Methods. From 2014 to 2017, environmental swabs were collected from public areas, healthcare settings, and shoe soles. Samples were considered positive for *C. difficile* following growth on CCFA plates and confirmatory PCR testing for toxin genes and fluorescent PCR ribotyping (RT). The rate of *C. difficile* positivity and associated RT distribution were compared between settings, including shoe soles which were investigated for their potential role in environmental transmission.

Results. A total of 11,986 unique isolates were obtained primarily from the US (n=11,002; 92%) in addition to 11 other countries including Taiwan (n=200) and India (n=187). Samples were categorized as being from outdoor environments (n=2,992), private residences (n=2,772), shoe soles (n=1,420), public buildings (n=1,104) or acute care settings (n=3,698). Worldwide *C. difficile* sample positivity was 26% and was similar between US and non-US sampling sites. In the US, private residences (26.2%) and outdoor environments (24.1%) had the highest positivity rate compared to public buildings (17.2%). In a Texas sub-analysis (n=8,571), positivity rates were highest from outdoor samples (27%) and were similar between private residences (24%) and healthcare buildings (24%). The most prevalent RTs overall were F014-020 (16.4%), F106 (14.9%), and FP310 (11%). Shoe soles had the highest positivity rate (45%) with similar RT distribution between shoe soles and environmental samples.

Conclusion. Using a worldwide sample, 26% of environmental samples tested positive for toxigenic *C. difficile* strains from healthcare and non-healthcare sites. Community stewardship efforts will be needed to reduce the risk of CDI in vulnerable patients. Shoe sole sampling may be an ideal surveillance tool to test for emerging epidemic strains.

Disclosures. **Kevin W. Garey, Pharm.D., M.S., FASHP**, **Summit Therapeutics** (Research Grant or Support)

19. The Impact of Investigational Purified Microbiome Therapeutic SER-109 on Health-Related Quality of Life (HRQoL) of Patients with Recurrent *Clostridioides difficile* Infection (rCDI) in ECOSPOR III, a Placebo-Controlled Clinical Trial

Elizabeth Hohmann, MD[1]; Paul Feuerstadt, MD, FACG[2]; Caterina Oneto, M.D.[3]; Charles Berenson, MD[4]; Christine Lee, MD, FRCPC[5]; Sissi Pham, PharmD[6]; Lei Zhu, PhD[7]; Pat Ray Reese, PhD[8]; Henry Wu, PhD[9]; Elaine E. Wang, MD[10]; Elaine E. Wang, MD[10]; Lisa von Moltke, MD[10]; Kevin W. Garey, Pharm.D., M.S., FASHP[11]; [1]Massachusetts General Hospital, Boston, Massachusetts; [2]Yale University School of Medicine/PACT-Gastroenterology Center, Westport, Connecticut; [3]NYU Langone, New York, New York [4]State University of New York at Buffalo, Buffalo, New York; [5]University of British Columbia, Victoria, British Columbia, Canada; [6]AESARA, Chapel Hill, North Carolina [7]Aesara, Chapel Hill, North Carolina [8]Aesara, Inc., Apex, North Carolina; [9]CR Medicon Research, Piscataway, New Jersey; [10]Seres Therapeutics, Cambridge, Massachusetts; [11]University of Houston College of Pharmacy, Houston, Texas

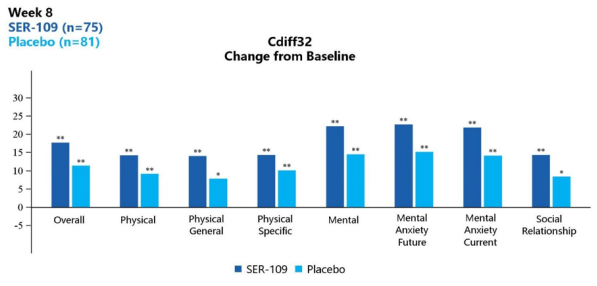
Session: O-04. Challenges in C. difficile

Background. Following standard of care antibiotics, investigational microbiome therapeutic, SER-109, achieved superiority vs placebo (PBO) at 8 weeks in reducing rCDI in patients with ≥3 prior episodes (12.4% vs 39.8%, respectively; p< 0.001). We evaluated the impact of SER-109 vs PBO on HRQoL with general (EQ-5D-5L) and disease-specific (Cdiff32) measures [Garey 2016].

Methods. EQ-5D-5L measures outcomes in 5 domains (mobility, self-care, activities, pain/discomfort, and anxiety/depression) while Cdiff32 measures outcomes in 3 domains (physical, mental, and social) including 5 associated subdomains. Patients completed EQ-5D-5L and Cdiff32 measures at baseline (BL), Wk 8, and at recurrence/early termination. Changes from BL were assessed between SER-109 vs PBO and by clinical outcome (recurrence versus nonrecurrence) in the ITT population and within each treatment arm. The between treatment group comparison analysis controlled for age, gender, prior antibiotics, and number of prior CDI episodes.

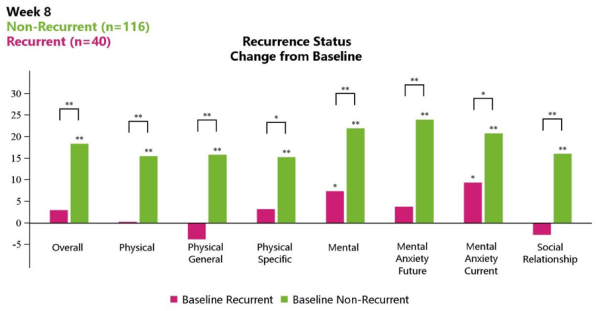
Results. Mean EQ-5D-5L and Cdiff32 scores were comparable between SER-109 and PBO at BL. EQ-5D-5L did not detect differences at Wk 8 from BL between SER-109 and PBO or by clinical outcome. In contrast, Cdiff32 detected significant improvements at Wk 8 from BL within both SER-109 subjects and PBO subjects (Fig1) and by recurrence status (Fig2). Subjects achieved significant improvement in all domains at Wk 8 from BL regardless of treatment group. When examining recurrence status within treatment arms, all PBO subjects with non-recurrence showed improvement in all health domains, while PBO subjects with recurrence had declines in several subdomains (Fig3B). Similarly, SER-109 subjects with non-recurrence showed improvement in all domains compared to BL. However, overall and mental domain/subdomains scores also improved in SER-109 subjects with recurrence (Fig3A).

Figure 1: Change from Baseline at Week 8 in Cdiff32 HRQoL Questionnaire by Treatment Group, ITT Population



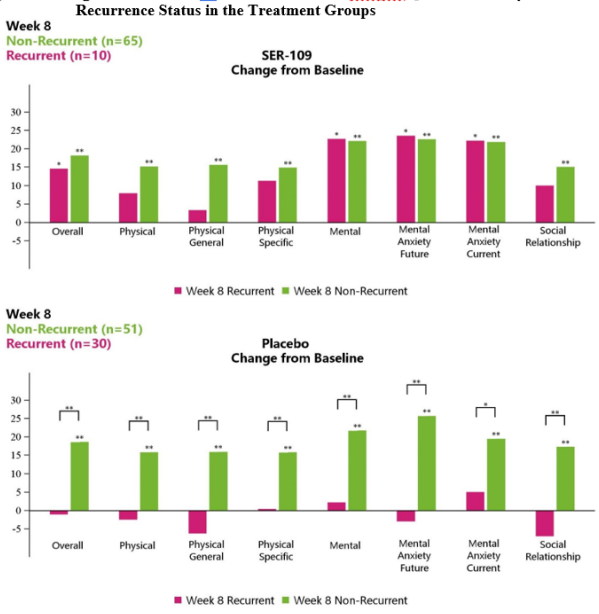
* *P*<0.05; ** *P*<0.001; ⊓ Between group comparison

Figure 2: Change from Baseline in Cdiff32 HRQoL Questionnaire by Recurrence Status at Weeks 8, ITT Population



* *P*<0.05; ** *P*<0.001; ⊓ Between group comparison

Figure 3: Change from Baseline At Week 8 in Cdiff32 HRQoL Questionnaire by Recurrence Status in the Treatment Groups



* *P*<0.05; ** *P*<0.001; ⊓ Between group comparison

Conclusion. Significant HRQoL improvements were associated with CDI nonrecurrence, which highlights the negative impact of this debilitating infection. SER-109 was associated with improved overall and mental scores, regardless of clinical outcome. Further investigation is warranted on the impact of SER-109 on mental health even among those with CDI recurrence.

Disclosures. **Elizabeth Hohmann, MD**, **Seres Therapeutics** (Research Grant or Support) **Paul Feuerstadt, MD, FACG**, **Ferring/Rebiotix Pharmaceuticals** (Consultant, Scientific Research Study Investigator, Speaker's Bureau)**Finch Pharmaceuticals** (Scientific Research Study Investigator)**Merck and Co** (Speaker's Bureau)**SERES Therapeutics** (Consultant, Scientific Research Study Investigator)**Takeda Pharmaceuticals** (Consultant) **Christine Lee, MD, FRCPC**, **Pfizer** (Board Member)**Rebiotix-Ferring** (Board Member)**Rebiotix-Ferring** (Grant/Research Support)**Seres** (Grant/Research Support)**Summit** (Grant/Research Support) **Sissi Pham, PharmD**, **Seres** (Consultant) **Pat Ray Reese, PhD**, **Reese Associates, LLC** (Consultant, Independent Contractor) **Elaine E. Wang, MD**, **Seres Therapeutics** (Employee) **Elaine E. Wang, MD**, **Seres Therapeutics** (Employee, Shareholder) **Lisa von Moltke, MD**, **Seres Therapeutics** (Employee, Shareholder) **Kevin W. Garey, Pharm.D., M.S., FASHP**, **Summit Therapeutics** (Research Grant or Support)

20. Risk Factors for Breakthrough Cytomegalovirus (CMV) Infection and *De Novo* Resistance in Hematopoietic Cell Transplantation (HCT) Recipients Receiving Letermovir Prophylaxis

Danniel Zamora, MD[1]; Garrett Perchetti, BS[1]; Melinda Biernacki, MD[2]; Hu Xie, MS[3]; JARED L. CASTOR, n/a[1]; Laurel Joncas-schronce, n/a[2]; Rachel Blazevic, BS[4]; Wendy Leisenring, ScD[3]; Meei-Li Huang, PhD[1]; Keith Jerome, MD, PhD[1]; Paul J. Martin, MD[2]; Michael Boeckh, MD PhD[4]; Alexander L. Greninger, MD, PhD[1]; [1]University of Washington, Seattle, Washington; [2]Fred Hutch, Seattle, Washington; [3]Fred Hutchinson Cancer Research Center; University of Washington, Seattle, Washington; [4]Fred Hutchinson Cancer Research Center, Seattle, WA

Session: O-05. Clinical Quandries in Viral Infections in ICH

Background. Subclinical CMV reactivation on letermovir prophylaxis may be important for CMV-specific immune reconstitution after HCT (Zamora et al. *Blood* 2021) but concerns remain regarding the development of antiviral resistance. Here we analyze risk factors associated with breakthrough CMV infection on letermovir and describe the incidence of *de novo* letermovir resistance.

Methods. All CMV-seropositive, allogeneic HCT recipients who received letermovir prophylaxis from 10/2018-2020 were analyzed. Weekly proportions and cumulative incidences of CMV reactivation in the first 100 days post-HCT were calculated at different levels. Clinically significant CMV infection was treated preemptively with (val)ganciclovir or foscarnet. Univariable/multivariable Cox regression models for breakthrough CMV reactivation at each viral threshold were performed. Patients with CMV reactivation ≥ 200 IU/mL were tested by UL56 sequencing to identify *de novo* letermovir resistance.

Results. Two hundred thirty HCT recipients who received letermovir prophylaxis were identified. Weekly proportions and cumulative incidences of CMV reactivation are shown in **Figure 1**. Nine of 15 patients with CMV reactivation had sufficient serum for letermovir resistance testing. One C325Y mutation was identified in an umbilical cord blood transplant recipient who developed 4 weeks of CMV DNAemia with a peak of 2512 IU/mL. The patient received 56 days of letermovir prior to reactivation and responded to treatment initially with foscarnet (due to cytopenias) followed by ganciclovir. Greater cumulative steroid exposure was associated with increased risk of CMV reactivation and the association remained statistically significant at any level (adjusted Hazard Ratio [aHR] 10.8 mg/kg*days, 95% confidence interval [CI] 5.18-22.7) and ≥ 150 IU/mL (aHR 15.9 mg/kg*days, 95% CI 7.07-35.6) after adjusting for underlying disease and GVHD prophylaxis (**Figure 2**).

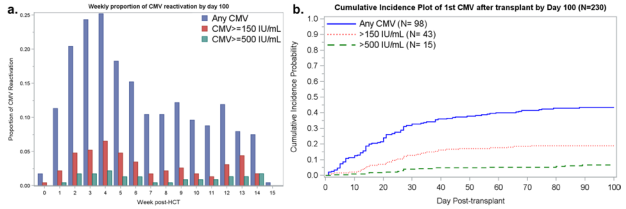


Figure 1. – Weekly Proportions and cumulative incidences of CMV reactivation by post-HCT day 100. All letermovir recipients (N=230) had weekly CMV DNA PCR surveillance in the first 100 days post-HCT. Weekly proportions (**a.**) and cumulative incidences (**b.**) of CMV reactivation are shown at: any level (blue), ≥ 150 IU/mL (red), and ≥ 500 IU/mL (green). Death was treated as a competing risk in all models. Patients who reactivated CMV in the first 100 days post-HCT were treated with either ganciclovir, valganciclovir, or foscarnet per institutional standards at CMV DNA PCR ≥150 IU/mL following high-risk HCT (i.e., umbilical cord blood, haploidentical donor, HLA-mismatched donor, after T-cell depleted HCT, or requiring ≥1 mg/kg of prednisone or its equivalent) or ≥ 500 IU/mL following low-risk HCT. A total of 43/230 (19%) letermovir recipients had CMV DNA PCR ≥150 IU/mL whereas 15/230 (7%) had ≥ 500 IU/mL.

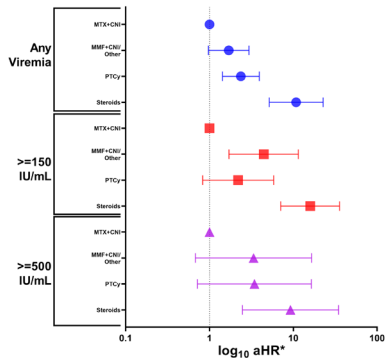


Figure 2. – Cox regression of clinical factors on time to CMV reactivation by day 100 after HCT. Cox regression models on time to CMV reactivation by day 100 post-HCT according to positive CMV DNA PCR results at: any level (blue), ≥ 150 IU/mL (red), and ≥ 500 IU/mL (purple). Multivariable models were adjusted for underlying disease, graft-versus-host disease (GVHD) prophylaxis, and cumulative steroid exposure prior to reactivation (time-dependent). Note, the x-axis was log-transformed for graphical purposes.
aHR=adjusted hazard ratio, CNI=calcineurin inhibitor, HR=hazard ratio, MMF=mycophenolate mofetil, MTX=methotrexate, PTCy=post-transplantation cyclophosphamide.
*For ≥500 IU/mL, only unadjusted model data are shown due to the decreased number of CMV events in that category.

Conclusion. Letermovir prophylaxis was effective at preventing clinically significant CMV infection but subclinical reactivation continued to occur. Cumulative steroid exposure was the strongest risk factor for reactivation while on letermovir. Development of *de novo* letermovir resistance on prophylaxis occurred infrequently.

Disclosures. **Michael Boeckh, MD PhD**, **AlloVir** (Consultant)**Ansun Biopharma** (Grant/Research Support)**Astellas** (Grant/Research Support)**EvrysBio** (Consultant, Other Financial or Material Support, Options to acquire equity, but have not exercised them)**Gilead Sciences** (Consultant, Grant/Research Support)**GlaxoSmithKline** (Consultant)**Helocyte** (Consultant, Other Financial or Material Support, Options to acquire equity, but have not exercised them)**Janssen** (Grant/Research Support)**Kyorin** (Consultant)**Merck** (Consultant, Grant/Research Support)**Moderna** (Consultant)**Symbio** (Consultant)**Takeda (formerly known as Shire)** (Consultant, Grant/Research Support)**VirBio** (Consultant, Grant/Research Support) **Alexander L. Greninger, MD, PhD**, **Abbott** (Grant/Research Support)**Gilead** (Grant/Research Support)**Merck** (Grant/Research Support)

21. Efficacy and Safety of Maribavir as a Rescue Treatment for Investigator Assigned Therapy in Transplant Recipients With Refractory or Resistant Cytomegalovirus Infections in the SOLSTICE Study: Phase 3 Trial Results

Marcus Pereira, MD[1]; Carlos Cervera, MD, PhD[2]; Camille Kotton, MD[3]; Joseph Sasadeusz, MBBS, PhD[4]; Jingyang Wu, MS[5]; Martha Fournier, MD[5]; [1]Columbia University College of Physicians and Surgeons, New York, New York [2]University of Alberta, Edmonton, AB, Canada; [3]Massachusetts General Hospital, Boston, MA; [4]Royal Melbourne Hospital, Melbourne, Victoria, Australia; [5]Shire Human Genetic Therapies, Inc., a Takeda company, Lexington, Massachusetts

Session: O-05. Clinical Quandries in Viral Infections in ICH

Background. Refractory or resistant (R/R) cytomegalovirus (CMV) infection after hematopoietic cell transplant (HCT) and solid organ transplant (SOT) cause serious, potentially fatal complications; therapeutic options are limited. In a Phase 3 study (NCT02931539), maribavir (MBV) was superior to investigator-assigned therapy (IAT; val/ganciclovir, foscarnet, cidofovir) for CMV clearance (Wk 8) and clearance plus symptom control (Wk 8 through Wk 16) in HCT/SOT recipients with R/R CMV infections. Here we present further study results on efficacy and safety of MBV in the rescue arm.

Methods. Patients (pts) were stratified and randomized 2:1 to MBV (400 mg/bid) or IAT for 8-wk treatment then 12-wk follow-up. After minimum 3 wks' treatment, pts in the IAT group meeting criteria (worsening/lack of improvement of CMV infection or failure to achieve viremia clearance plus IAT intolerance) could enter a MBV rescue arm (8-wk treatment, 12-wk follow-up). In the rescue arm, efficacy was evaluated by confirmed CMV viremia clearance (plasma CMV DNA < 137 IU/mL in 2 consecutive tests ≥ 5 days apart) at end of Wk 8 and confirmed clearance with symptom control at Wk 8 through Wk 16. Safety was assessed.

Results. A total of 352 pts were randomized (MBV: 235, IAT: 117, randomized set). Confirmed CMV viremia clearance at Wk 8 was achieved in 131 (55.7%) and 28 (23.9%) pts, respectively, in the randomized set. Having met criteria, 22 (18.8%) pts entered the MBV rescue arm; at entry, 6 (27.3%) pts had developed neutropenia and 9 (40.9%) had increased serum creatinine (**Table 1**). At Wk 8 of rescue therapy, 11 (50.0%) pts achieved confirmed CMV viremia clearance; 6 (27.3%) pts had CMV clearance with symptom control at Wk 8 maintained through Wk 16 (**Table 2**). All 22 pts reported treatment-emergent adverse events (TEAEs; **Table 3**); most common TEAEs of special interest were nausea, vomiting, and diarrhea (54.5%), and taste disturbance (50.0%). Neutropenia and acute kidney injury TEAEs were reported by 0 and 3 pts in the rescue arm, respectively.

Table 1. Summary of patients from IAT-randomized group meeting criteria for entry into MBV rescue arm*

Number (%) of patients	MBV rescue arm (n=22)
Met Criterion 1: Had increased CMV DNA of ≥1 log_{10} from baseline†	4 (18.2)
Met Criterion 2: Had <1 log_{10} decrease from baseline in CMV DNA and had persistent or new symptomatic CMV infection‡	3 (13.6)
Met Criterion 3: Did not achieve CMV viremia clearance necessitating continued anti-CMV treatment, plus had demonstrated intolerance to the IAT as evidenced by 1 of the following conditions:	15 (68.2)
Acute increase in serum creatinine§	9 (40.9)
Development of hemorrhagic cystitis¶	0
Development of neutropenia¥	6 (27.3)

* All patients who entered the MBV rescue arm had demonstrated persistence of CMV viremia despite treatment with IAT for at least 3 weeks. All patients entered the rescue arm between study Wk 3 and Wk 7, except for 1 patient who entered between Wk 7 and Wk 8.
† Whole blood or plasma CMV DNA levels were measured by local or central specialty laboratory qPCR assay.
‡ Patient had to meet 2 criteria: (i) whole blood or plasma CMV DNA had decreased <1 log_{10} from baseline as measured by local or specialty laboratory qPCR assay, and (ii) the presenting tissue-invasive CMV disease for symptomatic patients had not improved/worsened, or patient was asymptomatic at baseline and developed tissue-invasive CMV disease.
§ At least 50% increase from baseline value, attributed to treatment toxicity (eg, cidofovir, foscarnet).
¶ When on treatment with cidofovir or foscarnet.
¥ Absolute neutrophil count <500/mm^3 (0.5 x 10^9/L) when on treatment with val/ganciclovir.
CMV, cytomegalovirus; MBV, maribavir; qPCR, quantitative polymerase chain reaction.

Table 2. Patients achieving confirmed CMV viremia clearance at end of Wk 8 (end of treatment) or achieving confirmed CMV viremia clearance and symptom control at end of Wk 8 maintained through Wk 16

	Rescue arm*	Randomized set†	
Number (%) of patients	MBV (n=22)	MBV (n=235)	IAT (n=117)
Achieved confirmed CMV viremia clearance at end of Wk 8	11 (50.0)	131 (55.7)‡	28 (23.9)‡
Achieved confirmed CMV viremia clearance and symptom control at end of Wk 8 maintained through Wk 16	6 (27.3)	44 (18.7)§	12 (10.3)§

* Included all patients who entered the rescue arm and received any dose of MBV as rescue therapy.
† Included all patients who had signed informed consent, had begun some study procedures, and were randomized to the study; patients were analyzed in the treatment group to which they were randomized.
‡ A previous report of these study data showed significantly more patients randomized to MBV than IAT achieved confirmed CMV viremia clearance at end of Wk 8 (primary endpoint; adjusted difference [95% confidence interval]: 32.8% [22.80 to 42.74]; P<0.001). Presented at the 2021 Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR (Marty FM et al. Abstract LBA2).
§ A previous report of these study data showed significantly more patients randomized to MBV than IAT achieved confirmed CMV viremia clearance and symptom control at end of Wk 8, maintained through Wk 16 (key secondary endpoint; adjusted difference [95% confidence interval]: 9.5% [2.02 to 16.88]; P=0.013). Presented at the 2021 Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR (Marty FM et al. Abstract LBA2).
CMV, cytomegalovirus; IAT, investigator assigned therapy; MBV, maribavir.