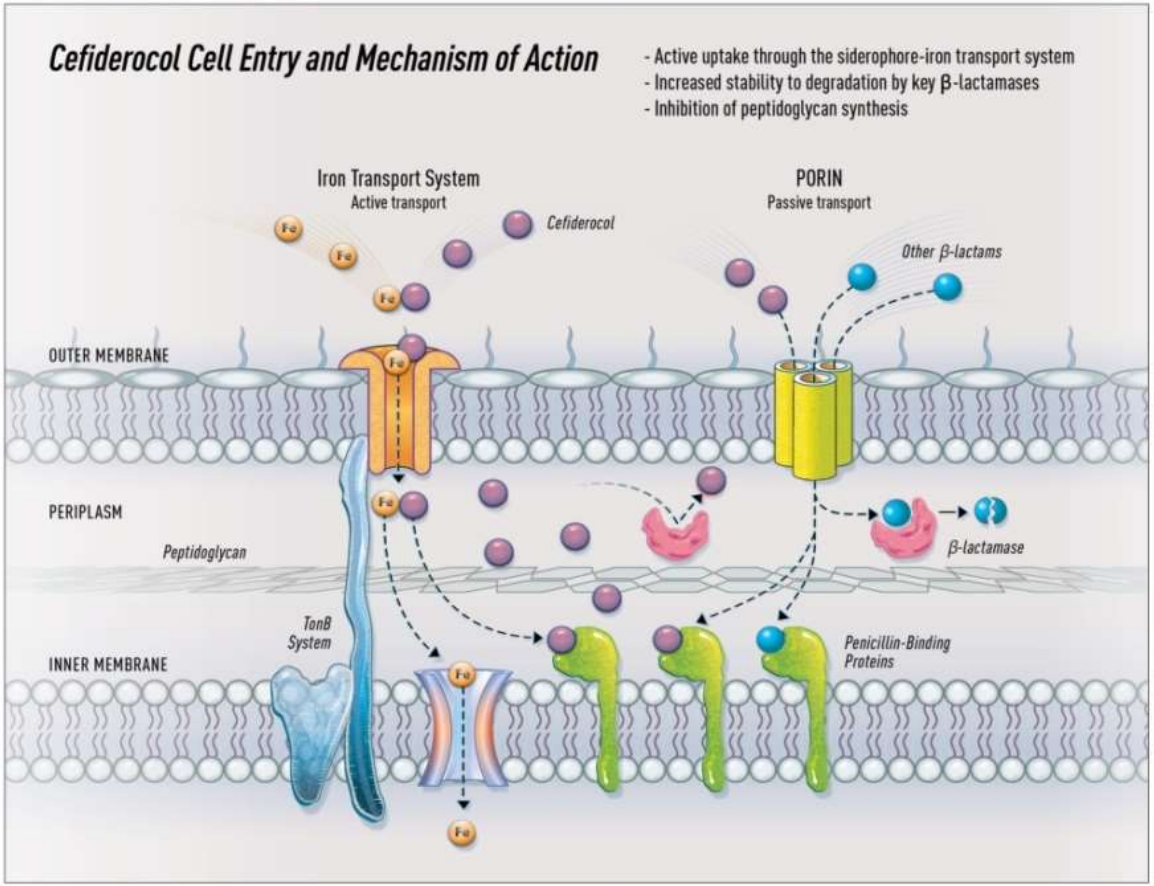
World Health Organization 25 Feb, 2017
GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVER, AND DEVELOPMET OF NEW ANTIBIOTICS

Cefiderocol (S-649266) is a siderophore cephalosporin

- **Chelating complex with trivalent iron**
- **Transported through outer cell membrane via active iron transport system**



A. Ito et al. AAC 2016;60:7396



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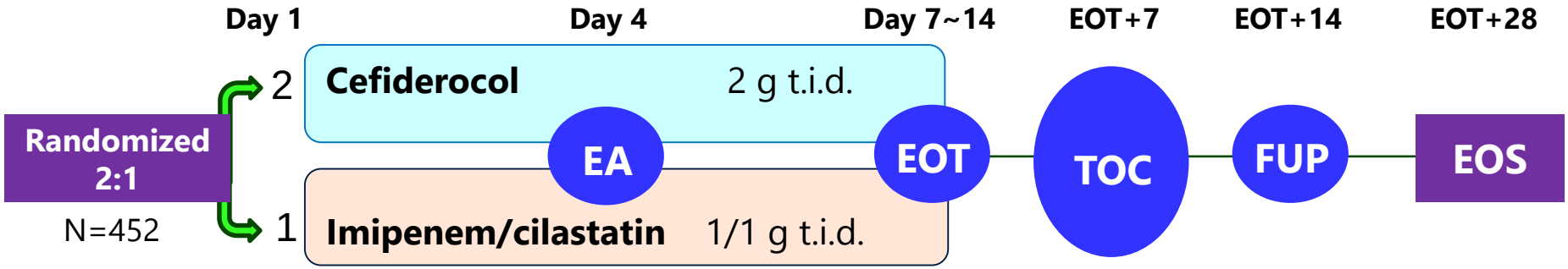
Cefiderocol (S-649266) developed for carbapenem resistant Gram-negative infections

- Highly stable to various types of carbapenemase
  KPC, OXA, IMP, VIM and NDM
- Potent activity against Gram-negatives including CR strains
  A*cinetobacter baumannii*
  P*seudomonas aeruginosa*
  E*scherichia coli*
  K*lebsiella pneumoniae*
  S*tenotrophomonas maltophilia*

  APEKS
- Not active against Gram-positives or anaerobes

T Ito et al. AAC 2016;60:4384, A Ito et al. JAC 2016;71:670, N Kohira et al. AAC 2016;60;729, I.M. Ghazi et al. ASM-Microbe2016 Poster, Y. Yamano et al. ECCMID2017 Poster #3221

APEKS-cUTI Study Design



- **Multicenter, double-blind, randomized, non-inferiority trial**
  - **2-sided 95% confidence interval, non-inferiority margin 15%**
- **<u>Primary endpoint</u>: composite clinical and microbiological response at TOC in MITT population**
- **<u>Secondary endpoint</u>: Microbiological response at TOC in MITT population**

MITT: patients who received at least 1 dose and have a baseline Gram-negative uropathogen
NB: No oral antibiotic step-down permitted

SCR: screening, EA: early assessment, EOT: end of treatment, TOC: test of cure, FUP: follow up, EOS: end of study

APEKS-cUTI targeted “at risk” population for MDR cUTI

- Key Inclusion
  - Hospitalized subjects with either cUTI with or without pyelonephritis or Acute Uncomplicated Pyelonephritis (AUP)
    - ➢ AUP was limited to no more than 30% of population
- Key Exclusion
  - Positive urine culture of Gram-negative uropathogen resistant to imipenem
  - More than 2 baseline uropathogens or confirmed fungal UTI
  - Patient receiving hemodialysis or peritoneal dialysis

- Allow patients with immunosuppression, immunosuppressive drugs, renal transplants
- Allow mild to moderate renal failure (CrCl ≥21)

APEKS-cUTI Results – Analysis Populations

Population	Cefiderocol (N=303)	Imipenem/cilastatin (N=149)	Total (N=452)
Safety Population	300	148	448
Microbiological Intent to Treat Population (MITT)	252 (84%)	119 (80.4%)	371 (82.8%)
Microbiologically Evaluable Population (ME)	228 (76%)	106 (71.6%)	334 (74.6%)

- % based on safety population denominator

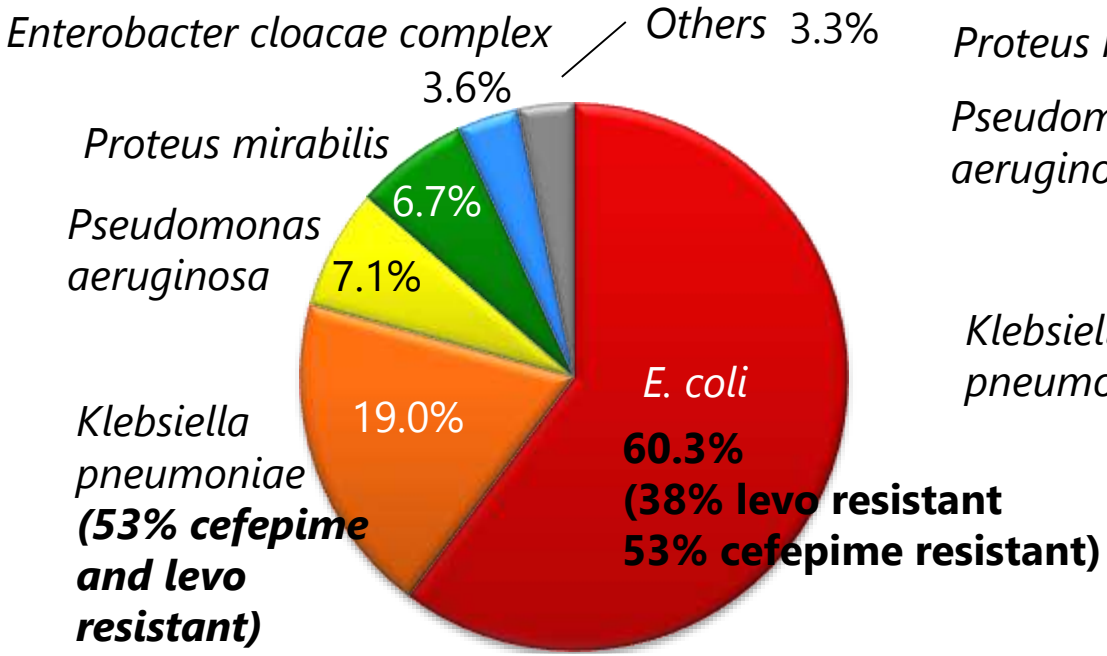
MITT: patients who received at least 1 dose and have a baseline Gram-negative uropathogen
ME: MITT population who follow important components of the trial with no major protocol violations

Baseline characteristics - population at risk for MDR infection

MITT Population	Cefiderocol (N = 252)	Imipenem/cilastatin (N = 119)
Gender (female %)	133 (52.8%)	71 (59.7%)
Age (years, mean)	62.3	61.3
≥ 65 years of age (%)	139 (55.2%)	65 (54.6%)
≥ 75 years of age (%)	61 (24.2%)	29 (24.4%)
Race (White, %)	241 (95.6%)	115 (96.6%)
Clinical Diagnosis at Baseline (%)		
cUTI w/ or w/o Pyelonephritis	187 (74.2%)	84 (70.6%)
Acute uncomplicated pyelonephritis	65 (25.8%)	35 (29.4%)
Creatinine Clearance Renal Grading		
>50 – 80 mL/min (mild) (%)	78 (31.0%)	41 (34.5%)
>30 - 50 mL/min (moderate) (%)	41 (16.3%)	23 (19.3%)
< 30 (Severe) (%)	7 (2.8%)	4 (3.4%)
Medical History		
Neoplasms	54 (21.4%)	21 (17.6%)
Chronic pyelonephritis	16 (6.3%)	2 (1.7%)

Baseline Uropathogens (MITT Population)

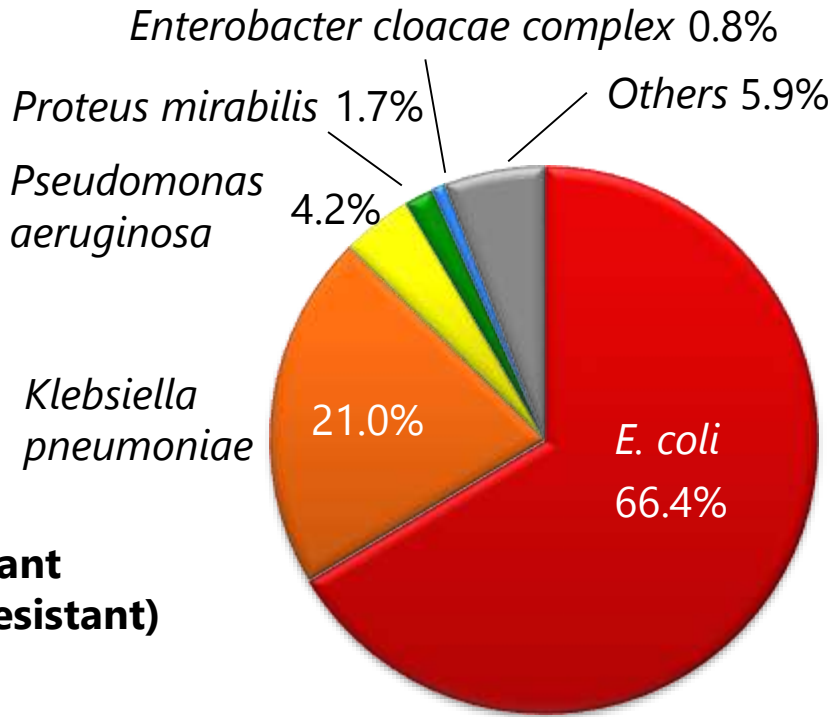
Cefiderocol (N=252)



(53% cefepime and levo resistant)

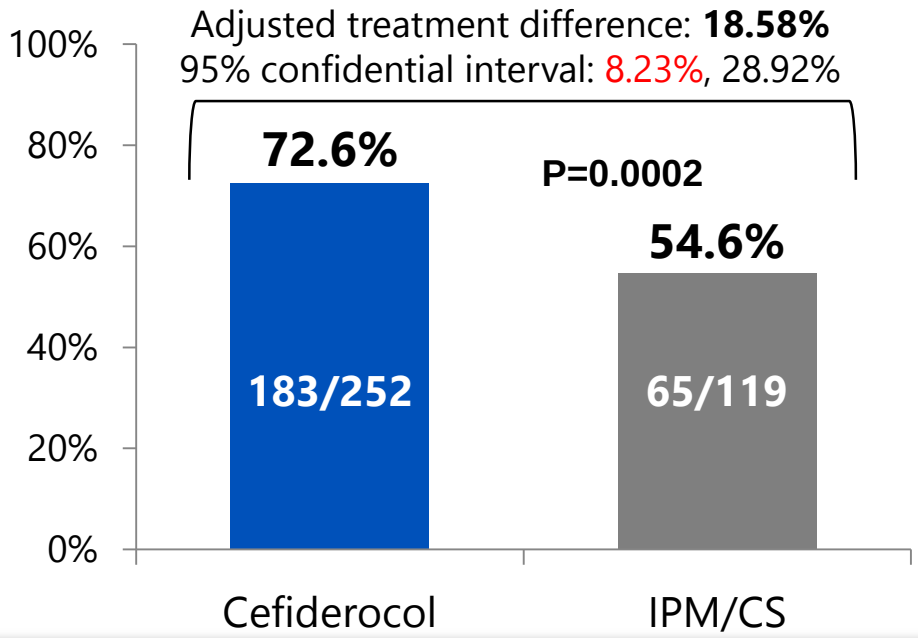
(38% levo resistant 53% cefepime resistant)

Imipenem/cilastatin (N=119)

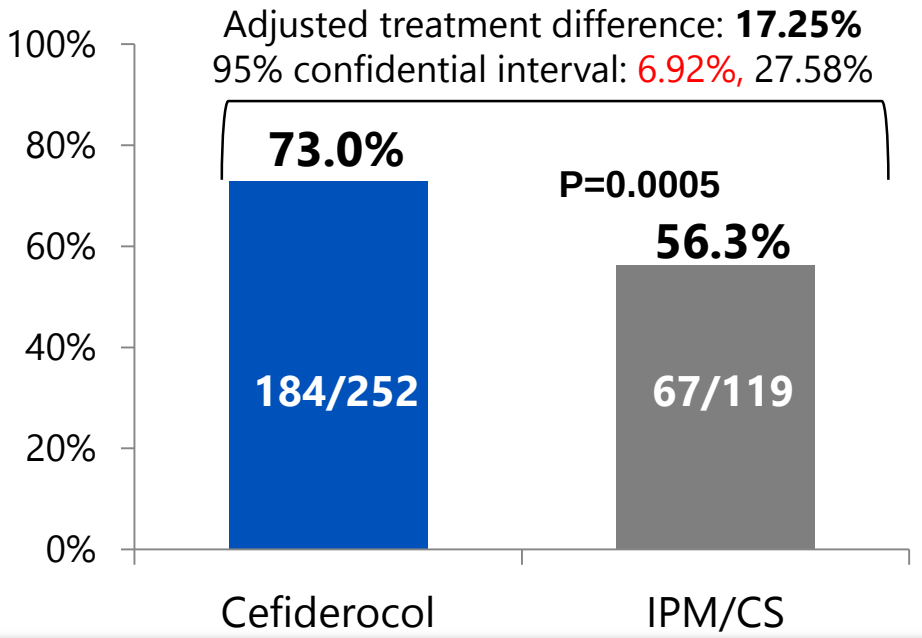


APEKS-cUTI Primary and secondary endpoint

Primary Endpoint
Composite Outcome at TOC
(Clinical Response and Microbiological Response)

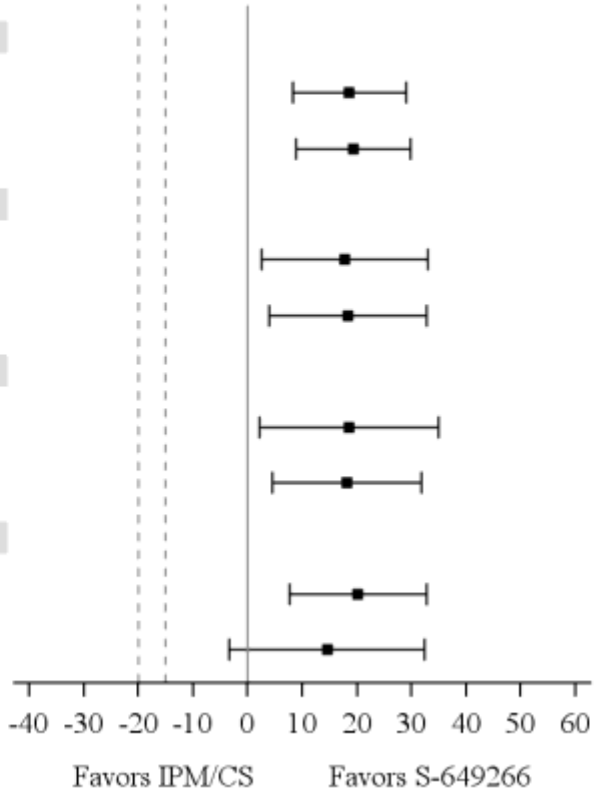


Secondary Endpoint
Microbiological Response at TOC



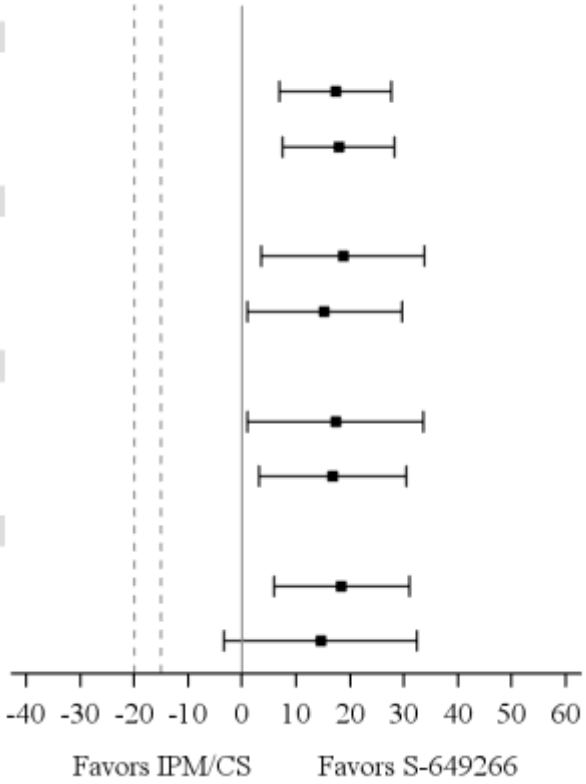
Treatment difference (S-649266 minus IPM/CS) is the adjusted estimate of the difference in the responder rate between the 2 treatment arms. The adjusted difference estimates and the 95% CIs (2-sided) are calculated using a stratified analysis with Cochran-Mantel-Haenszel weights based on the stratified factor at baseline (cUTI with or without pyelonephritis vs. acute uncomplicated pyelonephritis)

Composite endpoint at TOC: Clinical Cure and Micro eradication



Subgroup	S-649266	IPM/CS	Difference(95% CI)
Analysis Population			
Micro-ITT Population (Overall)	183/252(72.6)	65/119(54.6)	18.58(8.23, 28.92)
ME Population	182/228(79.8)	65/106(61.3)	19.35(8.87, 29.82)
Age Group 1			
< 65 years	87 /113 (77.0)	32 /54 (59.3)	17.73(2.50, 32.96)
>= 65 years	96 /139 (69.1)	33 /65 (50.8)	18.30(3.92, 32.67)
Gender			
Male	84 /119 (70.6)	25 /48 (52.1)	18.50(2.17, 34.84)
Female	99 /133 (74.4)	40 /71 (56.3)	18.10(4.38, 31.81)
Clinical Diagnosis			
cUTI with or without Pyelonephritis	129 /187 (69.0)	41 /84 (48.8)	20.17(7.60, 32.75)
Acute Uncomplicated Pyelonephritis	54 /65 (83.1)	24 /35 (68.6)	14.51(-3.37, 32.38)

Microbiological eradication at TOC



Subgroup	S-649266	IPM/CS	Difference(95% CI)
Analysis Population			
Micro-ITT Population (Overall)	184/252(73.0)	67/119(56.3)	17.25(6.92, 27.58)
ME Population	183/228(80.3)	67/106(63.2)	17.83(7.42, 28.24)
Age Group 1			
< 65 years	88 /113 (77.9)	32 /54 (59.3)	18.62(3.44, 33.79)
>= 65 years	96 /139 (69.1)	35 /65 (53.8)	15.22(0.87, 29.57)
Gender			
Male	85 /119 (71.4)	26 /48 (54.2)	17.26(1.00, 33.53)
Female	99 /133 (74.4)	41 /71 (57.7)	16.69(3.02, 30.36)
Clinical Diagnosis			
cUTI with or without Pyelonephritis	130 /187 (69.5)	43 /84 (51.2)	18.33(5.77, 30.89)
Acute Uncomplicated Pyelonephritis	54 /65 (83.1)	24 /35 (68.6)	14.51(-3.37, 32.38)

Safety Summary

Safety Population	Cefiderocol (N = 300)	Imipenem/cilastatin (N = 148)	Total (N=448)
Subject with AEs	120 (40.0%)	74 (50.0%)	194 (43.3%)
Subjects with Drug-related AEs	26 (8.7%)	17 (11.5%)	43 (9.6%)
Subjects Discontinuing due to AEs	5 (1.7%)**	3 (2.0%)	8 (1.8%)
Subject with SAEs	14 (4.7%)	12 (8.1%)	26 (5.8%)
Subjects who died	1 (0.3%)*	0 (0%)	1 (0.2%)

*Death was not considered drug related by investigator

**(Cefiderocol) *C. diff*, Hypersensitivity (itching), Increased hepatic enzymes, diarrhea

AEs with an incidence > 2% in each treatment group

AE incidence >2.0% in Safety Population	Cefiderocol (N = 300)	Imipenem/cilastatin (N = 148)	Total (N=448)
Diarrhoea	13 (4.3%)	9 (6.1%)	22 (4.9%)
Hypertension	13 (4.3%)	7 (4.7%)	20 (4.5%)
Constipation	10 (3.3%)	6 (4.1%)	16 (3.6%)
Infusion site pain	9 (3.0%)	5 (3.4%)	14 (3.1%)
Headache	7 (2.3%)	8 (5.4%)	15 (3.3%)
Nausea	7 (2.3%)	6 (4.1%)	13 (2.9%)
Cough	7 (2.3%)	1 (0.7%)	8 (1.8%)
Vomiting	6 (2.0%)	2 (1.4%)	8 (1.8%)
Hypokalaemia	5 (1.7%)	4 (2.7%)	9 (2.0%)
Insomnia	4 (1.3%)	3 (2.0%)	7 (1.6%)
Renal cyst	3 (1.0%)	5 (3.4%)	8 (1.8%)
Infusion site erythema	3 (1.0%)	3 (2.0%)	6 (1.3%)
Abdominal pain upper	2 (0.7%)	5 (3.4%)	7 (1.6%)
Cardiac failure	2 (0.7%)	3 (2.0%)	5 (1.1%)
Clostridium difficile colitis	1 (0.3%)	4 (2.7%)	5 (1.1%)
Vaginal infection	1 (0.3%)	3 (2.0%)	4 (0.9%)

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APEKS-cUTI: Summary

- APEKS-cUTI was a pivotal trial to compare cefiderocol with imipenem/cilastatin in hospitalised patients at risk for MDR cUTI
- Cefiderocol demonstrated non-inferiority over treatment with imipenem/cilastatin in the primary composite and the secondary microbiological endpoint. Results consistent with superiority
- Cefiderocol non-inferiority was consistent across patient clinical and microbiologic subgroups. 15-20% treatment difference is clinically important
- Cefiderocol was generally well tolerated, no unexpected safety concerns were identified

Acknowledgments

- Shionogi would like to thank
  - Patients
  - Investigators
  - Site personnel

Further Information (cefiderocol presentations at ECCMID)

Session Title	Poster / Oral	Date
Advances in Japanese Chemotherapy	#OS0750	Monday, April 24 14:54 – 15:04 PM
Cefiderocol	Poster #1316	Monday, April 24 12:30 – 13:30 PM
	Poster #1314	Monday, April 24 12:30 – 13:30 PM
	Poster #1313	Monday, April 24 12:30 – 13:30 PM

Thank you!